



Clinical trial results:

Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomized multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-13)

Summary

EudraCT number	2020-002755-38
Trial protocol	SI GR NL FR
Global end of trial date	18 November 2024

Results information

Result version number	v1 (current)
This version publication date	30 May 2025
First version publication date	30 May 2025

Trial information

Trial identification

Sponsor protocol code	CKJX839C12302
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04659863
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)	Yes
EMA paediatric investigation plan number(s)	EMA-002214-PIP01-17
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 November 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 November 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy, safety and tolerability of inclisiran in adolescents (aged 12 to <18 years) with homozygous familial hypercholesterolaemia (HoFH).

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

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	16 February 2021
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	Canada: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Lebanon: 1
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Türkiye: 2
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	13
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
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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)	13
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirteen participants were randomized from 9 study centers in 8 countries. The breakdown of countries and study centers for the randomized participants was as follows: Canada (1), France (1), Greece (1), Lebanon (1), Malaysia (1), Netherlands (1), Turkey (2), and United States (1).

Pre-assignment

Screening details:

The study had an approximately 4-week screening/run-in period

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1- Inclisiran

Arm description:

Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)

Arm type	Experimental
Investigational medicinal product name	Inclisiran
Investigational medicinal product code	KJX839
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Inclisiran sodium 300 mg(equivalent to 284 mginclisiran) in 1.5 mL solution

Arm title	Part 1 - Placebo
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Arm description:

Placebo sc injection (given at Day 1, 90 and 270)

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

Dosage and administration details:

Placebo formulation to the active drug formulation

Number of subjects in period 1	Part 1- Inclisiran	Part 1 - Placebo
Started	9	4
Completed	9	4

Period 2

Period 2 title	Part 2 (Open-label period)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part 2 – Inclisiran (Total)
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Arm description:

Inclisiran sodium 300 mg sc injection (given at Days 450 and 630). In addition, participants assigned to placebo in Part 1 received inclisiran sodium 300 mg sc injection on Day 360, while participants assigned to inclisiran in Part 1 received placebo sc injection on Day 360

Arm type	Experimental
Investigational medicinal product name	Inclisiran
Investigational medicinal product code	KJX839
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Inclisiran sodium 300 mg(equivalent to 284 mginclisiran) in 1.5 mL solution

Number of subjects in period 2	Part 2 – Inclisiran (Total)
Started	13
Completed	13

Baseline characteristics

Reporting groups

Reporting group title	Part 1- Inclisiran
Reporting group description: Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	
Reporting group title	Part 1 - Placebo
Reporting group description: Placebo sc injection (given at Day 1, 90 and 270)	

Reporting group values	Part 1- Inclisiran	Part 1 - Placebo	Total
Number of subjects	9	4	13
Age Categorical Units: participants			
<=18 years	9	4	13
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Age Continuous Units: years			
arithmetic mean	14.6	15.1	-
standard deviation	± 1.54	± 2.66	-
Sex: Female, Male Units: participants			
Female	7	2	9
Male	2	2	4
Race/Ethnicity, Customized Units: Subjects			
Asian	1	1	2
White	8	3	11

End points

End points reporting groups

Reporting group title	Part 1- Inclisiran
Reporting group description:	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)
Reporting group title	Part 1 - Placebo
Reporting group description:	Placebo sc injection (given at Day 1, 90 and 270)
Reporting group title	Part 2 – Inclisiran (Total)
Reporting group description:	Inclisiran sodium 300 mg sc injection (given at Days 450 and 630). In addition, participants assigned to placebo in Part 1 received inclisiran sodium 300 mg sc injection on Day 360, while participants assigned to inclisiran in Part 1 received placebo sc injection on Day 360

Primary: Percentage change in LDL-C from baseline to Day 330 (Part 1/Year 1)

End point title	Percentage change in LDL-C from baseline to Day 330 (Part 1/Year 1)
End point description:	Percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline to Day 330 (Year 1)
End point type	Primary
End point timeframe:	Baseline and Day 330

End point values	Part 1- Inclisiran	Part 1 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	4		
Units: percent change in LDL-C				
arithmetic mean (standard deviation)	-21.6 (± 13.36)	11.7 (± 30.52)		

Statistical analyses

Statistical analysis title	Mean difference
Comparison groups	Part 1- Inclisiran v Part 1 - Placebo
Number of subjects included in analysis	13
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Mean difference (net)
Point estimate	-33.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.17
upper limit	-7.34

