Clinical trial results:
ENVISION: A Phase 3 Randomized, Double-blind, Placebo-controlled Multicenter Study with an Open-label Extension to Evaluate the Efficacy and Safety of Givosiran in Patients with Acute Hepatic Porphyrias

Summary

EudraCT number	2017-002432-17
Trial protocol	GB DE ES DK CZ SE BG FI BE FR PL NL IT
Global end of trial date	31 May 2021

Results information

Result version number	v1 (current)
This version publication date	16 June 2022
First version publication date	16 June 2022

Trial information

Trial identification

Sponsor protocol code	ALN-AS1-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03338816
WHO universal trial number (UTN)	-
Other trial identifiers	IND: 126094

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals, Inc.
Sponsor organisation address	300 Third Street, Cambridge, United States, 02142
Public contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com
Scientific contact	Clinical Trial Information Line, Alnylam Pharmaceuticals, Inc., +1 8772569526, clinicaltrials@alnylam.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effect of subcutaneous givosiran (ALN-AS1), compared to placebo, on the rate of porphyria attacks in patients with Acute Hepatic Porphyrias (AHP).

Protection of trial subjects:

The Investigators were to ensure that the patients' confidentiality was maintained. On the CRFs or other documents submitted to the Sponsor or designees, patients were not identified by their names, but by the assigned patient number and initials. If patient names were included on copies of documents submitted to the Sponsor or designees, the names (except for initials) were obliterated and the assigned patient number was added to the document. Documents not for submission to the Sponsor (eg, signed ICFs) were maintained by the Investigator in strict confidence.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2017
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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Bulgaria: 1
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Australia: 4
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Japan: 3
Country: Number of subjects enrolled	Korea, Republic of: 2
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 32

Worldwide total number of subjects	94
EEA total number of subjects	38

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)	93
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with acute hepatic porphyrias (AHP) were enrolled at thirty-six sites in Australia, Bulgaria, Canada, Germany, Denmark, Spain, Finland, France, United Kingdom, Italy, Japan, Korea (the Republic of), Mexico, Netherlands, Poland, Sweden, Taiwan and the United States.

Pre-assignment

Screening details:

Patients who met all eligibility criteria were randomized in a 1:1 ratio to receive 2.5 mg/kg givosiran or placebo once monthly for a 6-month double-blind treatment period.

Period 1

Period 1 title	6-Month Double-blind Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo 6-Month DB

Arm description:

Matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC), monthly (QM), for 6 months during the 6-Month Double-blind (DB) Period.

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

Dosage and administration details:

Matching placebo (normal saline [0.9% NaCl]) by SC

Arm title	Givosiran 2.5 mg/kg 6-Month DB

Arm description:

Givosiran 2.5 mg/kg administered SC, QM, for 6 months during the 6-Month DB Period.
1 subject discontinued treatment during the 6-month DB period but completed the 6-month DB Visit.

Arm type	Experimental
Investigational medicinal product name	Givosiran
Investigational medicinal product code	
Other name	GIVLAARI, ALN-AS1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Givosiran by SC

Number of subjects in period 1	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB
Started	46	48
Completed	46	48

Period 2	
Period 2 title	6-Month DB + Open-Label Extension Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo/Givosiran

Arm description:

Patients who received placebo during the 6-Month DB Period then entered the Open-Label Extension (OLE) Period and were administered givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM for 29 months. Upon implementation of protocol Amendment 5, active patients receiving 1.25 mg/kg givosiran once monthly in the OLE had their dose increased to 2.5 mg/kg givosiran once monthly.

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

Dosage and administration details:

Matching placebo (normal saline [0.9% NaCl]) by SC

Investigational medicinal product name	Givosiran
Investigational medicinal product code	
Other name	GIVLAARI, ALN-AS1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Givosiran by SC

Arm title	Givosiran/Givosiran

Arm description:

Patients who received givosiran during the 6-Month DB Period then entered the OLE Period and were administered givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM mg/kg for 29 months. Upon implementation of protocol Amendment 5, active patients receiving 1.25 mg/kg givosiran once monthly in the OLE had their dose increased to 2.5 mg/kg
givosiran once monthly.

