Clinical trial results:
A Double-blind, Randomized, Placebo- and Active-Comparator Controlled Study to Evaluate the Efficacy of Inclisiran as Monotherapy in Patients with Primary Hypercholesterolemia Not Receiving Lipid-Lowering Therapy (VictORION-Mono)

Summary

EudraCT number	2022-001109-29
Trial protocol	HU DE
Global end of trial date	20 June 2024

Results information

Result version number	v1 (current)
This version publication date	03 July 2025
First version publication date	03 July 2025

Trial information

Trial identification

Sponsor protocol code	CKJX839D12304

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05763875
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@Novartis.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	20 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To demonstrate the superiority of inclisiran as monotherapy, compared with placebo, in reducing LDL-C as measured by percentage change from baseline to Day 150
- To demonstrate the superiority of inclisiran as monotherapy, compared with ezetimibe, in reducing LDL-C as measured by percentage change from baseline to Day 150

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2023
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Colombia: 20
Country: Number of subjects enrolled	Mexico: 30
Country: Number of subjects enrolled	United States: 236
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Hungary: 2
Worldwide total number of subjects	350
EEA total number of subjects	64

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)	337
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 42 investigative sites in 5 countries

Pre-assignment

Screening details:

There was a 14 day screening period

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Inclisiran

Arm description:

Inclisiran s.c and Placebo p.o

Arm type	Experimental
Investigational medicinal product name	Matching placebo for Ezetimibe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0mg over-encapsulated placebo tablet taken once a day

Investigational medicinal product name	Inclisiran
Investigational medicinal product code	KJX839
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

284 mg (equivalent to 300 mg inclisiran sodium) subcutaneous injection given on Day 1 and Day 90

Arm title	Ezetimibe

Arm description:

Placebo s.c. and Ezetimibe p.o.

Arm type	Active comparator
Investigational medicinal product name	Matching placebo for Inclisiran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0mg placebo injection solution for subcutaneous injection on Day 1 and Day 90

Investigational medicinal product name	Ezetimibe
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

10 mg over-encapsulated tablet taken once a day

Arm title	Placebo

Arm description:

Placebo s.c. and Placebo p.o.

Arm type	Placebo
Investigational medicinal product name	Matching placebo for EzetimIbe
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0mg over-encapsulated placebo tablet taken once a day

Investigational medicinal product name	Matching placebo for Inclisiran
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

0mg placebo injection solution for subcutaneous injection on Day 1 and Day 90

Number of subjects in period 1	Inclisiran	Ezetimibe	Placebo
Started	174	89	87
Completed	164	86	84
Not completed	10	3	3
Subject decision	5	2	1
Adverse event, non-fatal	1	-	-
Lost to follow-up	4	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Inclisiran
Reporting group description: Inclisiran s.c and Placebo p.o	
Reporting group title	Ezetimibe
Reporting group description: Placebo s.c. and Ezetimibe p.o.	
Reporting group title	Placebo
Reporting group description: Placebo s.c. and Placebo p.o.	

Reporting group values	Inclisiran	Ezetimibe	Placebo
Number of subjects	174	89	87
Age Categorical Units: participants			
<=18 years	0	0	0
Between 18 and 65 years	168	86	83
>=65 years	6	3	4
Age Continuous Units: years			
arithmetic mean	45.7	46.3	46.7
standard deviation	± 11.74	± 10.90	± 11.55
Sex: Female, Male Units: Participants			
Female	104	56	59
Male	70	33	28
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	10	10	9
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	20	7	10
White	140	71	67
More than one race	4	0	1
Unknown or Not Reported	0	0	0
Baseline Low-Density Lipoprotein Cholesterol (LDL-C) Units: mg/dL			
arithmetic mean	135.8	134.4	135.4
standard deviation	± 27.01	± 25.82	± 28.69

Reporting group values	Total		
Number of subjects	350		
Age Categorical Units: participants			
<=18 years	0		

Between 18 and 65 years	337		
>=65 years	13		

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	219		
Male	131		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	29		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	37		
White	278		
More than one race	5		
Unknown or Not Reported	0		
Baseline Low-Density Lipoprotein Cholesterol (LDL-C)			
Units: mg/dL			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Inclisiran
Reporting group description: Inclisiran s.c and Placebo p.o	
Reporting group title	Ezetimibe
Reporting group description: Placebo s.c. and Ezetimibe p.o.	
Reporting group title	Placebo
Reporting group description: Placebo s.c. and Placebo p.o.	

Primary: Percentage change in Low-density Lipoprotein Cholesterol (LDL-C) from Baseline to Day 150

End point title	Percentage change in Low-density Lipoprotein Cholesterol (LDL-C) from Baseline to Day 150

End point description:

Percentage change in LDL-C from Baseline (day 1) to Day 150, Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Primary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: Percentage change from baseline				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-46.54 (-50.20 to -42.88)	-11.17 (-15.34 to -7.00)	1.37 (-3.07 to 5.80)	
LS Mean (Monotherapy estimand)	-49.37 (-52.76 to -45.97)	-11.92 (-15.87 to -7.98)	-1.53 (-2.97 to 6.03)	

Statistical analyses

Statistical analysis title	Comparison inclisiran vs ezetimbe
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-35.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-40.88
upper limit	-29.86

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-47.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.62
upper limit	-42.2

Statistical analysis title	Comparison inclisiran vs ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-37.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.63
upper limit	-32.26

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-50.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.51
upper limit	-45.28

Secondary: Absolute change in LDL-C from Baseline to Day 150

End point title	Absolute change in LDL-C from Baseline to Day 150

End point description:

Absolute change in LDL-C from Baseline (Day 1) to Day 150, Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Secondary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: mg/dL				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-64.86 (-69.27 to -60.46)	-17.55 (-22.53 to -12.57)	-1.29 (-6.40 to 3.82)	
LS Mean (Monotherapy estimand)	-68.57 (-72.59 to -64.56)	-18.52 (-23.16 to -13.89)	-1.07 (-6.32 to 4.19)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-47.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.91
upper limit	-40.72

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-50.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.16
upper limit	-43.94

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-67.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.09
upper limit	-60.92

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-63.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-70.28
upper limit	-56.87

Secondary: Percentage change in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) from Baseline to Day 150

End point title	Percentage change in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) from Baseline to Day 150

End point description:

Percentage change in PCSK9 from Baseline (Day 1) to Day 150 , Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monoherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:

- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Secondary
End point timeframe:	
Baseline, Day 150	

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	89	87	
Units: Percentage change from baseline				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-67.12 (-73.21 to -61.03)	6.04 (-0.10 to 12.18)	7.82 (0.35 to 15.29)	
LS Mean (Monotherapy estimand)	-71.31 (-76.73 to -65.89)	5.56 (-0.67 to 11.79)	8.16 (0.59 to 15.74)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description:	
Treatment Policy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-73.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.76
upper limit	-64.56

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description:	
Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo

Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-79.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-88.77
upper limit	-70.17

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-76.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-85.12
upper limit	-68.62

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-74.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-84.51
upper limit	-65.37

Secondary: Percentage change in non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Day 150

End point title	Percentage change in non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Day 150

End point description:

Percentage change in non-HDL-C from Baseline (Day 1) to Day 150, Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Secondary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: Percentage change from baseline				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-40.45 (-43.50 to -37.40)	-9.97 (-13.34 to -6.61)	1.88 (-2.75 to 6.50)	
LS Mean (Monotherapy estimand)	-42.82 (-45.62 to -40.02)	-10.84 (-13.84 to -7.84)	2.04 (-2.63 to 6.71)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs placebo

Statistical analysis description:

Treatment Policy Estimand

Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-30.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.98
upper limit	-25.98

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-44.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.28
upper limit	-39.44

Statistical analysis title	Comparison Inclisiran vs Exetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-31.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.07
upper limit	-27.89

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-42.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.83
upper limit	-36.82

Secondary: Percentage change in Total Cholesterol (TC)/HDL-C ratio from Baseline to Day 150

End point title	Percentage change in Total Cholesterol (TC)/HDL-C ratio from Baseline to Day 150

End point description:

Percentage change in total cholesterol (TC)/HDL-C ratio from Baseline (Day 1) to Day 150 , Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Secondary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: Percentage change from baseline				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-31.54 (-35.43 to -27.65)	-6.70 (-10.61 to -2.78)	2.31 (-4.05 to 8.68)	
LS Mean (Monotherapy estimand)	-33.56 (-37.32 to -29.79)	-6.98 (-10.99 to -2.97)	2.51 (-3.90 to 8.91)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs Ezetimbe

Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-24.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.32
upper limit	-19.36

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-33.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.27
upper limit	-26.44

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-26.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.07
upper limit	-21.09

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-36.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.46
upper limit	-28.67

Secondary: Percentage change in Apolipoprotein B (Apo B) from Baseline to Day 150

End point title	Percentage change in Apolipoprotein B (Apo B) from Baseline to Day 150

End point description:

Percentage change in Apo B from Baseline (Day 1) to Day 150, Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Secondary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: Percentage change from baseline				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-37.39 (-40.25 to -34.54)	-8.41 (-11.71 to -5.12)	-0.73 (-4.18 to 2.72)	
LS Mean (Monotherapy estimand)	-39.36 (-42.00 to -36.72)	-9.20 (-12.13 to -6.28)	-0.58 (-4.07 to 2.90)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-28.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.3
upper limit	-24.65

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-36.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.1
upper limit	-32.22

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-30.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-34.08
upper limit	-26.23

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-38.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.12
upper limit	-34.43

Secondary: Percentage change in Apo B/Apo A-1 ratio from Baseline to Day 150

End point title	Percentage change in Apo B/Apo A-1 ratio from Baseline to Day 150

End point description:

Percentage change in Apo B/Apo A-1 ratio from baseline (Day 1) to Day 150, Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or

ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

End point type	Secondary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: Percentage change from baseline				
least squares mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	-37.79 (-43.03 to -32.55)	-7.55 (-11.74 to -3.36)	-2.65 (-5.69 to 0.39)	
LS Mean (Monotherapy estimand)	-40.03 (-45.25 to -34.82)	-7.69 (-12.00 to -3.37)	-2.65 (-5.81 to 0.50)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs Ezetimbe

Statistical analysis description:

Treatment Policy Estimand

Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-30.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.92
upper limit	-23.57

Statistical analysis title	Comparison Inclisiran vs placebo

Statistical analysis description:

Monotherapy Estimand

Comparison groups	Inclisiran v Placebo

Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-37.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.44
upper limit	-31.31

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-32.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.1
upper limit	-25.59

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-35.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-41.18
upper limit	-29.12

Secondary: Change in Lipoprotein (a) [Lp(a)] from Baseline to Day 150

End point title	Change in Lipoprotein (a) [Lp(a)] from Baseline to Day 150

End point description:

Day 150 / Baseline ratio in Lp(a) in Inclisiran arm versus Ezetimibe and placebo.

There were two estimands of interest in comparing efficacy of inclisiran as monotherapy against that of placebo or ezetimibe: a "Monotherapy Estimand" and a "Treament-policy Estimand".
Both differ on the treatment of interest used for each estimand as follows:
- Monotherapy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe)
- Treatment-policy Estimand: Inclisiran as monotherapy compared to the use of comparator (placebo or ezetimibe) with or without other lipid lowering therapies (LLTs) added during the study.

Due to right-skewness of Lp(a), the endpoint was analyzed by modeling the change in logarithm of Lp(a) from baseline to Day 150. The least squares estimates from the model, when transformed back using exponential function, were expressed in Day150/baseline ratio of Lp(a).

End point type	Secondary

End point timeframe:

Baseline, Day 150

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	173	88	87	
Units: Ratio from baseline				
geometric mean (confidence interval 95%)				
LS Mean (Treatment Policy estimand)	0.690 (0.611 to 0.780)	0.911 (0.830 to 1.000)	0.923 (0.803 to 1.060)	
LS Mean (Monotherapy estimand)	0.687 (0.612 to 0.722)	0.912 (0.836 to 0.95)	0.922 (0.800 to 1.062)	

Statistical analyses

Statistical analysis title	Comparison Inclisiran vs Ezetimbe

Statistical analysis description:

Treatment Policy Estimand

Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	ANCOVA
Parameter estimate	LS Geometric Mean
Point estimate	0.757

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	0.882

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0008
Method	ANCOVA
Parameter estimate	LS Geometric Mean
Point estimate	0.746
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.622
upper limit	0.893

Statistical analysis title	Comparison Inclisiran vs Ezetimbe
Statistical analysis description: Monotherapy Estimand	
Comparison groups	Inclisiran v Ezetimibe
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	LG Geometric Mean
Point estimate	0.753
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.652
upper limit	0.871

Statistical analysis title	Comparison Inclisiran vs placebo
Statistical analysis description: Treatment Policy Estimand	
Comparison groups	Inclisiran v Placebo

Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	ANCOVA
Parameter estimate	LS Geometric Mean
Point estimate	0.748
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.622
upper limit	0.898

Secondary: Incidence of Treatment Emergent Adverse Events (TEAE) and Serious Adverse Events (SAE)

End point title	Incidence of Treatment Emergent Adverse Events (TEAE) and Serious Adverse Events (SAE)

End point description:

Incidence of TEAEs (regardless of seriousness) and SAEs by treatment group, including changes in laboratory results qualifying and reported as AEs.

End point type	Secondary

End point timeframe:

From first dose of study treatment on Day 1 up to Day 180

End point values	Inclisiran	Ezetimibe	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	174	89	87	
Units: Participants				
AEs	54	27	25	
Treatment related AEs (Inclisiran/ placebo)	11	4	0	
Treatment related AEs (ezetimibe/placebo)	3	2	2	
SAEs	1	0	0	
Treatment related SAEs (inclisiran/placebo)	0	0	0	
Treatment related SAEs (ezetimibe/placebo)	0	0	0	
Fatal SAEs	0	0	0	
AEs leading to discontinuation of inclisiran/pbo	3	0	0	
AEs leading to discontinuation of ezetimibe/pbo	4	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From first dose of study treatment on Day 1 up to Day 180	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Inclisiran
Reporting group description: Inclisiran	
Reporting group title	Total
Reporting group description: Total	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Ezetimibe
Reporting group description: Ezetimibe	

Serious adverse events	Inclisiran	Total	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 174 (0.57%)	1 / 350 (0.29%)	0 / 87 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 174 (0.57%)	1 / 350 (0.29%)	0 / 87 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ezetimibe		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			

Femur fracture			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Inclisiran	Total	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 174 (10.92%)	50 / 350 (14.29%)	13 / 87 (14.94%)
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 174 (0.57%)	3 / 350 (0.86%)	0 / 87 (0.00%)
occurrences (all)	1	3	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 174 (0.00%)	3 / 350 (0.86%)	1 / 87 (1.15%)
occurrences (all)	0	3	1
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 174 (0.57%)	4 / 350 (1.14%)	2 / 87 (2.30%)
occurrences (all)	1	4	2
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 174 (3.45%)	6 / 350 (1.71%)	0 / 87 (0.00%)
occurrences (all)	6	6	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 174 (1.15%)	5 / 350 (1.43%)	2 / 87 (2.30%)
occurrences (all)	2	6	3
Vomiting			
subjects affected / exposed	2 / 174 (1.15%)	4 / 350 (1.14%)	0 / 87 (0.00%)
occurrences (all)	2	4	0
Renal and urinary disorders			
Hypertonic bladder			
subjects affected / exposed	0 / 174 (0.00%)	2 / 350 (0.57%)	0 / 87 (0.00%)
occurrences (all)	0	2	0

Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 174 (0.57%)	6 / 350 (1.71%)	3 / 87 (3.45%)
occurrences (all)	1	6	3
Gastroenteritis			
subjects affected / exposed	2 / 174 (1.15%)	4 / 350 (1.14%)	0 / 87 (0.00%)
occurrences (all)	3	5	0
Nasopharyngitis			
subjects affected / exposed	6 / 174 (3.45%)	12 / 350 (3.43%)	3 / 87 (3.45%)
occurrences (all)	8	15	4
Upper respiratory tract infection			
subjects affected / exposed	2 / 174 (1.15%)	5 / 350 (1.43%)	1 / 87 (1.15%)
occurrences (all)	2	6	1
Urinary tract infection			
subjects affected / exposed	3 / 174 (1.72%)	7 / 350 (2.00%)	2 / 87 (2.30%)
occurrences (all)	3	7	2

Non-serious adverse events	Ezetimibe		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 89 (20.22%)		
Investigations			
Blood pressure increased			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 89 (2.25%)		
occurrences (all)	2		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 89 (1.12%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 89 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1 2 / 89 (2.25%) 2		
Renal and urinary disorders Hypertonic bladder subjects affected / exposed occurrences (all)	2 / 89 (2.25%) 2		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	2 / 89 (2.25%) 2 2 / 89 (2.25%) 2 3 / 89 (3.37%) 3 2 / 89 (2.25%) 3 2 / 89 (2.25%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 February 2023	The study protocol was amended once prior to first participant first visit. • This amendment incorporated continued efforts to measure endpoints for all participants until Day 180, even for those who prematurely discontinued study treatment, to avoid missing data. • Included a "Treatment-policy Estimand" that assessed the efficacy of inclisiran in LDL-C lowering irrespective of the addition of other LLTs, in parallel to the original estimand, referred to as "Monotherapy Estimand". • Included additional guidance for the Investigator on lifestyle instructions to be given to the participants as recommended by the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease (Arnett et al 2019). • Updated discontinuation from study treatment criteria to provide additional guidance to the Investigator on specific reasons for discontinuation of study treatment, including liver enzyme elevation and CK criteria, severe and persistent (> 14 days despite appropriatetreatment) reactions at the injection site and any anaphylactic reactions, and intolerable adverse events. • To avoid unnecessary study treatment discontinuations, the action taken in response to addition of other LLTs had been updated so that study treatment was not automatically discontinued when other LLTs were taken after randomization (except for those targeting PCSK9, and RNAi-based therapies).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported