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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Inclisiran

Trial Indication(s)

Primary hypercholesterolemia

Protocol Number

CKJX839D12304

Protocol Title

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)

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: March 15, 2023 (Actual)

Primary Completion Date: June 20, 2024 (Actual)
Study Completion Date: June 20, 2024 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This study was a randomized, double-blind, placebo- and active comparator-controlled, multicenter study in adult participants with primary hypercholesterolemia not receiving any lipid lowering therapy (LLT) and who had a 10-year Atherosclerotic Cardiovascular Disease (ASCVD) risk of less than 7.5%, estimated using the pooled cohort equations (PCEs). This study evaluated the efficacy and safety of inclisiran sodium 300 mg, administered as a monotherapy in comparison to ezetimibe and placebo.

The study consisted of a screening period of up to 14 days, a double-blind treatment period of 150 ± 5 days based on the Day 1 randomization date, and a safety follow-up / End of Study (EOS) visit conducted 30 +5 days after the Day 150 Visit. The overall study duration was approximately 190 days but varied depending on individual screening and the visit windows allowed for the treatment period and EOS visit.

Centers

42 centers in 5 countries: United States(22), Germany(9), Hungary(2), Colombia(4), Mexico(5)

Objectives:

- 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

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

Inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) or matching placebo in 1.5 mL solution for injection in a prefilled syringe

Ezetimibe 10 mg or matching placebo in bottles containing 35 capsules each.

Statistical Methods

Primary endpoint:

Two Estimands were considered in parallel as:

• Monotherapy Estimand: assessed the treatment effect of inclisiran alone in the absence of confounding factors such as additional LLT

• Treatment-policy Estimand: assessed the treatment effect of inclisiran as compared to placebo or ezetimibe irrespective of adherence to the study drug or addition of other LLTs, with death being an unfavorable outcome

The statistical hypotheses to be tested are:

• HIP0: $\mu i - \mu p \geq 0$ vs. HIPa: $\mu i - \mu p < 0$

• HIE0: $\mu i - \mu e \geq 0$ vs. HIEa: $\mu i - \mu e < 0$

where μi, μp and μe are the mean percentage changes from baseline to Day 150 in the inclisiran group, placebo group, and ezetimibe group, respectively.

The primary and secondary efficacy endpoints were analyzed using an Analysis of Covariance (ANCOVA) model with treatment, stratification factor, and baseline value as fixed effects. Due to probable heterogeneity of variances between treatment groups, an ANCOVA model that assumes unequal variances between treatment groups was used.

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Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria at screening:

- informed consent signed prior to participation in study
- fasting LDL-C of >= 100 mg/dL but < 190 mg/dL
- fasting triglycerides <= 400 mg/dL
- 10-year ASCVD risk score < 7.5%
- not on any lipid-lowering therapy within 90 days of screening

Key Exclusion Criteria:

- history of ASCVD
- diabetes mellitus or fasting plasma glucose of >= 7.0 mmol/L or HbA1c >= 6.5%
- secondary hypercholesterolemia, e.g. hypothyroidism (TSH above upper limit of normal)

Participant Flow Table

Overall Study

	Inclisiran	Ezetimibe	Placebo	Total
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.	
Started	174	89	87	350
Completed	164	86	84	334
Not Completed	10	3	3	16
Subject decision	5	2	1	8
Lost to Follow-up	4	1	2	7

Adverse Event	1	0	0	1

Baseline Characteristics

	Inclisiran	Ezetimibe	Placebo	Total
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.	
Number of Participants [units: participants]	174	89	87	350
Baseline Analysis Population Description				
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation				
	45.7±11.74	46.3±10.90	46.7±11.55	46.1±11.46
Age Categorical (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
<=18 years	0	0	0	0
Between 18 and 65 years	168	86	83	337
>=65 years	6	3	4	13
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)				
Female	104	56	59	219
Male	70	33	28	131
Race (NIH/OMB) (units: Participants)				

Analysis Population Type: Participants Count of Participants (Not Applicable)				
American Indian or Alaska Native	10	10	9	29
Asian	0	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	20	7	10	37
White	140	71	67	278
More than one race	4	0	1	5
Unknown or Not Reported	0	0	0	0
Study Specific Characteristic **Baseline Low-Density Lipoprotein Cholesterol (LDL-C)** (units: mg/dL) Analysis Population Type: Participants Mean ± Standard Deviation				
	135.8±27.01	134.4±25.82	135.4±28.69	135.4±27.07

Primary Outcome Result(s)

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

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.
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants.

	Inclisiran	Ezetimibe	Placebo
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87
Percentage change in Low-density Lipoprotein Cholesterol (LDL-C) from Baseline to Day 150 (units: Percentage change from baseline)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-35.37	
95 % Confidence Interval 2-Sided	-40.88 to -29.86	

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	

P Value	<0.0001
Method	ANCOVA
Other LS Mean Difference	-47.91
95 % Confidence Interval 2-Sided	-53.62 to -42.20

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-37.44	
95 % Confidence Interval 2-Sided	-42.63 to -32.26	

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	

Other LS Mean Difference	-50.90
95 % Confidence Interval 2-Sided	-56.51 to -45.28

Secondary Outcome Result(s)

Absolute change in LDL-C from Baseline to Day 150

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.
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants.