Arm type	Experimental

Investigational medicinal product name	Givosiran
Investigational medicinal product code	
Other name	GIVLAARI, ALN-AS1
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Givosiran by SC

Number of subjects in period 2[1]	Placebo/Givosiran	Givosiran/Givosiran
Started	46	47
Completed	38	41
Not completed	8	6
Physician decision	1	-
Patient Desired Lower Dose	-	1
Adverse event, non-fatal	2	-
Death	-	1
Pregnancy	1	1
Withdrawal by Subject	3	3
Lost to follow-up	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: 1 subject discontinued treatment during the 6-month DB period due to an adverse event but completed the 6-month DB Visit

Baseline characteristics

Reporting groups	
Reporting group title	Placebo 6-Month DB
Reporting group description:	
Matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC), monthly (QM), for 6 months during the 6-Month Double-blind (DB) Period.	
Reporting group title	Givosiran 2.5 mg/kg 6-Month DB
Reporting group description:	
Givosiran 2.5 mg/kg administered SC, QM, for 6 months during the 6-Month DB Period. 1 subject discontinued treatment during the 6-month DB period but completed the 6-month DB Visit.	

Reporting group values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB	Total
Number of subjects	46	48	94
Age categorical Units: Subjects			
Adults (18-64 years)	46	47	93
From 65-84 years	0	1	1
Age continuous Units: years			
arithmetic mean	37.4	40.1	
standard deviation	± 10.5	± 12.1	-
Gender categorical Units: Subjects			
Female	41	43	84
Male	5	5	10
Ethnicity Units: Subjects			
Hispanic or Latino	3	5	8
Not Hispanic or Latino	42	42	84
Unknown or Not Reported	1	1	2
Ethnicity Units: Subjects			
Asian	7	8	15
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	1	0	1
White	34	39	73
More than One Race	1	0	1
Unknown or Not Reported	2	1	3

End points

End points reporting groups

Reporting group title	Placebo 6-Month DB

Reporting group description:

Matching placebo (normal saline [0.9% NaCl]) was administered subcutaneously (SC), monthly (QM), for 6 months during the 6-Month Double-blind (DB) Period.

Reporting group title	Givosiran 2.5 mg/kg 6-Month DB

Reporting group description:

Givosiran 2.5 mg/kg administered SC, QM, for 6 months during the 6-Month DB Period.
1 subject discontinued treatment during the 6-month DB period but completed the 6-month DB Visit.

Reporting group title	Placebo/Givosiran

Reporting group description:

Patients who received placebo during the 6-Month DB Period then entered the Open-Label Extension (OLE) Period and were administered givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM for 29 months. Upon implementation of protocol Amendment 5, active patients receiving 1.25 mg/kg givosiran once monthly in the OLE had their dose increased to 2.5 mg/kg givosiran once monthly.

Reporting group title	Givosiran/Givosiran

Reporting group description:

Patients who received givosiran during the 6-Month DB Period then entered the OLE Period and were administered givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM mg/kg for 29 months. Upon implementation of protocol Amendment 5, active patients receiving 1.25 mg/kg givosiran once monthly in the OLE had their dose increased to 2.5 mg/kg
givosiran once monthly.

Primary: Annualized Rate of Porphyria Attacks in Participants With Acute Intermittent Porphyria (AIP)

End point title	Annualized Rate of Porphyria Attacks in Participants With Acute Intermittent Porphyria (AIP)

End point description:

Porphyria attacks were defined as meeting all of the following criteria: an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs, no other medically determined cause, and required treatment with intravenous (IV) dextrose or hemin, carbohydrates, or analgesics, or other medications such as antiemetics at a dose or frequency beyond the participant's usual daily porphyria management. The annualized rate of porphyria attacks is a composite endpoint which included porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

This endpoint analyzed AIP patients in the Full Analysis Set (FASAIP): All randomized AIP participants (with identified mutation in the hydroxymethylbilane synthase [HMBS] gene) who received at least one dose of study drug.

End point type	Primary

End point timeframe:

6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: annualized attack rate				
arithmetic mean (confidence interval 95%)	12.52 (9.35 to 16.76)	3.22 (2.25 to 4.59)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Negative binomial regression model with treatment group and stratification factors (prior hemin prophylaxis status and historical attack rates) as fixed effects and the logarithm of the follow-up time as an offset variable.

Comparison groups	Placebo 6-Month DB v Givosiran 2.5 mg/kg 6-Month DB
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	Negative binomial regression model
Parameter estimate	Rate ratio
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.41

Notes:

[1] - P=6.040E-09

Secondary: The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Delta-aminolevulinic Acid (ALA) in Participants With AIP

End point title	The Pharmacodynamic (PD) Effect of Givosiran on Urine Levels of Delta-aminolevulinic Acid (ALA) in Participants With AIP

End point description:

The PD effect of givosiran was evaluated by spot urine ALA levels normalized to spot urine creatinine levels.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

3 and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: mmol/mol creatinine (Cr)				
least squares mean (standard error)				
Month 3	19.965 (± 1.475)	1.756 (± 1.413)		
Month 6	23.150 (± 2.534)	4.013 (± 2.352)		

Statistical analyses

No statistical analyses for this end point

Secondary: The PD Effect of Givosiran on Urine Levels of Porphobilinogen (PBG) in Participants With AIP

End point title	The PD Effect of Givosiran on Urine Levels of Porphobilinogen (PBG) in Participants With AIP

End point description:

The PD effect of givosiran was evaluated by spot urine PBG levels normalized to spot urine creatinine levels.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: mmol/mol Cr				
least squares mean (standard error)	49.110 (± 4.959)	12.906 (± 4.642)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Hemin Administration in Participants With AIP

End point title	Annualized Rate of Hemin Administration in Participants With AIP

End point description:

Annualized rate of hemin doses was evaluated as annualized days of hemin use.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: annualized rate of use				
arithmetic mean (confidence interval 95%)	29.71 (18.41 to 47.94)	6.77 (4.20 to 10.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Porphyria Attacks in Participants With AHP

End point title	Annualized Rate of Porphyria Attacks in Participants With AHP

End point description:

Porphyria attacks were defined as meeting all of the following criteria: an acute episode of neurovisceral pain in the abdomen, back, chest, extremities and/or limbs, no other medically determined cause, and required treatment with intravenous (IV) dextrose or hemin, carbohydrates, or analgesics, or other medications such as antiemetics at a dose or frequency beyond the participant's usual daily porphyria management. The annualized rate of porphyria attacks is a composite endpoint which included porphyria attacks requiring hospitalization, urgent healthcare visit, or IV hemin administration at home.

This endpoint analyzed AIP patients in the Full Analysis Set (FAS): All randomized patients who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	48		
Units: annualized attack rate				
arithmetic mean (confidence interval 95%)	12.26 (9.22 to 16.29)	3.35 (2.37 to 4.74)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve (AUC) of the Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory-Short Form (BPI-SF) Numeric Rating Scale (NRS) in Participants With AIP

End point title	Area Under the Curve (AUC) of the Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory-Short Form (BPI-SF) Numeric Rating Scale (NRS) in Participants With AIP

End point description:

Participants rated worst daily pain score in an eDiary using the 11-point BPI-SF NRS, in which 0=no pain and 10=worst pain. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the post baseline weekly mean score minus the baseline score. Lower scores indicate an improvement. The 6-month AUC was calculated based on change from baseline in weekly mean scores.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale*week				
median (inter-quartile range (Q1-Q3))	5.286 (-23.048 to 11.145)	-11.514 (-29.181 to 3.040)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory- Short Form (BPI-SF) Numeric Rating Scale (NRS) in Participants With AIP

End point title	Average Change From Baseline in Weekly Mean Score of Daily Worst Pain as Measured by the Brief Pain Inventory- Short Form (BPI-SF) Numeric Rating Scale (NRS) in Participants With AIP

End point description:

Participants rated worst daily pain score in an eDiary using the 11-point BPI-SF NRS, in which 0=no pain and 10=worst pain. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale				
median (inter-quartile range (Q1-Q3))	0.245 (-1.020 to 0.470)	-0.506 (-1.309 to 0.143)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of the Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS in Participants With AIP

End point title	AUC of the Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS in Participants With AIP

End point description:

Participants rated daily worst fatigue score in an eDiary using the 11-point BFI-SF NRS, in which 0=no fatigue and 10=worst fatigue. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the post baseline weekly mean score minus the baseline score. Lower scores indicate an improvement. The 6-month AUC was calculated based on change from baseline in weekly mean scores.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale*week				
least squares mean (standard error)	-4.208 (± 4.689)	-11.148 (± 4.501)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS in Participants With AIP

End point title	Average Change From Baseline in Weekly Mean Score of Daily Worst Fatigue Score as Measured by the Brief Fatigue Inventory-Short Form (BFI-SF) NRS in Participants With AIP

End point description:

Participants rated daily worst fatigue score in an eDiary using the 11-point BFI-SF NRS, in which 0=no fatigue and 10=worst fatigue. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale				
least squares mean (standard error)	-0.182 (± 0.209)	-0.502 (± 0.200)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC of the Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS in Participants With AIP

End point title	AUC of the Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS in Participants With AIP

End point description:

Participants rated worst daily nausea score in an eDiary using an 11-point NRS, in which 0=no nausea and 10=worst nausea. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement. The 6-month AUC was calculated based on change from baseline in weekly mean scores.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale				
least squares mean (standard error)	-4.011 (± 3.453)	1.481 (± 3.310)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS in Participants With AIP

End point title	Average Change From Baseline in Weekly Mean Score Daily Worst Nausea Score as Measured by NRS in Participants With AIP

End point description:

Participants rated worst daily nausea score in an eDiary using an 11-point NRS, in which 0=no nausea and 10=worst nausea. Daily eDiary entries were averaged into a weekly (i.e. 7 day) score. The change from baseline in weekly mean scores is defined as the postbaseline weekly mean score minus the baseline score. Lower scores indicate an improvement.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale				
least squares mean (standard error)	-0.181 (± 0.154)	0.067 (± 0.147)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Physical Component Summary (PCS) of the 12-Item Short Form Survey (SF-12) in Participants With AIP

End point title	Change From Baseline in the Physical Component Summary (PCS) of the 12-Item Short Form Survey (SF-12) in Participants With AIP

End point description:

The SF-12 is a survey designed for use in patients with multiple chronic conditions. This 12-item scale can be used to assess the physical and mental health of respondents. 10 of the 12 questions are answered on a 5 point likert scale and 2 are answered on a 3 point likert scale. The questions are then scored and weighted into 2 subscales, physical health and mental health. Respondents can have a score that ranges from 0-100 with 100 being the best score and indicating high physical or mental health. A 3 point change in SF-12 score reflects a meaningful difference. A higher score indicates improvement.

This endpoint analyzed AIP patients in the FASAIP: All randomized AIP participants (with identified mutation in the HMBS gene) who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline and 6 months

End point values	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	46		
Units: score on a scale				
least squares mean (standard error)	1.431 (± 1.220)	5.369 (± 1.169)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug through completion of the OLE Period (up to 39 months).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo 6-Month DB

Reporting group description:

Matching placebo (normal saline [0.9% NaCl]) was administered SC, QM, for 6 months during the 6-Month DB Period.

Reporting group title	Givosiran 2.5 mg/kg 6-Month DB

Reporting group description:

Givosiran 2.5 mg/kg administered SC, QM, for 6 months during the 6-Month DB Period.

Reporting group title	Placebo/Givosiran

Reporting group description:

Patients who received placebo during the 6-Month DB Period then entered the Open-Label Extension (OLE) Period and were administered givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM for 29 months. Upon implementation of protocol Amendment 5, active patients receiving 1.25 mg/kg givosiran once monthly in the OLE had their dose increased to 2.5 mg/kg givosiran once monthly.

MedDRA (23.0) was used for this reporting group.

Reporting group title	Givosiran/Givosiran

Reporting group description:

Patients who received givosiran during the 6-Month DB Period then entered the OLE Period and were administered givosiran 2.5 mg/kg or 1.25 mg/kg SC, QM mg/kg for 29 months. Upon implementation of protocol Amendment 5, active patients receiving 1.25 mg/kg givosiran once monthly in the OLE had their dose increased to 2.5 mg/kg givosiran once monthly.

MedDRA (23.0) was used for this reporting group.

Reporting group title	All Givosiran

Reporting group description:

All participants treated with any amount of givosiran.

MedDRA (23.0) was used for this reporting group.

Serious adverse events	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB	Placebo/Givosiran
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 46 (8.70%)	10 / 48 (20.83%)	17 / 46 (36.96%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
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			
Aortic dissection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Deep vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein occlusion			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Subclavian vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Surgical and medical procedures			
Hysterosalpingo-oophorectomy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Intrathecal pump insertion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain management	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 46 (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
General disorders and administration site conditions			
Administration site extravasation			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug withdrawal syndrome			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site reaction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 46 (2.17%)	1 / 48 (2.08%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Pelvic pain			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 46 (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
Nasal polyps			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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 embolism			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Drug dependence			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Major depression	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 46 (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
Panic attack			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood homocysteine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test abnormal	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	1 / 46 (2.17%)	0 / 48 (0.00%)	0 / 46 (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
Post procedural fever			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural inflammation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral venous sinus thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Headache			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Migraine with aura			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Tremor			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenitis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Splenic vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal vein occlusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Duodenal ulcer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Gastritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive pancreatitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Renal and urinary disorders			
Chronic kidney disease	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	2 / 48 (4.17%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Trismus			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Catheter bacteraemia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	2 / 46 (4.35%)	1 / 48 (2.08%)	0 / 46 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 46 (2.17%)	0 / 48 (0.00%)	0 / 46 (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
Gastroenteritis	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 46 (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
Helicobacter gastritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Kidney infection			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Pyelonephritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Sepsis	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 46 (2.17%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 46 (2.17%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Metabolism and nutrition disorders			
Electrolyte imbalance			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (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
Hypoglycaemia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	1 / 48 (2.08%)	0 / 46 (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