Secondary: Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Part 1/Year 1)

End point title	Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Part 1/Year 1)
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End point description:

Time-adjusted percent change in LDL-C (after Day 90 and up to Day 330), calculated as the average of percent changes from baseline to Days 150, 270 and 330

End point type	Secondary
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End point timeframe:

Baseline, after Day 90 up to Day 330

End point values	Part 1 - Inclisiran	Part 1 - Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	4		
Units: Time-adjusted percent change in LDL-C				
arithmetic mean (standard deviation)	-21.0 (± 15.11)	13.0 (± 41.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in LDL-C from baseline up to Day 720

End point title	Percent change in LDL-C from baseline up to Day 720
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End point description:

Percentage change in LDL-C from baseline to each assessment time up to Day 720.

End point type	Secondary
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End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in LDL-C				
arithmetic mean (standard deviation)				
Day 90	-26.1 (± 13.53)	999 (± 999)	6.8 (± 16.83)	
Day 150	-24.1 (± 14.65)	999 (± 999)	17.0 (± 41.22)	
Day 270	-17.3 (± 21.64)	999 (± 999)	10.2 (± 54.00)	
Day 330	-21.6 (± 13.36)	999 (± 999)	11.7 (± 30.52)	
Day 360	-19.3 (± 14.75)	999 (± 999)	5.4 (± 28.24)	
Day 450	999 (± 999)	-11.0 (± 25.28)	999 (± 999)	
Day 510	999 (± 999)	-12.5 (± 22.52)	999 (± 999)	
Day 630	999 (± 999)	-9.4 (± 26.16)	999 (± 999)	
Day 720	999 (± 999)	-12.6 (± 28.45)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in LDL-C from baseline up to Day 720

End point title Absolute change in LDL-C from baseline up to Day 720

End point description:

Absolute change in LDL-C from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 90	-70.6 (± 48.81)	999 (± 999)	16.5 (± 44.96)	
Day 150	-66.1 (± 61.85)	999 (± 999)	20.3 (± 91.34)	
Day 270	-47.1 (± 83.15)	999 (± 999)	-9.3 (± 134.14)	

Day 330	-62.9 (± 52.35)	999 (± 999)	11.8 (± 69.94)
Day 360	-50.8 (± 44.65)	999 (± 999)	-4.3 (± 69.84)
Day 450	999 (± 999)	-36.6 (± 75.08)	999 (± 999)
Day 510	999 (± 999)	-46.8 (± 73.04)	999 (± 999)
Day 630	999 (± 999)	-41.9 (± 92.47)	999 (± 999)
Day 720	999 (± 999)	-39.8 (± 96.59)	999 (± 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Apo B from baseline up to Day 720

End point title	Percent change in Apo B from baseline up to Day 720
End point description:	Percentage change in apolipoprotein B (Apo B) from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1 - Inclisiran	Part 2 - Inclisiran (Total)	Part 1 - Placebo
Subject group type	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	13	4
Units: Percent change in Apo B			
arithmetic mean (standard deviation)			
Day 150	-20.3 (± 12.92)	999 (± 999)	10.0 (± 27.05)
Day 330	-18.5 (± 10.47)	999 (± 999)	4.5 (± 17.91)
Day 360	-14.8 (± 10.11)	999 (± 999)	10.6 (± 21.33)
Day 510	999 (± 999)	-5.7 (± 25.96)	999 (± 999)
Day 720 (study completion)	999 (± 999)	-7.3 (± 29.36)	999 (± 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Apo B from baseline up to Day 720

End point title	Absolute change in Apo B from baseline up to Day 720
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End point description:

Absolute change in apolipoprotein B (Apo B) from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1 - Inclisiran	Part 2 - Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	-37.3 (± 33.35)	999 (± 999)	7.5 (± 48.72)	
Day 330	-35.8 (± 30.33)	999 (± 999)	0.3 (± 35.85)	
Day 360	-28.7 (± 27.16)	999 (± 999)	12.0 (± 32.89)	
Day 510	999 (± 999)	-18.8 (± 45.81)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-19.6 (± 51.64)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Lp(a) from baseline up to Day 720

End point title Percent change in Lp(a) from baseline up to Day 720

End point description:

Percentage change in lipoprotein (a) [Lp(a)] from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1 - Inclisiran	Part 2 - Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in Lp(a)				
arithmetic mean (standard deviation)				
Day 150	-0.7 (± 24.81)	999 (± 999)	-4.4 (± 9.20)	
Day 330	-0.3 (± 21.27)	999 (± 999)	-16.5 (± 27.29)	

Day 360	-1.7 (± 16.57)	999 (± 999)	-12.1 (± 31.51)	
Day 510	999 (± 999)	-7.2 (± 31.39)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-8.8 (± 22.03)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Lp(a) from baseline up to Day 720

End point title	Absolute change in Lp(a) from baseline up to Day 720
End point description:	Absolute change in lipoprotein (a) [Lp(a)] from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: nmol/L				
arithmetic mean (standard deviation)				
Day 150	8.9 (± 28.41)	999 (± 999)	-0.3 (± 1.26)	
Day 330	2.8 (± 15.01)	999 (± 999)	5.3 (± 15.86)	
Day 360	5.8 (± 7.03)	999 (± 999)	0.5 (± 9.75)	
Day 510	999 (± 999)	3.0 (± 14.45)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-0.3 (± 9.12)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in non-HDL-C from baseline up to Day 720

End point title	Percent change in non-HDL-C from baseline up to Day 720
End point description:	Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in non-HDL-C				
arithmetic mean (standard deviation)				
Day 150	-24.0 (± 13.83)	999 (± 999)	19.0 (± 43.34)	
Day 330	-23.3 (± 10.99)	999 (± 999)	9.4 (± 34.93)	
Day 360	-20.1 (± 10.91)	999 (± 999)	7.1 (± 24.38)	
Day 510	999 (± 999)	-11.8 (± 25.33)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-13.0 (± 23.65)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in non-HDL-C from baseline up to Day 720

End point title	Absolute change in non-HDL-C from baseline up to Day 720
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End point description:

Absolute change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to each assessment time up to Day 720.

End point type	Secondary
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End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	-73.8 (± 68.01)	999 (± 999)	28.8 (± 94.01)	
Day 330	-74.4 (± 57.63)	999 (± 999)	4.3 (± 82.16)	
Day 360	-60.0 (± 44.74)	999 (± 999)	6.0 (± 56.11)	
Day 510	999 (± 999)	-51.4 (± 81.53)	999 (± 999)	

Day 720 (study completion)	999 (± 999)	-45.8 (± 89.10)	999 (± 999)	
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Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in total cholesterol from baseline up to Day 720

End point title	Percent change in total cholesterol from baseline up to Day 720
End point description:	Percentage change in total cholesterol from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 - Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in total cholesterol				
arithmetic mean (standard deviation)				
Day 150	-19.0 (± 12.49)	999 (± 999)	16.0 (± 37.96)	
Day 330	-19.1 (± 10.30)	999 (± 999)	8.7 (± 30.54)	
Day 360	-16.1 (± 9.53)	999 (± 999)	6.8 (± 21.06)	
Day 510	999 (± 999)	-9.3 (± 20.73)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-9.6 (± 20.86)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in total cholesterol from baseline up to Day 720

End point title	Absolute change in total cholesterol from baseline up to Day 720
End point description:	Absolute change in total cholesterol from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	-69.7 (± 67.42)	999 (± 999)	29.5 (± 99.30)	
Day 330	-71.4 (± 56.65)	999 (± 999)	8.8 (± 84.68)	
Day 360	-57.3 (± 43.82)	999 (± 999)	10.0 (± 59.14)	
Day 510	999 (± 999)	-46.5 (± 80.87)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	40.4 (± 88.44)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in triglycerides from baseline up to Day 720

End point title	Percent change in triglycerides from baseline up to Day 720
End point description:	Percentage change in triglycerides from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in triglycerides				
arithmetic mean (standard deviation)				
Day 150	0.3 (± 31.92)	999 (± 999)	-15.7 (± 5.97)	
Day 330	-9.6 (± 30.66)	999 (± 999)	-5.8 (± 31.90)	
Day 360	11.4 (± 24.72)	999 (± 999)	14.1 (± 54.93)	
Day 510	999 (± 999)	4.7 (± 37.21)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	2.9 (± 26.02)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in triglycerides from baseline up to Day 720

End point title Absolute change in triglycerides from baseline up to Day 720

End point description:

Absolute change in triglycerides from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	-3.4 (± 23.80)	999 (± 999)	-15.0 (± 7.53)	
Day 330	-9.4 (± 21.98)	999 (± 999)	-2.3 (± 25.01)	
Day 360	8.7 (± 24.15)	999 (± 999)	28.0 (± 72.23)	
Day 510	999 (± 999)	3.3 (± 34.32)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	3.9 (± 27.40)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in HDL-C from baseline up to Day 720

End point title Percent change in HDL-C from baseline up to Day 720

End point description:

Percentage change in high density lipoprotein cholesterol (HDL-C) from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in HDL-C				
arithmetic mean (standard deviation)				

Day 150	10.0 (± 13.22)	999 (± 999)	-0.1 (± 20.06)	
Day 330	7.5 (± 12.93)	999 (± 999)	10.9 (± 12.48)	
Day 360	6.7 (± 20.60)	999 (± 999)	9.2 (± 21.20)	
Day 510	999 (± 999)	12.3 (± 17.63)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	13.9 (± 18.81)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in HDL-C from baseline up to Day 720

End point title Absolute change in HDL-C from baseline up to Day 720

End point description:

Absolute change in high density lipoprotein cholesterol (HDL-C) from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	4.1 (± 5.18)	999 (± 999)	0.8 (± 7.50)	
Day 330	3.0 (± 5.05)	999 (± 999)	4.5 (± 5.07)	
Day 360	2.7 (± 7.75)	999 (± 999)	4.0 (± 8.76)	
Day 510	999 (± 999)	4.9 (± 7.94)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	5.4 (± 7.81)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in VLDL-C from baseline up to Day 720

End point title Percent change in VLDL-C from baseline up to Day 720

End point description:

Percentage change in very low density lipoprotein cholesterol (VLDL-C) from baseline to each assessment time up to Day 720.

End point type Secondary

End point timeframe:

Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in VLDL-C				
arithmetic mean (standard deviation)				
Day 150	-7.0 (± 70.31)	999 (± 999)	74.5 (± 108.97)	
Day 330	-29.0 (± 49.96)	999 (± 999)	2.0 (± 113.44)	
Day 360	-17.0 (± 60.36)	999 (± 999)	34.6 (± 56.37)	
Day 510	999 (± 999)	9.5 (± 98.44)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-1.4 (± 69.03)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolut change in VLDL-C from baseline up to Day 720

End point title	Absolut change in VLDL-C from baseline up to Day 720
End point description:	Absolute change in very low density lipoprotein cholesterol (VLDL-C) from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	-7.7 (± 11.39)	999 (± 999)	8.5 (± 20.37)	
Day 330	-11.6 (± 11.71)	999 (± 999)	-7.5 (± 18.21)	
Day 360	-9.2 (± 17.89)	999 (± 999)	10.3 (± 21.00)	
Day 510	999 (± 999)	-4.6 (± 18.41)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-6.0 (± 18.81)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in Apo A1 from baseline up to Day 720

End point title	Percent change in Apo A1 from baseline up to Day 720
End point description:	Percentage change in apolipoprotein A1 (Apo A1) from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in Apo A1				
arithmetic mean (standard deviation)				
Day 150	-0.9 (± 10.72)	999 (± 999)	-1.3 (± 2.27)	
Day 330	-2.1 (± 10.87)	999 (± 999)	9.0 (± 7.02)	
Day 360	3.1 (± 16.49)	999 (± 999)	13.7 (± 12.99)	
Day 510	999 (± 999)	12.8 (± 12.08)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	6.5 (± 10.10)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change in Apo A1 from baseline up to Day 720

End point title	Absolute change in Apo A1 from baseline up to Day 720
End point description:	Absolute change in apolipoprotein A1 (Apo A1) from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: mg/dL				
arithmetic mean (standard deviation)				
Day 150	-1.2 (± 14.10)	999 (± 999)	-1.3 (± 2.36)	

Day 330	-2.7 (± 13.47)	999 (± 999)	10.3 (± 7.41)	
Day 360	4.2 (± 18.82)	999 (± 999)	16.0 (± 14.79)	
Day 510	999 (± 999)	14.9 (± 13.25)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	7.4 (± 12.40)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change in PCSK9 from baseline up to Day 720

End point title	Percent change in PCSK9 from baseline up to Day 720
End point description:	Percentage change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to each assessment time up to Day 720.
End point type	Secondary
End point timeframe:	Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: Percent change in PCSK9 arithmetic mean (standard deviation)				
Day 90	-56.8 (± 13.73)	999 (± 999)	-17.3 (± 14.77)	
Day 150	-60.4 (± 12.62)	999 (± 999)	-1.7 (± 11.11)	
Day 330	-65.3 (± 12.51)	999 (± 999)	-5.1 (± 19.60)	
Day 360	-59.7 (± 9.05)	999 (± 999)	-2.8 (± 22.65)	
Day 510	999 (± 999)	-68.1 (± 10.57)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-64.1 (± 12.12)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Absolut change in PCSK9 from baseline up to Day 720

End point title	Absolut change in PCSK9 from baseline up to Day 720
End point description:	Absolute change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to each assessment time up to Day 720.
End point type	Secondary

End point timeframe:
Baseline, up to Day 720

End point values	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	13	4	
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 90	-278.7 (± 113.31)	999 (± 999)	-98.5 (± 87.46)	
Day 150	-296.3 (± 118.18)	999 (± 999)	-6.1 (± 64.82)	
Day 330	-323.1 (± 129.32)	999 (± 999)	-35.3 (± 100.97)	
Day 360	-292.6 (± 100.44)	999 (± 999)	-14.0 (± 127.42)	
Day 510	999 (± 999)	-347.3 (± 106.3)	999 (± 999)	
Day 720 (study completion)	999 (± 999)	-327.7 (± 110.4)	999 (± 999)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 90 days post treatment or 30 days after last study visit, whichever was longer, up to a maximum duration of approximately 2 years.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Part 1- Inclisiran
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Reporting group description:

Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)

Reporting group title	Part 2 – Inclisiran (Total)
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Reporting group description:

Inclisiran sodium 300 mg sc injection (given at Days 450 and 630). In addition, participants assigned to placebo in Part 1 received inclisiran sodium 300 mg sc injection on Day 360, while participants assigned to inclisiran in Part 1 received placebo sc injection on Day 360

Reporting group title	Part 1 - Placebo
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Reporting group description:

Placebo sc injection (given at Day 1, 90 and 270)

Serious adverse events	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 13 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Part 1- Inclisiran	Part 2 – Inclisiran (Total)	Part 1 - Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	8 / 13 (61.54%)	1 / 4 (25.00%)
Investigations			
Carotid intima-media thickness increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			

Concussion subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
Head injury subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
Ligament sprain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 13 (7.69%) 1	0 / 4 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	2 / 13 (15.38%) 2	0 / 4 (0.00%) 0
General disorders and administration site conditions Injection site reaction subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 3	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	1 / 13 (7.69%) 1	0 / 4 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 3	1 / 13 (7.69%) 2	0 / 4 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2	1 / 13 (7.69%) 3	0 / 4 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
Toothache subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0

Reproductive system and breast disorders			
Vaginal discharge			
subjects affected / exposed	0 / 9 (0.00%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Xanthoma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Angioedema			
subjects affected / exposed	0 / 9 (0.00%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rash macular			
subjects affected / exposed	1 / 9 (11.11%)	0 / 13 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	0 / 9 (0.00%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Costochondritis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 13 (7.69%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 9 (0.00%)	2 / 13 (15.38%)	0 / 4 (0.00%)
occurrences (all)	0	3	0
Gingivitis			
subjects affected / exposed	0 / 9 (0.00%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 13 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Conjunctivitis			

subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
COVID-19 subjects affected / exposed occurrences (all)	4 / 9 (44.44%) 4	1 / 13 (7.69%) 1	1 / 4 (25.00%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 13 (7.69%) 1	0 / 4 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 13 (7.69%) 1	0 / 4 (0.00%) 0
Viral infection subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 2	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0
Metabolism and nutrition disorders Vitamin D deficiency subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 13 (0.00%) 0	0 / 4 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2020	The purpose of Amendment 1 was to modify participant eligibility criteria regarding HoFH. Based on the mechanism of action of inclisiran and in order to avoid exposing patients who are unlikely to respond to study medication, patients with a null (negative) mutation in both LDLR alleles were excluded from study participation and all participants were required to have a genetic diagnosis of HoFH. Additionally, participants with a history of poor response to therapy with any monoclonal antibody directed towards PCSK9 were excluded. Amendment 1 was issued before the original protocol was sent to the IRBs/IECs and Health Authorities, i.e., before any participants were screened or randomized.
17 February 2023	The purpose of Amendment 2 was to add an interim analysis (IA) for the PK data collected on Day 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: