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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Inclisiran

Trial Indication(s)

Familial Hypercholesterolemia - Heterozygous

Protocol Number

CKJX839C12301

Protocol Title

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 heterozygous familial hypercholesterolemia and elevated LDL-cholesterol (ORION-16)

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

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Study Start/End Dates

Study Start Date: January 27, 2021 (Actual)
Primary Completion Date: November 09, 2023 (Actual)
Study Completion Date: November 27, 2024 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a two-part (double-blind, inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) multicenter study in adolescents (aged 12 to < 18 years) with HeFH and elevated LDL-C (> 130 mg/dL; 3.4 mmol/L) on stable, individualized, optimal standard of care (SoC) background lipid-lowering therapy (including maximally tolerated statin treatment, at the Investigator's discretion) to evaluate the safety, tolerability, and efficacy of inclisiran in this pediatric patient population.

Following an approximately 4-week screening/run-in period, the study had 2 sequential parts as follows:

• **Part 1/Year 1**: 12 months double-blind, parallel group period, in which participants were randomized in a 2:1 ratio to receive either inclisiran sodium 300 mg subcutaneous (s.c.) or placebo. The primary endpoint was assessed at Day 330.

• **Part 2/Year 2**: 12 months single arm, open-label follow-up period, with all participants receiving inclisiran sodium 300 mg s.c.

Centers

51 centers in 26 countries: Hungary(1), Norway(1), Spain(4), Germany(2), Switzerland(1), Slovenia(1), Greece(1), Canada(1), Russia(2), Taiwan(1), Netherlands(2), France(3), Italy(4), Israel(2), Turkey(4), Brazil(3), Malaysia(1), Lebanon(1), United States(5), United Kingdom(1), South Africa(3), Poland(2), Jordan(1), Czech Republic(2), Slovakia (Slovak Republic)(1), Argentina(1)

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Objectives:

Primary Objective:

- The primary objective is to demonstrate superiority of inclisiran compared to placebo in reducing low density lipoprotein cholesterol (LDL-C) [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with heterozygous familial hypercholesterolemia (HeFH) and elevated LDL-C

Secondary Objectives:

- Demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [time-adjusted percent change] over Year 1
- Demonstrate superiority of inclisiran compared to placebo in reducing LDL C [absolute change] at Day 330 (Year 1)
- Demonstrate superiority of inclisiran compared to placebo in reducing apolipoprotein B (Apo B), lipoprotein (a) [Lp(a)], non-high density lipoprotein cholesterol (non-HDL-C), and total cholesterol [percent change] at Day 330 (Year 1)
- Evaluate the effect of inclisiran, compared to placebo (for Year 1) and long-term (up to Day 720), on lowering LDL-C, other lipoprotein and lipid parameters, and proprotein convertase subtilisin/kexin type 9 (PCSK9) over time
- Evaluate the safety and tolerability profile of inclisiran, compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to <18 years) with HeFH

Test Product (s), Dose(s), and Mode(s) of Administration

- Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL solution provided as single-use pre-filled syringes for s.c. injection.
- Placebo formulation to this active drug formulation provided as single-use pre-filled syringes for s.c. injection.

Statistical Methods

All analyses were performed by Novartis with the most recent version of statistical analysis software (SAS) available in Novartis.

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Heterozygous Familial Hypercholesterolemia (HeFH) diagnosed either by genetic testing or on phenotypic criteria
- Fasting LDL-C >130 mg/dL (3.4 mmol/L) at screening
- Fasting triglycerides <400 mg/dL (4.5 mmol/L) at screening
- On maximally tolerated dose of statin (investigator's discretion) with or without other lipid-lowering therapy; stable for ≥ 30 days before screening

Exclusion Criteria:

- Homozygous familial hypercholesterolemia (HoFH)
- Active liver disease
- Secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome
- Previous treatment with monoclonal antibodies directed towards PCSK9 (within 90 days of screening)
- Recent and/or planned use of other investigational medicinal products or devices

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Participant Flow Table

Part 1 (Double-blind period)

	Part 1- Inclisiran	Part 1 - Placebo	Part 2 – Inclisiran (Total)	Total
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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	
Started	93	48	0	141
Completed	91	48	0	139
Not Completed	2	0	0	2
Physician Decision	1	0	0	1
Participant/guardian decision	1	0	0	1

Part 2 (Open-label period)

	Part 1- Inclisiran	Part 1 - Placebo	Part 2 – Inclisiran (Total)	Total
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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	
Started	0	0	139	139
Completed	0	0	139	139
Not Completed	0	0	0	0

Baseline Characteristics

	Part 1- Inclisiran	**Part 1 - Placebo**	**Total**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	
Number of Participants [units: participants]	93	48	141
Baseline Analysis Population Description	Baseline Characteristics are based on all randomized participants		
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	15.2±2.02	14.9±1.80	15.1±1.94
Age Categorical (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
<=18 years	93	48	141
Between 18 and 65 years	0	0	0
>=65 years	0	0	0
Sex: Female, Male (units: participants)			

Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	51	24	75
Male	42	24	66
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Asian	4	0	4
Black or African American	5	0	5
Other	4	0	4
White	80	48	128

Primary Outcome Result(s)

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

Description	Percentage change in low-density lipoprotein cholesterol (LDL-C) from baseline to Day 330 (Year 1)
Time Frame	Baseline and Day 330
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization.

	Part 1- Inclisiran	**Part 1 - Placebo**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48

Percentage change in LDL-C from baseline to Day 330 (Part 1/Year 1) (units: percent change in LDL-C)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
	-27.14 (-32.04 to -22.24)	1.40 (-3.97 to 6.78)

Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority
P Value	<.0001
Method	ANCOVA
Other LS Mean	-28.54
95 % Confidence Interval 2-Sided	-35.81 to -21.27

Secondary Outcome Result(s)

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

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
Time Frame	Baseline, after Day 90 up to Day 330
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization

	Part 1- Inclisiran	Part 1 - Placebo
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48
Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Part 1/Year 1) (units: Time-adjusted percent change in LDL-C)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
	-26.04 (-30.11 to -21.98)	3.26 (-2.37 to 8.89)

Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority
P Value	<.0001
Method	Other MMRM
Other LS Mean	-29.30
95 % Confidence Interval 2-Sided	-36.24 to -22.36

Absolute change in LDL-C from baseline to up Day 330 (Part 1/Year 1)

Description	Absolute change in LDL-C from baseline to Day 330.
Time Frame	Baseline and Day 330

Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization

	Part 1- Inclisiran	Part 1 - Placebo
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48
Absolute change in LDL-C from baseline to up Day 330 (Part 1/Year 1) (units: mg/dL)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
	-50.54 (-59.22 to -41.86)	-0.55 (-10.48 to 9.38)

Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority
P Value	<.0001
Method	ANCOVA
Other LS Mean	-49.99
95 % Confidence Interval 2-Sided	-63.18 to -36.81

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Percent change in Apo B from baseline up to Day 330 (Part 1/Year 1)

Description	Percentage change in apolipoprotein B (Apo B) from baseline to Day 330.
Time Frame	Baseline and Day 330
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization

	Part 1- Inclisiran	**Part 1 - Placebo**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48
Percent change in Apo B from baseline up to Day 330 (Part 1/Year 1) (units: Percent change in Apo B)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
	-21.46 (-25.59 to -17.33)	4.24 (-0.07 to 8.56)

Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority
P Value	<.0001
Method	ANCOVA

Other LS Mean	-25.70
95 % Confidence Interval 2-Sided	-31.68 to -19.73

Percent change in Lp(a) from baseline up to Day 330 (Part 1/Year 1)

Description	Percentage change in lipoprotein (a) [Lp(a)] from baseline to Day 330.
Time Frame	Baseline and Day 330
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization

	Part 1- Inclisiran	**Part 1 - Placebo**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48
Percent change in Lp(a) from baseline up to Day 330 (Part 1/Year 1) (units: Percent change in Lp(a))	**Least Squares Mean** **(95% Confidence Interval)**	**Least Squares Mean** **(95% Confidence Interval)**
	-5.04 (-14.21 to 4.13)	1.14 (-5.48 to 7.77)

Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority

P Value	0.1419
Method	ANCOVA
Other LS Mean	-6.18
95 % Confidence Interval 2-Sided	-17.48 to 5.12

Percent change in non-HDL-C from baseline up to Day 330 (Part 1/Year 1)

Description	Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to Day 330.
Time Frame	Baseline and Day 330
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization

	Part 1- Inclisiran	**Part 1 - Placebo**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48
Percent change in non-HDL-C from baseline up to Day 330 (Part 1/Year 1) (units: Percent change in non-HDL-C)	**Least Squares Mean** **(95% Confidence Interval)**	**Least Squares Mean** **(95% Confidence Interval)**
	-25.04 (-29.68 to -20.41)	1.76 (-3.25 to 6.77)

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Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority
P Value	<.0001
Method	ANCOVA
Other LS Mean	-26.80
95 % Confidence Interval 2-Sided	-33.63 to -19.97

Percent change in total cholesterol from baseline up to Day 330 (Part 1/Year 1)

Description	Percentage change in total cholesterol from baseline to Day 330.
Time Frame	Baseline and Day 330
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization

	Part 1- Inclisiran	Part 1 - Placebo
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)
Number of Participants Analyzed [units: participants]	93	48

Percent change in total cholesterol from baseline up to Day 330 (Part 1/Year 1) (units: Percent change in total cholesterol)	Least Squares Mean (95% Confidence Interval)	Least Squares Mean (95% Confidence Interval)
	-18.72 (-22.48 to -14.96)	0.48 (-3.46 to 4.42)

Statistical Analysis

Groups	Part 1- Inclisiran, Part 1 - Placebo
Type of Statistical Test	Superiority
P Value	<.0001
Method	ANCOVA
Other LS Mean	-19.20
95 % Confidence Interval 2-Sided	-24.65 to -13.75

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

Description	Percentage change in LDL-C from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	Part 1 - Placebo	Part 2 – Inclisiran (Total)
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	93	48	139
Percent change in LDL-C from baseline up to Day 720 (units: Percent change in LDL-C)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 90	-23.9 ± 22.14	-0.1 ± 20.16	
DAY 150	-32.5 ± 21.47	6.4 ± 28.83	
DAY 270	-19.0 ± 28.31	2.1 ± 22.44	
DAY 330	-27.8 ± 22.95	1.5 ± 20.59	
DAY 360	-26.1 ± 22.71	1.5 ± 30.56	
DAY 450			-24.5 ± 26.45
DAY 510			-32.5 ± 22.80
DAY 630			-26.5 ± 24.33
Day 720 (study completion)			-33.7 ± 23.98

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

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

Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	93	48	139
Absolute change in LDL-C from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 90	-45.4 ± 45.26	-3.0 ± 35.02	
DAY 150	-61.0 ± 45.84	6.6 ± 46.22	
DAY 270	-38.4 ± 55.77	1.0 ± 36.92	
DAY 330	-51.9 ± 45.47	-0.3 ± 38.04	
DAY 360	-49.0 ± 44.49	-2.9 ± 51.74	
DAY 450			-46.3 ± 52.51
DAY 510			-60.8 ± 48.88

DAY 630	-50.9 ± 50.30
Day 720 (study completion)	-64.1 ± 53.91

Percent change in Apo B from baseline up to Day 720

Description	Percentage change in apolipoprotein B (Apo B) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in Apo B from baseline up to Day 720 (units: Percent change in Apo B)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-25.1 ± 18.18	2.2 ± 20.77	
DAY 330	-21.9 ± 19.51	3.9 ± 18.13	
DAY 360	-19.3 ± 21.36	1.7 ± 22.70	

DAY 510	-24.5 ± 21.77
Day 720 (study completion)	-25.7 ± 21.71

Absolute change in Apo B from baseline up to Day 720

Description	Absolute change in apolipoprotein B (Apo B) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in Apo B from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-33.3 ± 28.20	0.0 ± 27.38	
DAY 330	-29.2 ± 28.04	2.9 ± 23.47	
DAY 360	-26.1 ± 29.59	-0.6 ± 28.72	

DAY 510	-33.5 ± 32.13
Day 720 (study completion)	-35.4 ± 33.83

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

Description	Percentage change in lipoprotein (a) [Lp(a)] from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in Lp(a) from baseline up to Day 720 (units: Percent change in Lp(a))	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-13.4 ± 22.60	5.4 ± 23.96	
DAY 330	-7.2 ± 30.80	1.1 ± 24.25	
DAY 360	-9.3 ± 28.44	3.6 ± 23.27	

DAY 510	-13.3 ± 28.81
Day 720 (study completion)	-4.2 ± 163.74

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

Description	Absolute change in lipoprotein (a) [Lp(a)] from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in Lp(a) from baseline up to Day 720 (units: nmol/L)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-12.5 ± 34.73	3.2 ± 20.67	
DAY 330	-9.5 ± 33.81	5.3 ± 21.55	
DAY 360	-10.2 ± 31.16	4.4 ± 22.99	

DAY 510	-10.1 ± 34.98
Day 720 (study completion)	-9.0 ± 50.08

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

Description	Percentage change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in non-HDL-C from baseline up to Day 720 (units: Percent change in non-HDL-C)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-29.0 ± 20.15	5.1 ± 24.85	
DAY 330	-25.7 ± 21.69	1.8 ± 19.43	
DAY 360	-24.0 ± 21.74	1.2 ± 27.43	

DAY 510	-29.9 ± 21.60
Day 720 (study completion)	-31.0 ± 23.04

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

Description	Absolute change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in non-HDL-C from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-60.2 ± 47.41	5.7 ± 47.61	
DAY 330	-52.6 ± 46.93	0.5 ± 39.20	
DAY 360	-49.7 ± 46.30	-3.0 ± 52.75	

DAY 510	-62.0 ± 51.09
Day 720 (study completion)	-65.1 ± 56.16

Percent change in total cholesterol from baseline up to Day 720

Description	Percentage change in total cholesterol from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in total cholesterol from baseline up to Day 720 (units: Percent change in total cholesterol)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-22.6 ± 15.77	4.4 ± 20.49	
DAY 330	-19.2 ± 17.77	0.6 ± 15.46	
DAY 360	-18.5 ± 17.18	0.6 ± 21.81	

DAY 510	-23.0 ± 17.50
Day 720 (study completion)	-23.7 ± 18.29

Absolute change in total cholesterol from baseline up to Day 720

Description	Absolute change in total cholesterol from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in total cholesterol from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	-59.0 ± 47.79	6.6 ± 48.08	
DAY 330	-49.4 ± 47.77	-0.9 ± 38.48	
DAY 360	-48.2 ± 47.06	-3.1 ± 52.66	

DAY 510	-59.6 ± 51.06
Day 720 (study completion)	-62.3 ± 55.05

Percent change in triglycerides from baseline up to Day 720

Description	Percentage change in triglycerides from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in triglycerides from baseline up to Day 720 (units: Percent change in triglycerides)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	16.2 ± 78.18	2.8 ± 37.44	
DAY 330	1.8 ± 38.39	9.7 ± 43.04	
DAY 360	1.7 ± 40.03	3.8 ± 35.76	

DAY 510	3.4 ± 43.08
Day 720 (study completion)	1.9 ± 41.84

Absolute change in triglycerides from baseline up to Day 720

Description	Absolute change in triglycerides from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in triglycerides from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	6.9 ± 64.67	-4.8 ± 31.53	
DAY 330	-2.9 ± 35.01	3.5 ± 35.55	
DAY 360	-3.1 ± 38.13	-1.7 ± 28.47	

DAY 510	-4.2 ± 34.70
Day 720 (study completion)	-4.8 ± 36.21

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

Description	Percentage change in high density lipoprotein cholesterol (HDL-C) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in HDL-C from baseline up to Day 720 (units: Percent change in HDL-C)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	3.6 ± 18.88	3.6 ± 16.49	
DAY 330	7.4 ± 19.15	-1.9 ± 16.15	
DAY 360	4.4 ± 19.54	0.9 ± 12.39	

DAY 510	6.6 ± 19.84
Day 720 (study completion)	7.4 ± 20.40

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

Description	Absolute change in high density lipoprotein cholesterol (HDL-C) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in HDL-C from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	1.2 ± 10.23	0.9 ± 8.07	
DAY 330	3.2 ± 9.57	-1.4 ± 7.77	
DAY 360	1.5 ± 9.59	-0.1 ± 6.23	

DAY 510	2.4 ± 9.32
Day 720 (study completion)	2.8 ± 9.75

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

Description	Percentage change in very low density lipoprotein cholesterol (VLDL-C) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in VLDL-C from baseline up to Day 720 (units: Percent change in VLDL-C)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	11.8 ± 60.04	3.3 ± 38.25	
DAY 330	0.6 ± 39.00	10.0 ± 42.29	
DAY 360	1.0 ± 40.15	4.7 ± 35.65	

DAY 510	1.4 ± 41.13
Day 720 (study completion)	1.9 ± 42.20

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

Description	Absolute change in very low density lipoprotein cholesterol (VLDL-C) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolut change in VLDL-C from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	0.7 ± 10.02	-0.9 ± 6.37	
DAY 330	-0.7 ± 7.04	0.8 ± 7.07	
DAY 360	-0.7 ± 7.63	-0.2 ± 5.66	

DAY 510	-1.2 ± 6.90
Day 720 (study completion)	-1.0 ± 7.40

Percent change in Apo A1 from baseline up to Day 720

Description	Percentage change in apolipoprotein A1 (Apo A1) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Percent change in Apo A1 from baseline up to Day 720 (units: Percent change in Apo A1)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	3.7 ± 15.40	0.4 ± 13.22	
DAY 330	5.2 ± 14.49	-1.5 ± 10.58	
DAY 360	3.0 ± 15.12	-1.5 ± 9.98	

DAY 510	6.3 ± 16.19
Day 720 (study completion)	4.9 ± 15.56

Absolute change in Apo A1 from baseline up to Day 720

Description	Absolute change in apolipoprotein A1 (Apo A1) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	92	48	139
Absolute change in Apo A1 from baseline up to Day 720 (units: mg/dL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 150	3.3 ± 21.76	0.0 ± 17.72	
DAY 330	6.1 ± 21.16	-2.8 ± 14.24	
DAY 360	2.7 ± 21.87	-2.6 ± 13.89	

DAY 510	7.5 ± 22.24
Day 720 (study completion)	5.4 ± 21.61

Percent change in PCSK9 from baseline up to Day 720

Description	Percentage change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	90	48	136
Percent change in PCSK9 from baseline up to Day 720 (units: Percent change in PCSK9)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 90	-67.8 ± 15.17	11.6 ± 46.61	
DAY 150	-72.3 ± 11.37	3.8 ± 36.95	
DAY 330	-72.9 ± 12.12	4.8 ± 34.50	

DAY 360	-72.0 ± 10.47	11.7 ± 57.77	
DAY 510			-74.3 ± 10.46
Day 720 (study completion)			-71.6 ± 13.42

Absolut change in PCSK9 from baseline up to Day 720

Description	Absolute change in proprotein convertase subtilisin/kexin type 9 (PCSK9) from baseline to each assessment time up to Day 720.
Time Frame	Baseline, up to Day 720
Analysis Population Description	Full Analysis Set (FAS) comprised all participants to whom study treatment had been assigned by randomization. At each time point, only subjects with a value at both baseline and that time point are included.

	Part 1- Inclisiran	**Part 1 - Placebo**	**Part 2 – Inclisiran (Total)**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Number of Participants Analyzed [units: participants]	90	48	136
Absolut change in PCSK9 from baseline up to Day 720 (units: ng/mL)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
DAY 90	-259.6 ± 121.5	2.1 ± 223.16	
DAY 150	-274.8 ± 116.2	-27.7 ± 210.44	

DAY 330	-278.2 ± 119.8	-23.9 ± 210.85	
DAY 360	-275.4 ± 117.2	-9.1 ± 245.36	
DAY 510			-288.1 ± 156.9
Day 720 (study completion)			-279.5 ± 159.2

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (27.1)
Collection Approach for Table Default	Systematic Assessment

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All-Cause Mortality

	Part 1 - Inclisiran N = 93	Part 1 - Placebo N = 48	Part 2 - Inclisiran (Total) N = 139
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Total Number Affected	0	0	0
Total Number At Risk	93	48	139

Serious Adverse Events

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (27.1)
Collection Approach for Table Default	Systematic Assessment

	Part 1 - Inclisiran N = 93	Part 1 - Placebo N = 48	Part 2 - Inclisiran (Total) N = 139

Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Total # Affected by any Serious Adverse Event	3	1	6
Total # at Risk by any Serious Adverse Event	93	48	139
Cardiac disorders			
Supraventricular tachycardia	0 (0.00%)	1 (2.08%)	0 (0.00%)
Immune system disorders			
Anaphylactic reaction	1 (1.08%)	0 (0.00%)	1 (0.72%)
Infections and infestations			
Dengue fever	1 (1.08%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications			
Concussion	0 (0.00%)	0 (0.00%)	1 (0.72%)
Investigations			
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	1 (0.72%)
Nervous system disorders			
Status migrainosus	1 (1.08%)	0 (0.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	1 (0.72%)

Psychiatric disorders			
Anxiety	0 (0.00%)	0 (0.00%)	1 (0.72%)
Vascular disorders			
Varicose vein	0 (0.00%)	0 (0.00%)	1 (0.72%)

Other (Not Including Serious) Adverse Events

Time Frame	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.
Source Vocabulary for Table Default	MedDRA (27.1)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 3%

	Part 1 - Inclisiran N = 93	**Part 1 - Placebo N = 48**	**Part 2 - Inclisiran (Total) N = 139**
Arm/Group Description	Inclisiran sodium 300 mg subcutaneous (sc) injection (given at Days 1, 90 and 270)	Placebo sc injection (given at Day 1, 90 and 270)	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.
Total # Affected by any Other Adverse Event	57	29	52
Total # at Risk by any Other Adverse Event	93	48	139
Gastrointestinal disorders			
Nausea	4 (4.30%)	1 (2.08%)	4 (2.88%)
Vomiting	5 (5.38%)	1 (2.08%)	0 (0.00%)
General disorders and administration site conditions			
Fatigue	4 (4.30%)	1 (2.08%)	0 (0.00%)
Influenza like illness	4 (4.30%)	3 (6.25%)	2 (1.44%)
Injection site pain	4 (4.30%)	2 (4.17%)	4 (2.88%)
Injection site reaction	8 (8.60%)	1 (2.08%)	5 (3.60%)
Malaise	0 (0.00%)	2 (4.17%)	0 (0.00%)
Infections and infestations			
COVID-19	17 (18.28%)	12 (25.00%)	7 (5.04%)
Gastroenteritis	4 (4.30%)	1 (2.08%)	3 (2.16%)
Influenza	10 (10.75%)	6 (12.50%)	11 (7.91%)
Nasopharyngitis	13 (13.98%)	9 (18.75%)	14 (10.07%)
Pharyngitis	4 (4.30%)	2 (4.17%)	1 (0.72%)
Upper respiratory tract infection	6 (6.45%)	2 (4.17%)	4 (2.88%)
Injury, poisoning and procedural complications			
Ligament sprain	3 (3.23%)	1 (2.08%)	1 (0.72%)

Nervous system disorders			
Headache	12 (12.90%)	3 (6.25%)	6 (4.32%)
Migraine	4 (4.30%)	0 (0.00%)	2 (1.44%)
Syncope	5 (5.38%)	0 (0.00%)	1 (0.72%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	3 (3.23%)	2 (4.17%)	6 (4.32%)

Other Relevant Findings

Not Applicable

Conclusion:

The results of the ORION-16 study demonstrate that inclisiran sodium 300 mg s.c. administered on Day 1, Day 90, and then every 6 months is safe, well-tolerated, and exhibits clinically meaningful and durable reductions in low density lipoprotein cholesterol (LDL-C) levels in adolescents with heterozygous familial hypercholesterolemia (HeFH). The efficacy and safety data of this study support a positive benefit-risk profile for inclisiran in adolescents with HeFH.

Date of Clinical Trial Report

24 March 2025