Serious adverse events	Givosiran/Givosiran	All Givosiran	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 48 (41.67%)	37 / 94 (39.36%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon neoplasm			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsil cancer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Deep vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein occlusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hysterosalpingo-oophorectomy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intrathecal pump insertion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain management	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Administration site extravasation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal syndrome			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences causally related to treatment / all	1 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Drug dependence			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood homocysteine increased			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 48 (0.00%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	0 / 48 (0.00%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral venous sinus thrombosis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Chronic kidney disease	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	2 / 48 (4.17%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Trismus			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter bacteraemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 48 (0.00%)	0 / 94 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 48 (0.00%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	2 / 94 (2.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Electrolyte imbalance			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	1 / 48 (2.08%)	1 / 94 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo 6-Month DB	Givosiran 2.5 mg/kg 6-Month DB	Placebo/Givosiran
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 46 (80.43%)	43 / 48 (89.58%)	44 / 46 (95.65%)
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
General disorders and administration site conditions			
Asthenia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	4 / 46 (8.70%)	3 / 48 (6.25%)	4 / 46 (8.70%)
occurrences (all)	7	7	11
Fatigue	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	5 / 48 (10.42%)	13 / 46 (28.26%)
occurrences (all)	0	6	14
Influenza like illness			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Injection site pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Injection site reaction	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	0 / 46 (0.00%)	8 / 48 (16.67%)	14 / 46 (30.43%)
occurrences (all)	0	15	77
Oedema peripheral			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	9
Pyrexia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 46 (10.87%)	0 / 48 (0.00%)	6 / 46 (13.04%)
occurrences (all)	6	0	7
Immune system disorders			
Drug hypersensitivity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	7
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Oropharyngeal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	4
Psychiatric disorders			
Anxiety			

subjects affected / exposed	3 / 46 (6.52%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	3	0	0
Depression			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Product issues			
Device occlusion	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	1 / 46 (2.17%)
occurrences (all)	0	3	1
Investigations			
Alanine aminotransferase increased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	4 / 48 (8.33%)	4 / 46 (8.70%)
occurrences (all)	0	6	5
Amylase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Aspartate aminotransferase increased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	3 / 46 (6.52%)
occurrences (all)	0	4	4
Blood creatinine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	6
Blood homocysteine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	3
Glomerular filtration rate decreased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	2 / 46 (4.35%)
occurrences (all)	0	3	7
Lipase increased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	3 / 46 (6.52%)	0 / 48 (0.00%)	6 / 46 (13.04%)
occurrences (all)	3	0	10
Weight increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Contusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	5 / 46 (10.87%)
occurrences (all)	0	0	5
Fall			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	6
Ligament sprain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Cardiac disorders			
Palpitations			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	6
Nervous system disorders			
Dizziness	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	3 / 46 (6.52%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	3	0	1
Headache	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	7 / 46 (15.22%)	6 / 48 (12.50%)	7 / 46 (15.22%)
occurrences (all)	9	9	15
Hypoaesthesia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	5	0	0
Migraine			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Paraesthesia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Tremor			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Eye disorders			
Eye pruritus			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	3 / 46 (6.52%)	4 / 48 (8.33%)	8 / 46 (17.39%)
occurrences (all)	5	4	9
Abdominal pain upper			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	6
Constipation	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	4 / 46 (8.70%)
occurrences (all)	0	3	4
Diarrhoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	7 / 46 (15.22%)
occurrences (all)	0	0	7
Dyspepsia			
subjects affected / exposed	4 / 46 (8.70%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	4	0	0
Gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	4
Nausea	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 46 (10.87%)	13 / 48 (27.08%)	12 / 46 (26.09%)
occurrences (all)	6	15	21
Vomiting	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 46 (10.87%)	0 / 48 (0.00%)	8 / 46 (17.39%)
occurrences (all)	5	0	18
Skin and subcutaneous tissue disorders			
Eczema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Pruritus			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	5 / 46 (10.87%)
occurrences (all)	0	0	5
Rash	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Renal and urinary disorders			
Chronic kidney disease	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	1 / 46 (2.17%)
occurrences (all)	0	3	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Back pain	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	4 / 46 (8.70%)	0 / 48 (0.00%)	6 / 46 (13.04%)
occurrences (all)	4	0	7
Muscle spasms			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Myalgia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	3 / 46 (6.52%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	3	0	4
Neck pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Pain in extremity			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	2
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	4 / 46 (8.70%)
occurrences (all)	0	0	7
COVID-19			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	2 / 46 (4.35%)
occurrences (all)	0	0	2
Conjunctivitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	0 / 46 (0.00%)
occurrences (all)	0	0	0
Cystitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	4
Gastroenteritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	5 / 46 (10.87%)
occurrences (all)	0	0	7
Influenza			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	5 / 46 (10.87%)
occurrences (all)	0	0	6
Nasopharyngitis	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	3 / 46 (6.52%)	4 / 48 (8.33%)	11 / 46 (23.91%)
occurrences (all)	3	4	14
Pharyngitis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	3 / 46 (6.52%)
occurrences (all)	0	0	3
Tooth infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	0 / 46 (0.00%)	3 / 48 (6.25%)	0 / 46 (0.00%)
occurrences (all)	0	3	0
Upper respiratory tract infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	3 / 46 (6.52%)	4 / 48 (8.33%)	12 / 46 (26.09%)
occurrences (all)	4	4	13
Urinary tract infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	6 / 46 (13.04%)	3 / 48 (6.25%)	10 / 46 (21.74%)
occurrences (all)	6	4	14
Metabolism and nutrition disorders			
Hyperhomocysteinaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	6 / 46 (13.04%)
occurrences (all)	0	0	6
Iron overload			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 46 (0.00%)	0 / 48 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1

Non-serious adverse events	Givosiran/Givosiran	All Givosiran	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 48 (97.92%)	91 / 94 (96.81%)	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	7 / 94 (7.45%)	
occurrences (all)	3	7	
General disorders and administration site conditions			
Asthenia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	5 / 48 (10.42%)	9 / 94 (9.57%)	
occurrences (all)	13	24	
Fatigue	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	12 / 48 (25.00%)	25 / 94 (26.60%)	
occurrences (all)	21	35	
Influenza like illness			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 48 (10.42%)	6 / 94 (6.38%)	
occurrences (all)	8	9	
Injection site pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	3 / 94 (3.19%)	
occurrences (all)	3	3	
Injection site reaction	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	16 / 48 (33.33%)	30 / 94 (31.91%)	
occurrences (all)	52	129	
Oedema peripheral			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 48 (4.17%)	5 / 94 (5.32%)	
occurrences (all)	2	6	
Pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	7 / 94 (7.45%)	
occurrences (all)	5	14	
Pyrexia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	6 / 48 (12.50%)	12 / 94 (12.77%)	
occurrences (all)	9	16	
Immune system disorders			
Drug hypersensitivity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	4 / 94 (4.26%)	
occurrences (all)	1	8	

Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences (all)	4	5	
Dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences (all)	3	4	
Oropharyngeal pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 48 (8.33%)	6 / 94 (6.38%)	
occurrences (all)	4	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)	0 / 94 (0.00%)	
occurrences (all)	0	0	
Depression			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	7 / 94 (7.45%)	
occurrences (all)	4	8	
Product issues			
Device occlusion	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 48 (10.42%)	6 / 94 (6.38%)	
occurrences (all)	7	8	
Investigations			
Alanine aminotransferase increased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	4 / 48 (8.33%)	8 / 94 (8.51%)	
occurrences (all)	7	12	
Amylase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 48 (8.33%)	7 / 94 (7.45%)	
occurrences (all)	6	9	
Aspartate aminotransferase	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5		

increased	mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	4 / 48 (8.33%)	7 / 94 (7.45%)	
occurrences (all)	5	9	
Blood creatinine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 48 (10.42%)	7 / 94 (7.45%)	
occurrences (all)	7	13	
Blood homocysteine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences (all)	3	4	
Gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	5 / 94 (5.32%)	
occurrences (all)	5	8	
Glomerular filtration rate decreased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 48 (10.42%)	7 / 94 (7.45%)	
occurrences (all)	8	15	
Lipase increased	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	7 / 48 (14.58%)	13 / 94 (13.83%)	
occurrences (all)	12	22	
Weight increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences (all)	3	5	
Injury, poisoning and procedural complications			
Contusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 48 (4.17%)	7 / 94 (7.45%)	
occurrences (all)	5	10	
Fall			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 48 (2.08%)	5 / 94 (5.32%)	
occurrences (all)	1	7	
Ligament sprain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	6 / 94 (6.38%)	
occurrences (all)	3	7	
Cardiac disorders			
Palpitations			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	4 / 94 (4.26%)	
occurrences (all)	1	7	
Nervous system disorders			
Dizziness	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences (all)	4	4	
Headache	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	13 / 48 (27.08%)	20 / 94 (21.28%)	
occurrences (all)	26	41	
Hypoaesthesia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 94 (0.00%)	
occurrences (all)	0	0	
Migraine			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	6 / 48 (12.50%)	7 / 94 (7.45%)	
occurrences (all)	10	11	
Paraesthesia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	4 / 94 (4.26%)	
occurrences (all)	1	5	
Tremor			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	5 / 94 (5.32%)	
occurrences (all)	3	5	

Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 48 (2.08%)	4 / 94 (4.26%)	
occurrences (all)	1	4	
Eye disorders			
Eye pruritus			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	3 / 94 (3.19%)	
occurrences (all)	4	4	
Gastrointestinal disorders			
Abdominal pain	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	6 / 48 (12.50%)	14 / 94 (14.89%)	
occurrences (all)	8	17	
Abdominal pain upper			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 48 (8.33%)	8 / 94 (8.51%)	
occurrences (all)	4	10	
Constipation	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	6 / 48 (12.50%)	10 / 94 (10.64%)	
occurrences (all)	7	11	
Diarrhoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	8 / 48 (16.67%)	15 / 94 (15.96%)	
occurrences (all)	9	16	
Dyspepsia			
subjects affected / exposed	0 / 48 (0.00%)	0 / 94 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	7 / 94 (7.45%)	
occurrences (all)	3	7	
Nausea	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		

subjects affected / exposed	22 / 48 (45.83%)	34 / 94 (36.17%)	
occurrences (all)	34	55	
Vomiting	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	7 / 48 (14.58%)	15 / 94 (15.96%)	
occurrences (all)	16	34	
Skin and subcutaneous tissue disorders			
Eczema			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 48 (4.17%)	5 / 94 (5.32%)	
occurrences (all)	2	6	
Pruritus			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	8 / 94 (8.51%)	
occurrences (all)	3	8	
Rash	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 48 (10.42%)	5 / 94 (5.32%)	
occurrences (all)	5	5	
Renal and urinary disorders			
Chronic kidney disease	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	5 / 48 (10.42%)	6 / 94 (6.38%)	
occurrences (all)	6	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 48 (10.42%)	8 / 94 (8.51%)	
occurrences (all)	5	8	
Back pain	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	7 / 48 (14.58%)	13 / 94 (13.83%)	
occurrences (all)	9	16	
Muscle spasms			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	4 / 48 (8.33%)	7 / 94 (7.45%)	
occurrences (all)	6	10	
Myalgia	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	3 / 48 (6.25%)	7 / 94 (7.45%)	
occurrences (all)	3	7	
Neck pain			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 48 (10.42%)	6 / 94 (6.38%)	
occurrences (all)	5	6	
Pain in extremity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 48 (10.42%)	7 / 94 (7.45%)	
occurrences (all)	6	8	
Infections and infestations			
Bronchitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 48 (4.17%)	6 / 94 (6.38%)	
occurrences (all)	3	10	
COVID-19			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	5 / 94 (5.32%)	
occurrences (all)	3	5	
Conjunctivitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	3 / 94 (3.19%)	
occurrences (all)	8	8	
Cystitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	6 / 94 (6.38%)	
occurrences (all)	4	8	
Gastroenteritis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 48 (6.25%)	8 / 94 (8.51%)	
occurrences (all)	3	10	
Influenza			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 48 (8.33%)	9 / 94 (9.57%)	
occurrences (all)	5	11	
Nasopharyngitis	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	14 / 48 (29.17%)	25 / 94 (26.60%)	
occurrences (all)	23	37	
Pharyngitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	6 / 94 (6.38%)	
occurrences (all)	3	6	
Tooth infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	4 / 48 (8.33%)	4 / 94 (4.26%)	
occurrences (all)	6	6	
Upper respiratory tract infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	7 / 48 (14.58%)	19 / 94 (20.21%)	
occurrences (all)	17	30	
Urinary tract infection	Additional description: Reporting Groups Placebo 6-Month DB and Givosiran 2.5 mg/kg 6-Month DB = MedDRA 21.0 Reporting Groups Placebo/Givosiran, Givosiran/Givosiran and All Givosiran = MedDRA 23.0		
subjects affected / exposed	9 / 48 (18.75%)	19 / 94 (20.21%)	
occurrences (all)	16	30	
Metabolism and nutrition disorders			
Hyperhomocysteinaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	9 / 94 (9.57%)	
occurrences (all)	3	9	
Iron overload			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 48 (6.25%)	4 / 94 (4.26%)	
occurrences (all)	3	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2018	This amendment was issued as part of the response to a single case of anaphylactic reaction reported in Study 002 as described above. The following changes were made to the protocol in light of these results: • Provided details of an anaphylactic reaction reported in Study 002 • Added anaphylactic reaction to givosiran potential risks • Provided guidance on monitoring and management of potential anaphylactic reactions due to study drug • Added guidance and procedures for management of potential cases of anaphylactic reaction • Added anaphylactic reactions to list of AEs of Clinical Interest • Added guidance for diagnosing anaphylactic reactions • In addition, the following changes were made: • Addition of 2 QOL measures: – PGIC at Months 6 and 12 – PPEQ at Months 6, 12, 18, and 24 • Updated guidance and procedures on patient withdrawal from study • Clarified that ALA/PBG levels measured during Screening are acceptable for use as entry criteria • Provided the following additional clarifications: – predose samples (not restricted to 60 minutes before dosing) – interim analysis for sample size reassessment is blinded – definition of sexual abstinence – contraception with an intrauterine hormone-releasing system also requires use of a barrier method
26 July 2018	This protocol amendment was generated in response to liver transaminase elevations observed during the study. The primary purpose for this amendment was to: • Require Investigators to review predose LFTs prior to study drug administration • Implement a standard hepatic assessment panel if patients develop significant ALT elevation • Provide specific guidance for rechallenge using a lower dose in patients whose ALT resolves after study drug dosing has been withheld due to ALT elevation • Expand the medical history collection to include a specific inquiry into iron overload and other liver disease
21 September 2018	In light of liver transaminase elevations observed in the study, a lower givosiran dose of 1.25 mg/kg once monthly was introduced in protocol Amendment 2 as a rechallenge dose for patients who resume dosing after resolution of liver transaminase elevations. In order to generate additional data at this dose level, evaluation of the 1.25 mg/kg once monthly dose was proposed for patients crossing over to the OLE period under this amendment, after their completion of the DB period. The primary purpose for this protocol amendment was to: • Implement the inclusion of an additional, lower dose of givosiran (1.25 mg/kg once monthly) during the OLE period • Provide specific guidance for increasing dose from 1.25 mg/kg once monthly to 2.5 mg/kg once monthly in patients who tolerate 1.25 mg/kg once monthly dose but who are experiencing inadequate disease control. • Add statistical analyses to evaluate the durability of the treatment effect.

28 May 2019	The primary purpose for this protocol amendment was to update information from a completed drug-drug interaction study (ALN-AS1-004). The results of the study indicated that givosiran treatment resulted in moderate reduction in CYP1A2 and CYP2D6 activity, weak reduction in CYP3A4 and CYP2C19 activity, and no change in the activity of CYP2C9. Investigators were provided guidance to review concomitant medications that are primarily metabolized by these enzymes and monitor the patient's clinical response and to select medications not primarily metabolized by CYP2D6 or CYP1A2 for patients requiring new medications. Additional updates included: • Clarification that patients may continue to receive givosiran until it is commercially available in the patient's territory, • Addition of guidance for serious breaches of protocol
12 February 2020	The primary purpose for this protocol amendment was to increase the dose of givosiran for patients receiving 1.25 mg/kg givosiran SC once monthly to the recommended dose of 2.5 mg/kg givosiran SC once monthly. Additional updates included: • Allow patients who developed a transaminase elevation meeting protocol-defined dose-holding rules while receiving 2.5 mg/kg givosiran SC once monthly to resume dosing at either the 1.25 or 2.5 mg/kg givosiran SC once monthly dose after resolution of ALT to ≤2×ULN (or ≤2×baseline for patients who had elevated baseline ALT) per the Investigator's judgement and after discussion with the medical monitor • Discontinuation of monitoring by the DMC after all patients completed at least 6 months during the OLE period • Removal of the requirement to test and review the results for INR within 14 days prior to dosing
23 April 2020	The main purpose of this protocol amendment was to incorporate changes related to USMs that were communicated to Investigators in a Dear Investigator Letter dated 07 April 2020 to assure the safety of study participants while minimizing risks to study integrity amid the COVID-19 pandemic. In addition, study administration-related text was updated to provide clarification on Investigator responsibilities regarding communication of new study information to patients and IRBs/IECs. With the implementation of changes in Amendment 6, the global amendment became aligned with prior country-specific amendments for Sweden; therefore, a country-specific amendment was no longer required.
29 March 2021	This protocol amendment was generated based on the observation that blood homocysteine levels increased during the study compared to levels before givosiran treatment; the clinical relevance of blood homocysteine increases is unknown. The purpose of the amendment was to recommend the following: • measuring blood homocysteine levels • that patients with increased blood homocysteine levels receive a supplement containing vitamin B6

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported