Clinical trial results:
A Phase 2, Randomized, Double-blind, Placebo-controlled Study of Cemdisiran in Adult Patients with IgA Nephropathy

Summary

EudraCT number	2018-002716-27
Trial protocol	GB SE ES
Global end of trial date	27 June 2023

Results information

Result version number	v1 (current)
This version publication date	12 July 2024
First version publication date	12 July 2024

Trial information

Trial identification

Sponsor protocol code	ALN-CC5-005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03841448
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alnylam Pharmaceuticals Inc.
Sponsor organisation address	675 W Kendall St, 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 877ALNYLAM, 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	27 June 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effect of cemdisiran on proteinuria in adults with immunoglobulin A nephropathy (IgAN), who excrete >1 gram (gm) of protein per day despite standard of care, which includes treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). These participants are at high risk for progression of kidney disease, which can result in end-stage renal failure.

Protection of trial subjects:

This study was conducted in accordance with the protocol, all applicable regulatory requirements, and the guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Malaysia: 8
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Taiwan: 1
Worldwide total number of subjects	31
EEA total number of subjects	10

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)	31
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in the study at 19 investigative centers in Canada, France, Malaysia, Philippines, Singapore, Spain, Sweden, Taiwan, and the United Kingdom from 30 Sept 2019 to 27 June 2023.

Pre-assignment

Screening details:

A total of 31 participants were enrolled in this study to receive cemdisiran or placebo. This study has two parts: Double Blind Treatment (DBT) Period and Open-Label Extension (OLE) Period.

Period 1

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

Blinding implementation details:

During the DB Treatment Period participants were randomized in a 2:1 ratio to receive 600 mg of SC cemdisiran or SC placebo every 4 weeks in combination with standard of care.

Modified Intent-to-treat (mITT) Analysis Set included all participants who received any amount of study drug and had at least one post baseline 24-hour urine protein/creatinine ratio (UPCR) assessment.

Arms

Are arms mutually exclusive?	Yes
Arm title	DBT Period: Placebo

Arm description:

Participants received cemdisiran matching placebo, subcutaneous (SC) injection, once every 4 weeks (Q4W) in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.

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

Dosage and administration details:

Placebo was administered by SC injection.

Arm title	DBT Period: Cemdisiran

Arm description:

Participants received cemdisiran, 600 milligrams (mg), SC injection, Q4W in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.

Arm type	Experimental
Investigational medicinal product name	Cemdisiran
Investigational medicinal product code	
Other name	ALN-CC5
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Subcutaneous use

Dosage and administration details:

Cemdisiran 600 mg was administered by SC injection.

Number of subjects in period 1	DBT Period: Placebo	DBT Period: Cemdisiran
Started	9	22
Modified ITT (mITT) Analysis Set	9	22
Completed	8	21
Not completed	1	1
Death	1	1

Period 2

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

Blinding implementation details:

Participants who were randomized to receive placebo and cemdisiran the DBT period started receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

Arms

Are arms mutually exclusive?	Yes
Arm title	DBT Period: Placebo to OLE Period: Cemdisiran

Arm description:

Participants who were randomized to receive cemdisiran matching placebo in the DBT period started receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

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

Dosage and administration details:

Placebo was administered by SC injection.

Investigational medicinal product name	Cemdisiran
Investigational medicinal product code	
Other name	ALN-CC5
Pharmaceutical forms	Solution for injection
Routes of administration	Injection , Subcutaneous use

Dosage and administration details:

Cemdisiran 600 mg was administered by SC injection.

Arm title	DBT Period: Cemdisiran to OLE Period: Cemdisiran

Arm description:

Participants who were randomized to receive cemdisiran in the DBT period continued receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

Arm type	Experimental
Investigational medicinal product name	Cemdisiran
Investigational medicinal product code	
Other name	ALN-CC5
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use, Injection

Dosage and administration details:

Cemdisiran 600 mg was administered by SC injection.

