



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2026
EMADOC-1700519818-2398086
Committee for Medicinal Products for Human Use (CHMP)

CHMP group of variations including an extension of indication assessment report

Invented name: Leqvio

International non-proprietary name: Inclisiran

Procedure No. EMA/VR/0000293324

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

A-120190	Inclisiran antisense strand
A-122088	Inclisiran sense strand
ADA	Antidrug antibodies
ASCVD	Atherosclerotic cardiovascular disease
AUC	Area under the concentration-time curve
AUC ₀₋₂₄	Area under the concentration-time curve from time zero to 24 hours post-dose
AUC _{inf}	Area under the concentration-time curve from time zero to infinity
BA	Bioanalytical
CCP	Confirmatory cut point
C _{max}	Maximum plasma concentration
CRL	Charles River Laboratories
CV	Coefficient of variation
CVD	Cardiovascular disease
DDI	Drug-drug interaction
FH	Familial hypercholesterolaemia
HeFH	Heterozygous familial hypercholesterolaemia
HoFH	Homozygous familial hypercholesterolaemia
KJX839	Inclisiran
LC-MS/MS	liquid chromatography - tandem mass spectrometry
LDL-C	Low density lipoprotein-cholesterol
LLOQ	Lower limit of quantification
LPC	Low positive control
LTS	Long term stability
MD	Multiple dose
MRD	Minimum required dilution
MRM	Multiple reaction monitoring
N/A	Not applicable
OL	Open label
PC	Positive Control
PCSK9	Proprotein convertase subtilisin/kexin type 9
PI	Product information
PK	Pharmacokinetic(s)
PL	Patient Leaflet
SC	Subcutaneous
SCPF	Screening cut point factor
SD	Standard deviation
siRNA	Small interfering ribonucleic acid
SmPC	Summary of product characteristics
ULOQ	Upper limit of quantification

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Limited submitted to the European Medicines Agency on 22 August 2025 an application for group of variations.

The following variations were requested in the group:

Variation(s) requested		Type
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	Variation type II
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	Variation type II

Grouping of two Type II C.I.6 variations to support the extension of the LEQVIO indication to paediatric patients aged 12 to less than 18 years with heterozygous and homozygous familial hypercholesterolaemia, as follows:

C.I.6: Extension of indication to include the treatment of paediatric patients aged 12 to less than 18 years with heterozygous familial hypercholesterolaemia (HeFH) for LEQVIO based on the final results from study CKJX839C12301 (ORION-16). ORION-16 is a two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicentre study to evaluate safety, tolerability, and efficacy of inclisiran in paediatric patients (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol.

C.I.6: Extension of indication to include the treatment of paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia (HoFH) for LEQVIO based on the final results from study CKJX839C12302 (ORION-13). ORION-13 is a two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicentre study to evaluate safety, tolerability, and efficacy of inclisiran in paediatric patients (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol.

As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted.

The requested variation(s) proposed amendments to the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0322/2023 on the agreement of a paediatric investigation plan (PIP). The original PIP P/0321/2018 was modified twice, on 2 December 2022 (EMA decision P/0495/2022) and on 11 August 2023 (EMA decision P/0322/2023).

At the time of submission of the application, the PIP P/0322/2023 was not yet completed as some measures were deferred.

EMA issued on 25 April 2025 a positive partial compliance check for the PIP P/0322/2023 confirming the completion of Study 1, ORION- 13 (CKJX839C12302) and Study 2, identifier ORION-16 (CKJX839C1230).

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Derogation(s) of market exclusivity

N/A

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Ewa Balkowiec Iskra

Timetable	Actual dates
Submission date	22 August 2025
Start of procedure:	13 September 2025
CHMP Rapporteur’s preliminary assessment report circulated on:	14 November 2025
CHMP CoRapporteur’s preliminary assessment report circulated on:	19 November 2025
Joint Rapporteur’s updated assessment report circulated on:	5 December 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	11 December 2025
MAH responses submitted to the CHMP on:	19 February 2026
CHMP Rapporteur’s preliminary assessment report on the MAH’s responses circulated on:	24 April 2026
Joint Rapporteur’s updated assessment report on the MAH’s responses circulated on:	13 May 2026
2 nd Request for supplementary information and extension of timetable adopted by the CHMP on:	21 May 2026
MAH responses submitted to the CHMP on:	28 May 2026

Timetable	Actual dates
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	11 June 2026
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	18 June 2026
CHMP opinion:	25 June 2026

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Familial hypercholesterolemia (FH) is a genetic disorder of lipoprotein metabolism manifested by lifelong and marked elevation in LDL cholesterol (LDL-C) levels from birth. If left untreated, it is characterised by premature cardiovascular disease (CVD). FH is caused by variants in genes encoding proteins which regulate LDLR-mediated clearance of LDL-C; there are two clinical manifestations, heterozygous FH (HeFH) and the more severe homozygous FH (HoFH), depending on the presence of one or two affected alleles in these genes.

State the claimed the therapeutic indication (new: underlined)

Primary hypercholesterolaemia and mixed dyslipidaemia

Leqvio is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, and in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH):

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolaemia (HoFH)

Leqvio is indicated in paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Epidemiology

The overall disease prevalence for HeFH is currently estimated as about 1 in every 250 - 300 people (Beheshti et al 2020¹, Hu et al 2020², Cuchel et al 2023³), while HoFH is a rare disease with an estimated prevalence of 1 in every 250,000 – 360,000 people (Cuchel et al 2023).

Aetiology and pathogenesis

The three main known genetic mutations in familial hypercholesterolemia are classified as defects in the LDL receptor ([LDLR]; most common), apolipoprotein B (ApoB), or proprotein convertase subtilisin / kexin type 9 (PCSK9). Each of these three mutations leads to impairment of LDL receptors and a reduction in uptake of LDL-cholesterol (LDL-C) and subsequently causes high LDL-C concentration. Patients can have a heterozygous or a homozygous defect, which will determine the severity of the disease and the age of onset of cardiovascular (CV) disease manifestations. Children who carry both defect genes from two heterozygote parents almost do not have LDLR to uptake LDL-C and subsequently present with extremely high LDL-C levels and early-onset CV disease. Over 1600 gene mutations in LDLR are detected in 85% to 90% of patients with familial hypercholesterolaemia (FH). ApoB mutations account for about 10% of patients with FH, and from this amount, the Arg3500Gln gene mutation is the most common cause. PCSK9 gene mutation causes less than 5% of patients with FH. Moreover, only severe mutations in PCSK9 can lead to FH. However, a less common mutation in signal-transducing adaptor family member 1 (STAP1) was also reported to cause FH. (Vaezi et al 2025⁴)

Clinical presentation

LDL-C levels in affected individuals are elevated and in spite of aggressive statin use there is still a 2-fold excess of coronary heart disease (CHD) related deaths relative to age-matched controls within this population. A strong positive correlation and causal relationship between LDL-C levels and risk of CV disease (CVD) has been derived from a large body of clinical and epidemiological studies. There is also a strong relationship to other clinical manifestations in the body like cerebrovascular disease (i.e. ischaemic stroke) or peripheral vascular disease. Epidemiologic data indicate a continuous increasing relative risk of CVD from very low to high levels of LDL-C, with a higher absolute risk in patients at the higher end of LDL-C levels.

Management

The underlying atherosclerotic vascular lesions that cause CHD, CVD, and peripheral vascular occlusive disease are caused by an elevated LDL-C level. An outstanding role to reduce the risk of major CV events is lowering of LDL-C, which has been established for a long time. Data to support the relationship between LDL-C and CV events and specifically the relationship with inhibition of PCSK9 has been shown in genetic studies of variations in the genes that influence LDL-C and from studies in patients with FH. In Mendelian randomisation studies evaluating multiple genetic targets that impact

¹ Beheshti S, Madsen C, Varbo A, et al (2020) Worldwide prevalence of familial hypercholesterolemia: Meta-analyses of 11 million subjects. JACC; (20):2553-66.

² Hu P, Dharmayat KI, Stevens CAT, et al (2020) Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation; 141(22):1742-59.

³ Cuchel M, Raal FJ, Hegele RA, et al (2023) 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: New Treatments and Clinical Guidance. Eur Heart J; 44(25):2277-91.

⁴ Vaezi Z, Amini A. Familial Hypercholesterolemia. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK556009/>

LDL-C levels, the variants in genes that regulate LDL-C levels (e.g., LDL-R, PCSK9) have demonstrated that lowering of LDL-C is associated with a lower risk for CV events. To minimise this risk factor, lipid-lowering therapies are recommended. To reach this goal, specific targets have been suggested. It has been shown that the higher the CV risks, the more aggressive the lipid-lowering therapy should be.

Early initiation of treatment in patients with FH is considered crucial for ASCVD risk reduction (Reijman et al 2021⁵). Despite the availability of multiple options of lipid-lowering therapies, including statins, ezetimibe, and newer treatments like anti-PCSK9 or anti-ANGPTL3 (HoFH only) monoclonal antibodies, many patients with HeFH or HoFH, including adolescents, do not reach recommended LDL-C goals and a relevant unmet medical need is considered to remain, in particular for the young patient population, who is at high risk of future CV events and thus requires intensive management of hypercholesterolemia. In addition, as adherence to lipid-lowering therapies is known to be a particular challenge in adolescents (Joyce et al 2016⁶, Langslet et al 2021⁷, Weinstock et al 2023⁸), effective treatments to reduce LDL-C, which do not require frequent self-administration, might be especially beneficial in this age group.

2.1.2. About the product

Inclisiran is a cholesterol-lowering, double-stranded, small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilises the RNA interference mechanism and directs catalytic breakdown of mRNA for proprotein convertase subtilisin kexin type 9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

The currently approved therapeutic indication is primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in adults as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The recommended dose is 284 mg inclisiran administered as a single subcutaneous injection initially, again at 3 months, and then followed by every 6 months.

2.1.3. The development programme / compliance with CHMP guidance / scientific advice

The Paediatric Investigation Plan (PIP) for inclisiran was first approved on 12 September 2018 (EMA decision P/0321/2018); the original PIP was modified twice, on 2 December 2022 (EMA decision P/0495/2022) and on 11 August 2023 (EMA decision P/0322/2023).

At the time of submission of the application, the PIP has not yet been completed as some measures have been deferred.

⁵ Reijman MD, Kusters DM, Wiegman A (2021) Advances in familial hypercholesterolaemia in children. *Lancet Child Adolesc Health*. 5(9):652-61.

⁶ Joyce NR, Wellenius GA, Eaton CB, et al. (2016). Patterns and predictors of medication adherence to lipid-lowering therapy in children aged 8 to 20 years. *J Clin Lipidol*; 10(4):824-32.

⁷ Langslet G, Johansen AK, Bogsrud MP, et al. (2021). Thirty percent of children and young adults with familial hypercholesterolemia treated with statins have adherence issues. *Am J Prev Cardiol*; 6:100180.

⁸ Weinstock RS, Trief PM, Burke BK, et al. (2023). Antihypertensive and lipid-lowering medication adherence in young adults with youth-onset type 2 diabetes. *JAMA Netw Open*; 6(10):e2336964.

A partial compliance check was completed on 25 April 2025, confirming compliance with the latest PIP P/0322/2023 (Compliance Report EMA/PE/0000248841). The partial compliance check was performed on the two PIP studies that were completed before the submission of the new paediatric indications in adolescents with HeFH and HoFH, study ORION-13 (CKJX839C12302) (study 1) in paediatric patients from ≥ 12 years to < 18 years of age with homozygous familial hypercholesterolaemia (HoFH) and study ORION-16 (CKJX839C12301) (study 2) in paediatric patients from ≥ 12 years to < 18 years of age with heterozygous familial hypercholesterolaemia (HeFH).

The currently approved PIP also contains two additional clinical studies in younger children from ≥ 6 years to < 12 years of age with HeFH and HoFH.

2.1.4. General comments on compliance with GCP

In both study reports, ORION-13 (CKJX839C12302) and ORION-16 (CKJX839C12301), it is stated that these studies were conducted in compliance with Good Clinical Practice (GCP).

2.2. Non-clinical aspects

2.2.1. Ecotoxicity / environmental risk assessment

Table 1: Summary of main study results: Phase I

Substance (INN/Invented Name):		Inclisiran	
CAS-number (if available):		1639324-62-1 (sodium form); 1639324-58-5 (free acid)	
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log Kow	OECD 107	logDow = <-1.4 at pH 5.2 logDow = <-1.4 at pH 7 logDow = <-1.4 at pH 8.9	Potential PBT: N
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion
Bioaccumulation	log Dow	-1.4 at pH 5.2 – 8.9	not B
	BCF _{Kgl}	Not applicable	
Persistence	Ready biodegradability	N	potentially P
	DT50, whole system at 12°C	> 1000 d	vP
Toxicity	NOEC _{aquatic} / Fish	2.5 mg/L	not T
PBT/vPvB statement:	Inclisiran is considered to be not PBT, nor vPvB		
Phase I			
Parameter	Value	Unit	Conclusion
PEC _{sw} , refined with treatment regime	0.0123	µg/L	≥ 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Table 2: Summary of main study results: Phase II

Phase II Physical-chemical properties and fate			
Study type	Test protocol	Result	Remarks
Water solubility	none	> 300,00 mg/L at 25 °C	Not validated, no standardised test protocol
Adsorption-Desorption	OECD 106	K _{D, soil 1} = 5076 L/kg	terrestrial studies not triggered, no correlation with oc observed; Values not reliable as test design of OECD 106 does not suitable for the molecule structure, no use for PEC _{sediment} calculation possible
Soil 1 = Silty clay loam			
Soil 2 = Loam		K _{D, soil 2} = 10271 L/kg	
Soil 3 = Sandy Loam		K _{D, soil 3} = 18264 L/kg	
Sludge 1 = municipal		K _{D, sludge 1} = 17.7 L/kg	
Sludge 2 = municipal		K _{D, sludge 2} = 9.51 L/kg	

Ready Biodegradability Test	OECD 301 B	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems Sediment 1 = loam	OECD 308	DT ₅₀ , water 1 = 4.2 d DT ₅₀ , sediment 1 = n.a. DT ₅₀ , whole system 1 = 70 d CO ₂ = 77 % NER _{total} = 9.9 % NER _{type I} = n.a.	20 °C CO ₂ and NER values at test end
Sediment 2 = sand		DT ₅₀ , water 2 = 3 d DT ₅₀ , sediment 2 = n.a. DT ₅₀ , whole system 2 >1000 d CO ₂ = 24 % NER _{total} = 29 % NER _{type I} = n.a.	20 °C CO ₂ and NER values at test end
Transformation products		>10% = Y TP1 (max) = 34 % DT ₅₀ TP1: n.a.	at day 14, sed 1 TP1 = 2'-O-methyluridine and other nucleosides
Phase II Aquatic effect studies			
Study type	Test protocol	Endpoint	Value Unit Remarks
Algae, Growth Inhibition Test/ <i>Raphidoelis subcapitata</i>	OECD 201	NOEC	110,000 µg/L growth rate
<i>Daphnia</i> sp. Reproduction Test	OECD 211	NOEC	12,000 µg/L
Fish, Early Life Stage Toxicity Test/ <i>Pimephales promelas</i>	OECD 210	NOEC	2,500 µg/L larvae survival
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	>1,000 mg/L total respiration
Phase II Sediment effect studies			
Sediment Dwelling Organism Test/ <i>Chironomus riparius</i>	OECD 218	NOEC	6.0 mg/kgdw No normalisation to 10% C _{org} as no OC-correlation observed
Risk characterisation			
Compartment	PEC	PNEC	RQ Conclusion
STP	0.123 µg/L	10 ⁵ µg/L	1.2 * 10 ⁻⁶ No risk
Surface water	0.0123 µg/L	250 µg/L	4.9 * 10 ⁻⁵ No risk
Groundwater	0.0031 µg/L	25 µg/L	1.24 * 10 ⁻⁴ No risk
Sediment	Risk approach of the EMA ERA Guideline is not suitable for this molecule, scientific evidence suggests that risk is unlikely.		

The Applicant provides a fully revised ERA according to EMA guideline 2024 including the available study reports validated in 2021 (EMEA/H/C/5333/IB/07).

All study reports were valid and plausible. The PEC calculation was adapted for the requirements in the revised guideline. For surface water, groundwater and sewage treatment no risks are identified. Inclisiran is vP but not PBT or vPvB. Assessment for soil and a calculation for secondary poisoning is not needed. The risk for the sediment compartment was identified by the Assessor in Tier A by strictly following the guideline approach. However, the Applicant provided sufficient evidence to underpin the assumption that the proposed test designs are not suitable to this large molecule. Therefore, based on consideration of all fate and sediment effect tests provided, it is concluded that a risk to sediment organisms seems unlikely until new approaches are available for these kinds of molecules.

2.2.2. Discussion and conclusion on the non-clinical aspects

Environmental Risk Assessment

Considering the above data from Phase I and Phase II, inclisiran is not expected to pose a risk to the environment. Considering the above data of the definitive hazard assessment, inclisiran is not a PBT or vPvB substance.

2.3. Clinical aspects

2.3.1. Introduction

GCP

According to the MAH the Clinical trials were performed in accordance with GCP.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

• Tabular overview of clinical studies

Table 3: Summary of clinical studies

Key features	ORION-16	ORION-13
Controlled study	Yes (Part 1 / Year 1)	Yes (Part 1 / Year 1)
Phase	III	III
Brief study title	To evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with HeFH and elevated LDL-cholesterol	To evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with HoFH and elevated LDL-cholesterol
Study design	Two-part (1-year double-blind inclisiran versus placebo (2:1) Part 1 / Year 1 followed by 1 year open-label inclisiran Part 2 / Year 2) randomised multicenter study	Two-part (1-year double-blind inclisiran versus placebo (2:1) Part 1 / Year 1 followed by 1 year open-label inclisiran Part 2 / Year 2) randomised multicenter study
Population	HeFH On maximally tolerated dose of statin (Investigator's discretion) and with LDL-C >130 mg/dL	HoFH On maximally tolerated dose of statin (Investigator's discretion) and with LDL-C >130 mg/dL
Age range	12 to <18 years	12 to <18 years
Treatment /Treatment duration	Inclisiran sodium 300 mg / Placebo (Part 1 / Year 1) Inclisiran sodium 300 mg (Part 2 / Year 2)	Inclisiran sodium 300 mg / Placebo (Part 1 / Year 1) Inclisiran sodium 300 mg (Part 2 / Year 2)
PK Sampling	Day 1 (first dose): pre-dose (prior to injection), 4 and 24 hours, post-dose (Part 1 / Year 1)	Day 1 (first dose): pre-dose (prior to injection), 4 and 24 hours, post-dose (Part 1 / Year 1)
ADA Sampling	Day 1 (first dose): pre-dose (prior to injection) and 4 hours post-dose, Day 150 and Day 330 (Part 1 / Year 1) Day 510 and Day 720 (Part 2 / Year 2)	Day 1 (first dose): pre-dose (prior to injection) and 4 hours post-dose, Day 150 and Day 330 (Part 1 / Year 1) Day 510 and Day 720 (Part 2 / Year 2)

Heterozygous Familial Hypercholesterolemia (HeFH), Homozygous familial hypercholesterolemia (HoFH)
Source: [ORION-16], [ORION-13]

2.3.2. Pharmacology

2.3.2.1. Methods

Bioanalytical methods

The bioanalytical methods used in the ORION-16 and ORION-13 inclisiran clinical studies are listed in the table below.

For both studies, analysis of inclisiran (KJX839) concentrations in human plasma was conducted at LabCorp Early Development Laboratories Inc. (3301 Kinsman Boulevard, Madison, Wisconsin 53704, USA). Analysis of inclisiran anti-drug antibody (ADA) in human serum was conducted at Charles River Laboratories Montreal ULC (Senneville Site, 22022 Transcanadienne, Senneville, QC H9X 3R3, Canada).