	Inclisiran	**Ezetimibe**	**Placebo**
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87
Absolute change in LDL-C from Baseline to Day 150 (units: mg/dL)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-47.37	
95 % Confidence Interval 2-Sided	-53.91 to -40.72	

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-63.57	
95 % Confidence Interval 2-Sided	-70.28 to -56.87	

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand

Type of Statistical Test	Superiority
P Value	<0.0001
Method	ANCOVA
Other LS Mean Difference	-50.05
95 % Confidence Interval 2-Sided	-56.16 to -43.94

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-67.51	
95 % Confidence Interval 2-Sided	-74.09 to -60.92	

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

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 "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.
Time Frame	Baseline, Day 150

Analysis Population Description	Full Analysis Set, all randomized participants with a valid assessment for the outcome measure.

	Inclisiran	Ezetimibe	Placebo
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	172	89	87
Percentage change in Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) from Baseline to Day 150 (units: Percentage change from baseline)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-73.16	
95 % Confidence Interval 2-Sided	-81.76 to -64.56	

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Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-74.94	
95 % Confidence Interval 2-Sided	-84.51 to -65.37	

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-76.87	
95 % Confidence Interval 2-Sided	-85.12 to -68.62	

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand

Type of Statistical Test	Superiority
P Value	<0.0001
Method	ANCOVA
Other LS Mean Difference	-79.47
95 % Confidence Interval 2-Sided	-88.77 to -70.17

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

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.
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants.

	Inclisiran	**Ezetimibe**	**Placebo**
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87
Percentage change in non-High-Density Lipoprotein Cholesterol (non-HDL-C) from Baseline to Day 150 (units: Percentage change from baseline)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-30.48	
95 % Confidence Interval 2-Sided	-34.98 to -25.98	

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-42.32	
95 % Confidence Interval 2-Sided	-47.83 to -36.82	

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-31.98	
95 % Confidence Interval 2-Sided	-36.07 to -27.89	

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-44.86	
95 % Confidence Interval 2-Sided	-50.28 to -39.44	

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

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.
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants.

	Inclisiran	Ezetimibe	Placebo
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87
Percentage change in Total Cholesterol (TC)/HDL-C ratio from Baseline to Day 150 (units: Percentage change from baseline)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-24.84	

95 % Confidence Interval 2-Sided	-30.32 to -19.36

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-33.85	
95 % Confidence Interval 2-Sided	-41.27 to -26.44	

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-26.58	
95 % Confidence Interval 2-Sided	-32.07 to -21.09	

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Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-36.06	
95 % Confidence Interval 2-Sided	-43.46 to -28.67	

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

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.
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants.

	Inclisiran	Ezetimibe	Placebo
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87

Percentage change in Apolipoprotein B (Apo B) from Baseline to Day 150 (units: Percentage change from baseline)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-28.98	
95 % Confidence Interval 2-Sided	-33.30 to -24.65	

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	

Other LS Mean Difference	-36.66
95 % Confidence Interval 2-Sided	-41.10 to -32.22

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-30.16	
95 % Confidence Interval 2-Sided	-34.08 to -26.23	

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-38.78	
95 % Confidence Interval 2-Sided	-43.12 to -34.43	

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

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.
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants.

	Inclisiran	Ezetimibe	Placebo
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87
Percentage change in Apo B/Apo A-1 ratio from Baseline to Day 150 (units: Percentage change from baseline)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	

Method	ANCOVA
Other LS Mean Difference	-30.24
95 % Confidence Interval 2-Sided	-36.92 to -23.57

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-35.15	
95 % Confidence Interval 2-Sided	-41.18 to -29.12	

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-32.34	

95 % Confidence Interval 2-Sided	-39.10 to -25.59

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LS Mean Difference	-37.38	
95 % Confidence Interval 2-Sided	-43.44 to -31.31	

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

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).
Time Frame	Baseline, Day 150
Analysis Population Description	Full Analysis Set, all randomized participants with a valid assessment for the outcome measure.

	Inclisiran	Ezetimibe	Placebo

Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	173	88	87
Change in Lipoprotein (a) [Lp(a)] from Baseline to Day 150 (units: Ratio from baseline)	**Geometric Least Squares Mean (95% Confidence Interval)**	**Geometric Least Squares Mean (95% Confidence Interval)**	**Geometric Least Squares Mean (95% Confidence Interval)**
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 Analysis

Groups	Inclisiran, Ezetimibe	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	0.0002	
Method	ANCOVA	
Other LS Geometric Mean	0.757	
95 % Confidence Interval 2-Sided	0.650 to 0.882	

Statistical Analysis

Groups	Inclisiran, Placebo	Treatment Policy Estimand
Type of Statistical Test	Superiority	
P Value	0.0010	

Method	ANCOVA
Other LS Geometric Mean	0.748
95 % Confidence Interval 2-Sided	0.622 to 0.898

Statistical Analysis

Groups	Inclisiran, Ezetimibe	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	ANCOVA	
Other LG Geometric Mean	0.753	
95 % Confidence Interval 2-Sided	0.652 to 0.871	

Statistical Analysis

Groups	Inclisiran, Placebo	Monotherapy Estimand
Type of Statistical Test	Superiority	
P Value	0.0008	
Method	ANCOVA	
Other LS Geometric Mean	0.746	

95 % Confidence Interval 2-Sided	0.622 to 0.893

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

Description	Incidence of TEAEs (regardless of seriousness) and SAEs by treatment group, including changes in laboratory results qualifying and reported as AEs.
Time Frame	From first dose of study treatment on Day 1 up to Day 180
Analysis Population Description	Safety Analysis Set, all participants who received at least one dose of study treatment.