Number of subjects in period 2[1]	DBT Period: Placebo to OLE Period: Cemdisiran	DBT Period: Cemdisiran to OLE Period: Cemdisiran
Started	8	20
Completed	0	0
Not completed	8	20
Physician decision	1	3
Adverse event, non-fatal	1	2
Death	-	1
Other Reason not Specified	2	5
Study Terminated by Sponsor	4	9

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One participant in the DBT Period: Cemdisiran to OLE Period: Cemdisiran arm completed the DB Treatment Period but did not start the OLE Period.

Baseline characteristics

Reporting groups	
Reporting group title	DBT Period: Placebo
Reporting group description:	
Participants received cemdisiran matching placebo, subcutaneous (SC) injection, once every 4 weeks (Q4W) in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.	
Reporting group title	DBT Period: Cemdisiran
Reporting group description:	
Participants received cemdisiran, 600 milligrams (mg), SC injection, Q4W in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.	

Reporting group values	DBT Period: Placebo	DBT Period: Cemdisiran	Total
Number of subjects	9	22	31
Age categorical Units: Subjects			
Adults (18-64 years)	9	22	31
Age continuous Units: years			
arithmetic mean	37.6	40.5	
standard deviation	± 10.4	± 10.1	-
Gender categorical Units: Subjects			
Female	6	9	15
Male	3	13	16
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	7	18	25
Unknown or Not Reported	1	1	2
Race/Ethnicity, Customized Units: Subjects			
Asian	4	12	16
White	4	8	12
Other	0	1	1
Not reported	1	1	2
Urine Protein to Creatinine Ratio (UPCR) Units: g/g			
arithmetic mean	1.972	1.554	
standard deviation	± 0.815	± 1.032	-

End points

End points reporting groups

Reporting group title	DBT Period: Placebo

Reporting group description:

Participants received cemdisiran matching placebo, subcutaneous (SC) injection, once every 4 weeks (Q4W) in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.

Reporting group title	DBT Period: Cemdisiran

Reporting group description:

Participants received cemdisiran, 600 milligrams (mg), SC injection, Q4W in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.

Reporting group title	DBT Period: Placebo to OLE Period: Cemdisiran

Reporting group description:

Participants who were randomized to receive cemdisiran matching placebo in the DBT period started receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

Reporting group title	DBT Period: Cemdisiran to OLE Period: Cemdisiran

Reporting group description:

Participants who were randomized to receive cemdisiran in the DBT period continued receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

Subject analysis set title	DBT Period: Cemdisiran to OLE Period: Cemdisiran
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants who were randomized to receive cemdisiran in the DBT period continued receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period. The data reported for this group is for the DBT and OLE Periods inclusively, in which all participants were receiving treatment with cemdisiran.

Subject analysis set title	All Cemdisiran
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who received at least one dose of cemdisiran, including participants who received cemdisiran during the DB Period and participants who first received placebo during the DB Period and switched to cemdisiran during the OLE Period.

Primary: Percent Change From Baseline in UPCR as Measured in 24-hour Urine at Week 32

End point title	Percent Change From Baseline in UPCR as Measured in 24-hour Urine at Week 32

End point description:

UPCR is a way of assessing the amount of protein in the urine. The primary analysis for UPCR was performed using Mixed-Effect Model Repeated Measures (MMRM) approach. Geometric mean (GM)ratios were obtained by exponentially back-transforming the arithmetic mean of change in log-transformed 24h UPCR. Standard error of the mean (SEM) was calculated as exponential (mean of change in log-transformed data) * (standard error of change in log-transformed data). Adjusted GM ratio to baseline and 90% confidence interval (CIs) were calculated by exponentially back-transforming the model-based least square (LS) mean and the corresponding 90% CI.

End point type	Primary

End point timeframe:

Baseline to Week 32

End point values	DBT Period: Placebo	DBT Period: Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[1]	22[2]		
Units: percent change				
geometric mean (standard error)	1.095 (± 0.258)	0.686 (± 0.098)		

Notes:

[1] - mITT Analysis Set

[2] - mITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments:
Placebo-adjusted GM percent change, 90% CIs were calculated by exponentially back-transforming the model based LS mean difference (cemdisiran - placebo) and the corresponding 90% CI then subtracting by 1.

Comparison groups	DBT Period: Placebo v DBT Period: Cemdisiran
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1032
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Placebo-adjusted GM Percent Change
Point estimate	-37.367
Confidence interval	
level	90 %
sides	2-sided
lower limit	-60.951
upper limit	0.46

Secondary: Percent Change From Baseline in 24-hour Proteinuria at Week 32

End point title	Percent Change From Baseline in 24-hour Proteinuria at Week 32

End point description:

Proteinuria is high levels of protein in the urine. 24-hour proteinuria assessment included 24-hour urine collections to assess total protein excretion per 24 hours. Analysis was performed using the MMRM model. GM ratios were obtained by exponentially back-transforming the arithmetic mean of change in log-transformed 24h urine protein (UP). SEM was calculated as exp (mean of change in log-transformed data) *(standard error of change in log-transformed data). Adjusted GM ratio to baseline and 90% CIs are calculated by exponentially back-transforming the model-based LS Means and the corresponding 90% CI.

End point type	Secondary

End point timeframe:

Baseline to Week 32

End point values	DBT Period: Placebo	DBT Period: Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[3]	22[4]		
Units: percent change				
geometric mean (standard error)	1.051 (± 0.266)	0.671 (± 0.104)		

Notes:

[3] - mITT Analysis Set

[4] - mITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments:
Placebo-adjusted GM percent change, 90% CIs were calculated by exponentially back-transforming the model based LS mean difference (cemdisiran - placebo) and the corresponding 90% CI then subtracting by 1.

Comparison groups	DBT Period: Placebo v DBT Period: Cemdisiran
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1432
Method	MMRM
Parameter estimate	Placebo-adjusted GM Percent Change
Point estimate	-36.167
Confidence interval	
level	90 %
sides	2-sided
lower limit	-61.552
upper limit	5.978

Secondary: Percentage of Participants With Partial Clinical Remission at Week 32

End point title	Percentage of Participants With Partial Clinical Remission at Week 32

End point description:

Partial clinical remission was defined as having UP <1.0 g/24-hours.

End point type	Secondary

End point timeframe:

Week 32

End point values	DBT Period: Placebo	DBT Period: Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[5]	22[6]		
Units: percentage of participants				
number (not applicable)	0	22.7		

Notes:

[5] - mITT Analysis Set

[6] - mITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments:
Odds ratio was estimated with logit method using a correction of 0.5 in every cell of the 2x2 table that contains a zero.

Comparison groups	DBT Period: Placebo v DBT Period: Cemdisiran
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1177 [7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.43
upper limit	21.27

Notes:

[7] - p-value was based on Cochran-Mantel-Haenszel test stratified by baseline 24-hour UP (≥1.0 g and <2 g/day versus ≥2.0 g/day).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Estimation Comments:
Difference in proportions (cemdisiran - placebo) (90% CI) was based on the Wilson score method with continuity correction.

Comparison groups	DBT Period: Placebo v DBT Period: Cemdisiran
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportions
Point estimate	0.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.13
upper limit	0.42

Secondary: Percentage of Participants With >50% Reduction in 24-hour Proteinuria at Week 32

End point title	Percentage of Participants With >50% Reduction in 24-hour Proteinuria at Week 32

End point description:

End point type	Secondary

End point timeframe:

Week 32

End point values	DBT Period: Placebo	DBT Period: Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[8]	22[9]		
Units: percentage of participants				
number (not applicable)	0	22.7		

Notes:

[8] - mITT Analysis Set

[9] - mITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments:
Odds ratio was estimated with logit method using a correction of 0.5 in every cell of the 2x2 table that contains a zero.

Comparison groups	DBT Period: Placebo v DBT Period: Cemdisiran
Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1533 [10]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.45
upper limit	20.34

Notes:

[10] - p-value was based on Cochran-Mantel-Haenszel test stratified by baseline 24-hour UP (≥1.0 g and <2 g/day versus ≥2.0 g/day).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Estimation Comments:
Difference in proportions (cemdisiran - placebo) (90% CI) was based on the Wilson score method with continuity correction.

Comparison groups	DBT Period: Placebo v DBT Period: Cemdisiran

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in Proportions
Point estimate	0.23
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.13
upper limit	0.42

Secondary: Change From Baseline in UPCR as Measured in a Spot Urine at Week 32

End point title	Change From Baseline in UPCR as Measured in a Spot Urine at Week 32

End point description:

UPCR was calculated by dividing the level of protein in a spot urine test by the creatinine level. Analysis was performed using MMRM model. GM ratios were obtained by exponentially back-transforming the arithmetic mean of change in log-transformed spot UPCR. SEM was calculated as exp (mean of change in log-transformed data) *(standard error of change in log-transformed data). Adjusted GM ratio to baseline and 90% CIs are calculated by exponentially back-transforming the model-based LS Means and the corresponding 90% CI.

End point type	Secondary

End point timeframe:

Baseline to Week 32

End point values	DBT Period: Placebo	DBT Period: Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[11]	22[12]		
Units: g/g				
geometric mean (standard error)	1.344 (± 0.139)	0.729 (± 0.109)		

Notes:

[11] - mITT Analysis Set

[12] - mITT Analysis Set

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation Comments:
Placebo-adjusted GM percent change, 90% CIs were calculated by exponentially back-transforming the model based LS means difference (cemdisiran - placebo) and the corresponding 90% CI then subtracting by 1.

Comparison groups	DBT Period: Cemdisiran v DBT Period: Placebo

Number of subjects included in analysis	31
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	MMRM
Parameter estimate	Placebo-adjusted GM Percent Change
Point estimate	-45.771
Confidence interval	
level	90 %
sides	2-sided
lower limit	-60.093
upper limit	-26.309

Secondary: Number of Participants With Change From Baseline in Hematuria at Week 32

End point title	Number of Participants With Change From Baseline in Hematuria at Week 32

End point description:

Hematuria is the presence of blood in the urine. Hematuria from spot urine collections was evaluated to assess the effect of cemdisiran on disease course in participants. The degree of hematuria was assessed by microscopic examination of the spun urine sediment (red blood cell (RBC)/ high power field [hpf]) and by urine dipstick.

End point type	Secondary

End point timeframe:

Baseline to Week 32

End point values	DBT Period: Placebo	DBT Period: Cemdisiran		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8[13]	20[14]		
Units: Count of Participants				
Post-Baseline Category: Negative	0	4		
Post-Baseline Category: Small	2	11		
Post-Baseline Category: Moderate	2	4		
Post-Baseline Category: Large	4	1		

Notes:

[13] - mITT Analysis Set participants with data available for analysis.

[14] - mITT Analysis Set participants with data available for analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adverse Events (AEs)

End point title	Number of Participants With Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

End point type	Secondary

End point timeframe:

Baseline up to 240 weeks

End point values	DBT Period: Placebo	DBT Period: Cemdisiran	DBT Period: Placebo to OLE Period: Cemdisiran	DBT Period: Cemdisiran to OLE Period: Cemdisiran
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	9[15]	22[16]	8[17]	22[18]
Units: Count of Participants	8	19	8	22

Notes:

[15] - mITT Analysis Set

[16] - mITT Analysis Set

[17] - All Cemdisiran Treated Set

[18] - All Cemdisiran Treated Set

End point values	All Cemdisiran			
Subject group type	Subject analysis set			
Number of subjects analysed	30[19]			
Units: Count of Participants	30			

Notes:

[19] - All Cemdisiran Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

DBT Period: from the first dose of study drug up to 88 weeks. OLE Period: from Week 32 up to 240 weeks. All Cemdisiran: from the first dose of study drug up to 240 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	DBT Period: Placebo

Reporting group description:

Participants received cemdisiran matching placebo, SC injection, Q4W in combination with standard of care up to a maximum of 38 weeks in the DBT period.

Reporting group title	DBT Period: Cemdisiran

Reporting group description:

Participants received cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 38 weeks in the DBT period.

Reporting group title	DBT Period: Placebo + OLE Period: Cemdisiran

Reporting group description:

Participants who were randomized to receive cemdisiran matching placebo in the DBT period started receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

Reporting group title	DBT Period: Cemdisiran + OLE Period: Cemdisiran

Reporting group description:

Participants who were randomized to receive cemdisiran in the DBT period continued receiving cemdisiran, 600 mg, SC injection, Q4W in combination with standard of care treatment up to a maximum of 88 weeks in the OLE treatment period.

Reporting group title	All Cemdisiran

Reporting group description:

All participants who received at least one dose of cemdisiran, including participants who received cemdisiran during the DB Period and participants who first received placebo during the DB Period and switched to cemdisiran during the OLE Period.

Serious adverse events	DBT Period: Placebo	DBT Period: Cemdisiran	DBT Period: Placebo + OLE Period: Cemdisiran
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	3 / 8 (37.50%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events	0	1	0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
End stage renal disease			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Helicobacter gastritis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (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			
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	DBT Period: Cemdisiran + OLE Period: Cemdisiran	All Cemdisiran	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	5 / 30 (16.67%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	1	1	
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
End stage renal disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Helicobacter gastritis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DBT Period: Placebo	DBT Period: Cemdisiran	DBT Period: Placebo + OLE Period: Cemdisiran
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)	19 / 22 (86.36%)	8 / 8 (100.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	2 / 8 (25.00%)
occurrences (all)	1	0	2
Hypotension			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Dyspepsia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Asthenia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Feeling cold			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Injection site bruising			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Injection site reaction			
subjects affected / exposed	2 / 9 (22.22%)	9 / 22 (40.91%)	5 / 8 (62.50%)
occurrences (all)	7	25	31
Injection site recall reaction			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	3 / 8 (37.50%)
occurrences (all)	0	2	3
Malaise			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	1 / 9 (11.11%)	3 / 22 (13.64%)	1 / 8 (12.50%)
occurrences (all)	1	5	1
Pyrexia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 22 (4.55%)	2 / 8 (25.00%)
occurrences (all)	1	1	2
Suprapubic pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Swelling face			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vaccination site reaction			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Milk allergy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Seasonal allergy			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Haematospermia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Testicular pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vaginal discharge			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2

Dyspnoea			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	0 / 8 (0.00%)
occurrences (all)	0	3	0
Productive cough			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	0 / 8 (0.00%)
occurrences (all)	0	2	0
Sneezing			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	1 / 8 (12.50%)
occurrences (all)	0	3	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Blood pressure increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase			

abnormal			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Liver function test increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Low density lipoprotein increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urine sodium increased			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Weight increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Muscle contusion			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Skin laceration			

subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 9 (11.11%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	1	1	0
Migraine			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Nephrogenic anaemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Splenomegaly			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			

Cerumen impaction			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Deafness unilateral			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Keratosis obturans			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	1	2	0
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	2 / 8 (25.00%)
occurrences (all)	0	1	2
Toothache			

subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Drug eruption			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Dyshidrotic eczema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	1 / 8 (12.50%)
occurrences (all)	0	2	1
Rash erythematous			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Urticaria			

subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Proteinuria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Renal impairment			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	2 / 9 (22.22%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	2	0	1
Joint stiffness			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Limb discomfort			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Muscle twitching			

subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Asymptomatic COVID-19			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
COVID-19			
subjects affected / exposed	0 / 9 (0.00%)	2 / 22 (9.09%)	5 / 8 (62.50%)
occurrences (all)	0	2	5
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Eyelid infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	1 / 8 (12.50%)
occurrences (all)	0	1	1
Nasopharyngitis			
subjects affected / exposed	3 / 9 (33.33%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	3	0	2
Oral candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0

Pneumonia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Superinfection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Tooth infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 22 (0.00%)	0 / 8 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 22 (4.55%)	0 / 8 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			

subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Hyperphosphataemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	2 / 8 (25.00%)
occurrences (all)	0	0	2
Hyponatraemia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1
Vitamin D deficiency			
subjects affected / exposed	0 / 9 (0.00%)	0 / 22 (0.00%)	1 / 8 (12.50%)
occurrences (all)	0	0	1

Non-serious adverse events	DBT Period: Cemdisiran + OLE Period: Cemdisiran	All Cemdisiran	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	30 / 30 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 22 (4.55%)	3 / 30 (10.00%)	
occurrences (all)	3	5	
Hypotension			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Dyspepsia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Chest pain			

subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	2	21	
Injection site bruising			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Injection site reaction			
subjects affected / exposed	9 / 22 (40.91%)	14 / 30 (46.67%)	
occurrences (all)	52	83	
Injection site recall reaction			
subjects affected / exposed	2 / 22 (9.09%)	5 / 30 (16.67%)	
occurrences (all)	3	6	
Malaise			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	3 / 22 (13.64%)	4 / 30 (13.33%)	
occurrences (all)	6	7	
Pyrexia			
subjects affected / exposed	3 / 22 (13.64%)	5 / 30 (16.67%)	
occurrences (all)	5	7	
Suprapubic pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Swelling face			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vaccination site reaction			

subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Milk allergy			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Seasonal allergy			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Haematospermia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Menorrhagia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Testicular pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Vaginal discharge			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	0 / 22 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			

subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	3	3	
Productive cough			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Sneezing			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 22 (9.09%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 22 (9.09%)	3 / 30 (10.00%)	
occurrences (all)	2	3	
Blood pressure increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase abnormal			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Low density lipoprotein increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Urine sodium increased			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Weight increased			
subjects affected / exposed	1 / 22 (4.55%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Ligament sprain			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Muscle contusion			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Skin laceration			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Headache			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Migraine			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Restless legs syndrome			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Nephrogenic anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Splenomegaly			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Deafness unilateral			

subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Keratosis obturans			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Abdominal pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	4	4	
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Haemorrhoids			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Mouth ulceration			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 22 (4.55%)	3 / 30 (10.00%)	
occurrences (all)	1	3	
Toothache			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

Pain			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Dermatitis contact			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Drug eruption			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Dyshidrotic eczema			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Rash			
subjects affected / exposed	3 / 22 (13.64%)	4 / 30 (13.33%)	
occurrences (all)	3	4	
Rash erythematous			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	3 / 22 (13.64%)	3 / 30 (10.00%)	
occurrences (all)	3	3	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Proteinuria			

subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Renal impairment			
subjects affected / exposed	1 / 22 (4.55%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Endocrine disorders			
Hyperparathyroidism secondary			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	2 / 30 (6.67%)	
occurrences (all)	1	1	
Joint stiffness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Joint swelling			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Limb discomfort			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Muscle spasms			
subjects affected / exposed	1 / 22 (4.55%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Muscle twitching			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			

Asymptomatic COVID-19			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Bronchitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	9 / 22 (40.91%)	14 / 30 (46.67%)	
occurrences (all)	10	15	
Conjunctivitis			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Cystitis			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Eyelid infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Helicobacter infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 22 (4.55%)	2 / 30 (6.67%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Oral candidiasis			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Pneumonia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Rhinitis			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	

Superinfection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Tooth infection			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 22 (18.18%)	4 / 30 (13.33%)	
occurrences (all)	9	9	
Urinary tract infection			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Viral infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 22 (0.00%)	0 / 30 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gout			
subjects affected / exposed	2 / 22 (9.09%)	2 / 30 (6.67%)	
occurrences (all)	2	2	
Hyperglycaemia			
subjects affected / exposed	1 / 22 (4.55%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hyperphosphataemia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Hyponatraemia			

subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Iron deficiency			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 22 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2018	Amendment 1: The main purpose of this protocol amendment was to incorporate changes requested by a Health Authority.
20 September 2019	Amendment 2: The primary purpose for this protocol amendment was to incorporate changes previously made to a regional protocol amendment into the global protocol.
27 April 2020	Amendment 3: The purpose of this protocol amendment was to incorporate Urgent Safety Measures (USMs) that were communicated to investigators in a Dear Investigator Letter (DIL) dated 06 April 2020.
19 January 2021	Amendment 4: The primary purpose for this protocol amendment was to extend the open-label extension (OLE) period by an additional 2 years.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
27 June 2023	The study was terminated early having identified clinically meaningful magnitude of proteinuria reduction due to cemdisiran (study goal). Participants completed DBT period and were in OLE period. Sponsor had no concerns with safety and integrity of participants	-

Notes:

Limitations and caveats

None reported