	Inclisiran	Ezetimibe	Placebo
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.
Number of Participants Analyzed [units: participants]	174	89	87
Incidence of Treatment Emergent Adverse Events (TEAE) and Serious Adverse Events (SAE) (units: Participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
AEs	54 (31.03%)	27 (30.34%)	25 (28.74%)
Treatment related AEs (Inclisiran/ placebo)	11 (6.32%)	4 (4.49%)	0 (%)
Treatment related AEs (ezetimibe/placebo)	3 (1.72%)	2 (2.25%)	2 (2.3%)
SAEs	1 (.57%)	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 treatment discontinuation of inclisiran/placebo	3 (1.72%)	0 (%)	0 (%)
AEs leading to treatment discontinuation of ezetimibe/placebo	4 (2.3%)	0 (%)	0 (%)

Other Pre-Specified Outcome Result(s)

No data identified.

Post-Hoc Outcome Result(s)

No data identified.

Safety Results

Time Frame	From first dose of study treatment on Day 1 up to Day 180
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Inclisiran N = 174	**Ezetimibe N = 89**	**Placebo N = 87**	**Total N = 350**

Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.	Total
Total Number Affected	0	0	0	0
Total Number At Risk	174	89	87	350

Serious Adverse Events

Time Frame	From first dose of study treatment on Day 1 up to Day 180
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment

	Inclisiran N = 174	**Ezetimibe N = 89**	**Placebo N = 87**	**Total N = 350**
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.	Total
Total # Affected by any Serious Adverse Event	1	0	0	1
Total # at Risk by any Serious Adverse Event	174	89	87	350
Injury, poisoning and procedural complications				
Femur fracture	1 (0.57%)	0 (0.00%)	0 (0.00%)	1 (0.29%)

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Other (Not Including Serious) Adverse Events

Time Frame	From first dose of study treatment on Day 1 up to Day 180
Source Vocabulary for Table Default	MedDRA (27.0)
Collection Approach for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	2%

	Inclisiran N = 174	**Ezetimibe N = 89**	**Placebo N = 87**	**Total N = 350**
Arm/Group Description	Inclisiran s.c and Placebo p.o	Placebo s.c. and Ezetimibe p.o.	Placebo s.c. and Placebo p.o.	Total
Total # Affected by any Other Adverse Event	19	18	13	50
Total # at Risk by any Other Adverse Event	174	89	87	350
Gastrointestinal disorders				
Diarrhoea	2 (1.15%)	1 (1.12%)	2 (2.30%)	5 (1.43%)
Vomiting	2 (1.15%)	2 (2.25%)	0 (0.00%)	4 (1.14%)
Infections and infestations				

COVID-19	1 (0.57%)	2 (2.25%)	3 (3.45%)	6 (1.71%)
Gastroenteritis	2 (1.15%)	2 (2.25%)	0 (0.00%)	4 (1.14%)
Nasopharyngitis	6 (3.45%)	3 (3.37%)	3 (3.45%)	12 (3.43%)
Upper respiratory tract infection	2 (1.15%)	2 (2.25%)	1 (1.15%)	5 (1.43%)
Urinary tract infection	3 (1.72%)	2 (2.25%)	2 (2.30%)	7 (2.00%)
Injury, poisoning and procedural complications				
Fall	0 (0.00%)	2 (2.25%)	1 (1.15%)	3 (0.86%)
Investigations				
Blood pressure increased	1 (0.57%)	2 (2.25%)	0 (0.00%)	3 (0.86%)
Nervous system disorders				
Headache	6 (3.45%)	0 (0.00%)	0 (0.00%)	6 (1.71%)
Renal and urinary disorders				
Hypertonic bladder	0 (0.00%)	2 (2.25%)	0 (0.00%)	2 (0.57%)
Vascular disorders				
Hypertension	1 (0.57%)	1 (1.12%)	2 (2.30%)	4 (1.14%)

Other Relevant Findings

N/A

Conclusion:

The results of the VictORION-Mono study indicate that inclisiran sodium 300 mg as a monotherapy is safe, well-tolerated and exhibits potent reductions in LDL-C levels from Baseline to Day 150 in comparison to both placebo and ezetimibe in adult participants with primary hypercholesterolemia who are not receiving any lipid lowering therapy and have a low or borderline-low 10-year ASCVD risk.

Date of Clinical Trial Report

16th of December 2024