Table 4: Summary of bioanalytical methods used in inclisiran clinical studies ORION-13 and ORION-16

Analyte	Matrix	LLOQ (ng/mL)	Method validation report	BA laboratory	Study	BA data report
KJX839	Plasma	10 ^a	DMPK R2000084-pk DMPK R2000084-pk-01	LabCorp	ORION-16	DMPK RCKJX839C1230 1-pk
KJX839	Plasma	10 ^a	DMPK R2000084-pk DMPK R2000084-pk-01	LabCorp	ORION-13	DMPK RCKJX839C1230 2-pk
Anti-KJX839 antibodies	Serum	600 ^b	DMPK R2100159-ig-01	CRL ^c	ORION-16	DMPK RCKJX839C1230 1-ig
Anti-KJX839 antibodies	Serum	600 ^b	DMPK R2100159-ig-01	CRL ^c	ORION-13	DMPK RCKJX839C1230 2-ig

a: LLOQ = lower limit of quantification

b: LPC (Low Positive Control)

c: CRL (Charles River Laboratories)

Source: [DMPK R2000084-pk], [DMPK R2000084-pk-01], [DMPK R2100159-ig-01]

Pharmacokinetics

Determination of inclisiran (KJX839) in human K₂EDTA plasma

Inclisiran (also known as KJX839) was quantified from K₂EDTA human plasma using the test items A-120190 (antisense strand of KJX839) and A-122088 (sense strand of KJX839) following solid phase extraction (SPE) by means of a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with internal standard ALN-60519 (mixture of A-122230 sense strand (IS for A-120190) and A-122227 antisense strand (IS for A-122088)) across a validated concentration range of 10.0 ng/mL and 10000 ng/mL using 100 µL of plasma (analytical method code INCLHPP).

Pre-study method validation

Method validation report [DMPK R2000084-pk](#) (Labcorp Study No. 8442942), dated 25 Aug 2022 and amendment No.1 [DMPK R2000084-pk-01](#), dated 19 Oct 2022, reporting additional long-term stability were submitted as part of sequence 0061 supporting the variation.

Bioanalytical Test Site: Labcorp Early Development Laboratories Inc. 3301 Kinsman Boulevard, Madison, Wisconsin 53704, USA

GLP: No formal claim of compliance with GLP regulations was made, However, it was stated that all validation activities were conducted following the Principles of GLP. It was stated that the validation was performed in compliance with Labcorp Policies and SOPs.

Quality Assurance: Quality Assurance statement was included indicating that the method validation was subject to QA oversight as per QA SOPs.

Duration of analytical data acquisition: 01-Dec-2020 to 09-Aug-2022 (DMPK R2000084-pk) and 19-Aug-2022 and 01-Sep-2022 (DMPK R2000084-pk-01).

Analytical method: INCLHPP (-MAD)

Reference standards: lots, purity and expiry/re-test dates were specified and CoAs provided. Stock solutions used during the method validation were stated to have been prepared prior to the expiration of the reference standards and subsequently used within established stability (142 days)

Instrumental conditions

Robotic system Nimbus96

LC system Pumps: Shimadzu, Nexera, 30 Series

LC conditions ACQUITY UPLC BEH C18 Column, 130Å, 1.7 µm, (2.1 mm X 50 mm), column temperature 70°C, Gradient elution (Mobile Phase A - Water: Diisopropylamine: HFIP (100:0.14:0.264) {Fresh}, Mobile Phase B -Methanol: Diisopropylamine: HFIP (100:0.14:0.264) {Fresh}), flow rate 0.850 mL/min, injection volume 10 µL, column pressure 500 bars, total run time 2 seconds, Retention times ~1.25 min (A-120190). 1.31 (A-122088), 1.39 min (ALN-60519 anti-sense strand), and 1.13 (ALN-60519 sense strand)

Mass spectrometer Thermo Q Exactive Hybrid Quadrupole-Orbitrap

MS conditions HESI-II negative ion mode

Quantitation Pairing A-120190/ISTD1 (A-122227),
A-122088/ISTD2 (A-122230)

Trace Parameters

Compound Name	Base Peak Mass (m/z)	Retention Time (min ± 30%)
A-120190	1923.0552, 1923.3047, 1923.5554, 1923.8079, 1924.0557, 2564.3993, 2564.7334, 2565.0673, 2565.4003, 2565.7345	1.25
ISTD1 (A-122227)	1889.2579, 1889.5084, 1889.7595, 1890.0103, 1890.2600, 2519.3331, 2519.6680, 2520.0026, 2520.3369, 2520.6703	1.13
A-122088	2158.7431, 2158.9942, 2159.2449, 2159.4954, 2159.7456, 2878.6496, 2878.9830, 2879.3170, 2879.6530, 2879.9865	1.31
ISTD2 (A-122230)	2182.5149, 2182.7667, 2183.0172, 2183.2680, 2183.5179, 2910.3401, 2910.6746, 2911.0089, 2911.3418, 2911.6759	1.39

Data processing

Electronic raw data repository/archive

Calibration model $y = ax^2 + bx + c$, quadratic regression

Weighting factors $1/x^2$

y Peak area ratio of the analyte to the internal standard

x Concentration of the analyte in C standards

LLOQ / ULOQ: 10.0 ng/mL and 10000 ng/mL using 100 µL of plasma

Pre-study validation results for quantification of KJX839 in K2EDTA human plasma (DMPK R2000084-pk; amendment No.1 DMPK R2000084-pk-01 for long-term stability):

Validation item	Acceptance Criteria	Parameters / Results
<i>Selectivity</i>	Interference of A-120190 $\leq 20.0\%$ of analytical response at the LLOQ	fulfilled
	Interference of A-122088 $\leq 20.0\%$ of analytical response at the LLOQ	fulfilled
	Interference of ALN-60519 $\leq 5.0\%$ of analytical response at the working concentration	fulfilled
<i>Matrix effect</i>	Mean matrix factor of A-120190 of the nominal concentration and %RSD $\leq 20.0\%$	fulfilled
	Mean matrix factor of A-122088 of the nominal concentration and %RSD $\leq 20.0\%$	fulfilled
	At least six individual matrices calculated individual concentration values within $\pm 20.0\%$ bias of the nominal concentration	fulfilled
<i>Matrix Factor</i>	Mean normalised matrix factors of A-120190 at two concentration levels	1.13 & 1.01
	Precision of $\leq 15.0\%$	fulfilled
	Mean normalised matrix factors of A-122088 at two concentration levels	1.13 & 1.06
	Precision of $\leq 15.0\%$	fulfilled
<i>Recovery</i>	Mean recovery for A-120190 at 3 concentration levels Range of recovery for A-120190	76.3 & 81.2% 73.6 - 106.2% & 79.2 - 84.6%
	Precision of $\leq 15.0\%$ at each concentration level	fulfilled
	Mean recovery for A-122088 at 3 concentration levels Range of recovery for A-122088	78.7% 74.9- 93.6%
	Precision of $\leq 15.0\%$ at each concentration level	fulfilled
	ALN-60519 normalised recovery of A-120190 at 3 concentration levels	87.3 & 81.0%
	Range of recovery for ALN-60519	80.0 - 99.5 & 78.9 - 82.6%
	Precision of $\leq 15.0\%$	fulfilled
	ALN-60519 normalised recovery of A-122088 at 3 concentration levels	76.8%
	Range of recovery for ALN-60519	73.8 - 98.5%
	Precision of $\leq 15.0\%$	fulfilled
<i>Carryover</i>	Response after injection of blank sample following injection of the ULOQ $\leq 20.0\%$ of the response observed for the LLOQ for A-120190	fulfilled
	Response after injection of blank sample following injection of the ULOQ $\leq 20.0\%$ of the response observed for the LLOQ for A-122088	fulfilled
	Response after injection of blank sample following injection of the ALN-60519 at the working concentration $\leq 5.0\%$ of the ALN-60519 response observed at the working concentration	fulfilled
<i>Calibration</i>	Deviation of $\pm 15.0\%$ ($\pm 20.0\%$ at the LLOQ) for 75.0% of the C standards and 50.0% at each C standard level from the nominal values at a minimum of 6 different levels	fulfilled

Validation item	Acceptance Criteria	Parameters / Results
<i>Intra-day accuracy and precision</i>	Mean bias within $\pm 15.0\%$ ($\pm 20\%$ at the LLOQ) of the nominal values Precision of $\leq 15.0\%$ ($\leq 20.0\%$ at the LLOQ)	fulfilled fulfilled
<i>Inter-day accuracy and precision</i>	Mean bias within $\pm 15.0\%$ ($\pm 20.0\%$ at LLOQ) of the nominal values Precision of $\leq 15.0\%$ ($\leq 20.0\%$ at the LLOQ)	fulfilled fulfilled
<i>Dilutions</i>	Bias within $\pm 15.0\%$ of the nominal concentration for samples Precision $\leq 15.0\%$	fulfilled fulfilled
<i>Haemolysis</i>	Mean bias within $\pm 15.0\%$ of the nominal values Precision of $\leq 15.0\%$	fulfilled fulfilled
<i>Hyperlipidaemia</i>	Mean bias within $\pm 15.0\%$ of the nominal values Precision of $\leq 15.0\%$	fulfilled fulfilled
<i>Stability of A-120190</i>	<u>Matrix stability solutions (bench-top):</u> Mean bias $\pm 10.0\%$ and mean precision $\leq 15.0\%$ At room temperature Number of hours <u>Internal Standard Working solutions (bench-top):</u> Mean bias $\pm 10.0\%$ and mean precision $\leq 15.0\%$ Storage temperature Number of hours <u>Freeze-thaw stability of spiked human plasma:</u> Mean bias $\pm 15.0\%$ of the nominal values Cycles: Thaw conditions Storage temperature <u>Long-term stability in spiked human plasma:</u> Mean bias $\pm 15.0\%$ of the nominal values Storage temperature Number days <u>Processed Sample Viability:</u> Precision (RSD%) values must be $\leq 15.0\%$ and mean concentration values must be within $\pm 15.0\%$ bias of the nominal concentration for each QC sample concentration. Calibration standards must have back calculated values within the range $\pm 15.0\%$ of nominal ($\pm 20.0\%$ at the LLOQ). No more than 25% of the calibration standards may be excluded from the calibration curve and a minimum of six acceptable concentrations must be included. Storage temperature Number of hours <u>Processed-Sample Stability:</u> Mean bias $\pm 15.0\%$ and mean precision $\leq 15.0\%$ Storage temperature Number of hours <u>Stability in Blood:</u> Stability is considered acceptable if the concentration or the mean peak area ratio of the stored sample is within $\pm 15.0\%$ of the T0 sample. Storage temperature Number of hours Storage temperature Number of hours	fulfilled 12 fulfilled Room temperature 24 fulfilled 5 Room temperature -10 to -30°C -60 to -80°C fulfilled fulfilled -10 to -30°C -60 to -80°C 623 fulfilled fulfilled 2-8°C 155 fulfilled 2-8°C 121 fulfilled Room temperature 2 Wet ice 2

Validation item	Acceptance Criteria	Parameters / Results
Stability of A-122088	<u>Matrix stability solutions (bench-top):</u> Mean bias $\pm 10.0\%$ and mean precision $\leq 15.0\%$ At room temperature Number of hours	fulfilled 24
	<u>Internal Standard Working solutions (bench-top):</u> Mean bias $\pm 10.0\%$ and mean precision $\leq 15.0\%$ Storage temperature Number of hours	fulfilled Room temperature 24
	<u>Freeze-thaw stability of spiked human plasma:</u> Mean bias $\pm 15.0\%$ of the nominal values Cycles: Thaw conditions Storage temperature	fulfilled 5 Room temperature -10 to -30°C -60 to -80°C
	<u>Long-term stability in spiked human plasma:</u> Mean bias $\pm 15.0\%$ of the nominal values Storage temperature Number days	fulfilled fulfilled -10 to -30°C -60 to -80°C 636
	<u>Processed Sample Viability:</u> Precision (RSD%) values must be $\leq 15.0\%$ and mean concentration values must be within $\pm 15.0\%$ bias of the nominal concentration for each QC sample concentration. Calibration standards must have back calculated values within the range $\pm 15.0\%$ of nominal ($\pm 20.0\%$ at the LLOQ). No more than 25% of the calibration standards may be excluded from the calibration curve and a minimum of six acceptable concentrations must be included. Storage temperature Number of hours	fulfilled 2-8°C 155
	<u>Processed-Sample Stability:</u> Mean bias $\pm 15.0\%$ and mean precision $\leq 15.0\%$ Storage temperature Number of hours	fulfilled 2-8°C 121
	<u>Stability in Blood:</u> Stability is considered acceptable if the concentration or the mean peak area ratio of the stored sample is within $\pm 15.0\%$ of the T0 sample. Storage temperature Number of hours Storage temperature Number of hours	fulfilled Room temperature 2 Wet ice 2

Source: [DMPK R2000084-pk] and [DMPK R2000084-pk-01]

LabCorp Early Development Laboratories Inc. validated a bioanalytical method (INCLHPP (-MAD)) for the quantitative detection of A-120190 (antisense strand) and A- 122088 (sense strand) of the KJX839 duplex using internal standard ALN-60519. No statement on compliance with regulatory guidelines was made; however, acceptance criteria were specified and appear to be overall compliant with the Guideline on bioanalytical method validation [EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**] applicable at the time of conduct.

Using single stranded analyte reference standards (A-120190 and A-122088), calibration standards (n=8) were prepared at 10 ng/mL, 20 ng/mL, 80 ng/mL, 300 ng/mL, 1000 ng/mL, 4500 ng/mL, 9000 ng/mL and 10000 ng/mL) and QC samples at LLOQ QC: 10.0 ng/mL, Low QC: 30.0 ng/mL, Low-medium QC: 400 ng/mL, Mid-QC: 5,000 ng/mL, HQC: 8,000 ng/mL, and DQC: 100,000 ng/mL (diluted by factor of 100x with blank plasma).

Using single stranded analyte reference standards (A-120190 and A-122088), calibration standards (n=8) were prepared at 10 ng/mL, 20 ng/mL, 80 ng/mL, 300 ng/mL, 1000 ng/mL, 4500 ng/mL, 9000 ng/mL and 10000 ng/mL) and QC samples at LLOQ QC: 10.0 ng/mL, Low QC: 30.0 ng/mL, Low-medium QC: 400 ng/mL, Mid-QC: 5,000 ng/mL, HQC: 8,000 ng/mL, and DQC: 100,000 ng/mL (diluted by factor of 100x with blank plasma).

Validation met specified acceptance criteria for selectivity, intra-day and inter-day accuracy and precision, effect of haemolysis and hyperlipidaemia, matrix effect and recovery. Somewhat conflicting information was given regarding carryover. According to the "summary of method validation" included in the report, validation of carryover fulfilled acceptance criteria; however, validation of carryover is not listed in the validation run summary table 5-1 of the report, and according to the Method Specific Requirements in report amendment 1 "significant column carryover was occasionally observed with extracted batches. To lower the carryover, the post elution gradient was modified during the validation. Still, the recommendation was issued to use special sample ordering and extra carryover blanks as a precaution, and to ensure that extracted samples are completely dry prior to reconstitution to help minimise carryover".

Extended long-term stability in matrix was reported in report amendment 1 [DMPK-R2000084-pk-01] to be 623 Days for A-120190 (antisense strand) and 636 Days for A-122088 (sense strand). Of note, the A-122088 run acceptance QCs in runs 15-17 trended or failed due to low %bias for the LMQC and LQC levels and the LQC long term stability QCs consistently failed due to low %bias in these same runs. An evaluation was started and a preparation issue for the A-122088 analyte was suspected as possible cause of the stability failures. New stock and intermediate solutions were prepared and the long-term stability assessment was repeated in run 18 where it met acceptance for A-122088.

Overall, the method was concluded to be suitable for the determination of A-120190 and A-122088 concentrations in human K2EDTA plasma over the range of inclisiran concentrations of 10.0 (LLOQ) to 10,000 (ULOQ) ng/mL using 100 µL of human plasma.

Method description INCLHPP, version 6, effective date 22 Sep 2022 was included in Appendix C of amendment No.1 DMPK R2000084-pk-01). Review of chromatography is mentioned for several runs in the report. It was stated regarding integration parameters that "a small amount of crosstalk is observed between compounds even with strict m/z mass tolerance criteria (< 10 ppm). The interferences peaks are baseline separated since the internal standards are analogues, but careful attention to integration parameters is still required to exclude the nearby peak; adjusting the baseline window to < 20 was typically sufficient during method development". In response to second response for a supplementary information (RSI), relevant Labcorp Policies and SOPs were provided and the applicant confirmed that no manual (re-)integration occurred. However, based on the Applicant's response, it was not possible to fully verify correct peak integration claimed by the Applicant. Possible implications: selectivity of the method, matrix effect, carryover; potentially impacting the validity of pharmacokinetic data.

Furthermore, the bioanalytical method (INCLHPP) and the contract facility (Labcorp) used in the ORION-16 and ORION-13 studies differ from the method (LC-TOF-MS) and contract facility (QPS LLC, Delaware Technology Park, 3 Innovation Way, Suite 240, Newark, DE 19711 (actual testing facility QPS LCC, 110 Executive Drive, Suite 7 Newark, DE 19702, USA)) used in the earlier PK studies supporting the original approval. According to ICH M10, cross validation is required to demonstrate how the reported data are related when multiple bioanalytical methods and/or multiple bioanalytical laboratories are involved. Since the Applicant compares the inclisiran plasma concentration data of the ORION-16/ORION-13 studies with the earlier data (i.e. with data reported in PK Report ALN-PCSSC-001-Table 15.1.1.1.5) and additionally combines them in a population PK analysis for inclisiran (report KJX839C Population PK report), cross validation data is necessary in support. In response to second RSI, the applicant clarified that there is no direct cross-validation comparing LabCorp Madison single

strand method INCLHPP, validated in [DMPK R2000084-pk], [DMPK R2000084-pk-01] and applied in the ORION-16 and ORION-13 studies, and original QPS duplex assay method 319-1418. Instead, method comparison is to rely on a chain of separate cross-validations, first DMPK R2200200-pk, cross-validating original QPS duplex assay method 319-1418 with LabCorp Madison duplex assay 839DHPP, and second DMPK R2200365-pk, cross-validating LabCorp Madison duplex assay 839DHPP with LabCorp Madison single strand method INCLHPP. In this indirect comparison, LabCorp Madison duplex assay 839DHPP that has not yet been applied to study sample analysis has to serve as “bridge”.

According to weighted Deming regression, LabCorp Madison duplex assay results are generally higher than those at QPS with difference increasing with concentration. Bland-Altman Plot of mean percentage difference revealed that while overall mean is higher, Labcorp Madison duplex results are lower than those for QPS in the lower concentration range (i.e. at LQC (30ng/mL) and LMQC (400ng/mL)) and higher in the higher concentration range (i.e. at MQC (5000ng/mL) and HQC (8000ng/mL)).

Weighted Deming regression analysis of intra-lab cross-validation comparing LabCorp Madison duplex assay method 839DHPP with LabCorp Madison single strand assay INCLHPP also submitted in response to RSI (KJX839-Statistical Memo) revealed proportional and fixed bias for A-120190 (the predicted Value 2 INCLHPP Converted Duplex (Y) for a given Value 1 839DHPP (X) is: $Y = (1.132 * X) - 6.818$), but no evidence of proportional and fixed bias for A-122088 and the duplex resp. converted duplex, respectively. While the latter may be considered reassuring, in absence of a direct cross-validation, a stronger bias for the Labcorp Madison single strand assay INCLHPP than detected for the Labcorp Madison duplex assay 839DHPP vs. the original QPS duplex assay 319-1418 cannot be ruled out.

However, given that most samples reported in the ORION-16 and -13 studies had a measured concentration below 2000 ng/mL, the impact on PK data was considered acceptable.

Study sample analysis and in-study validation in the ORION-16 study (Bioanalytical report DMPK RCKJX839C12301-pk)

As part of the documentation relating to the ORION-16 study and submitted already with sequence 0058 in support of the P46 PAM, bioanalytical report ([DMPK RCKJX839C12301-pk](#)), entitled “Determination of A-120190 and A-122088 in human plasma”, dated 28 Mar 2024 and issued by CRO Labcorp Early Development Laboratories Inc. (CRO study number 8451416) was submitted.

Bioanalytical Test Site: Labcorp Early Development Laboratories Inc. 3301 Kinsman Boulevard, Madison, Wisconsin 53704, USA

GCP/GLP: As part of a clinical study, it was stated that the work was conducted in accordance with ICH E6 (R2): Good Clinical Practice, CPMP/ICH/135/95 (June 2017). No formal claim of compliance with GLP regulations was made, although facility is subject to the GLP monitoring programs of US FDA and following laboratory procedures commensurate with International Standards of GLP. It was stated that the bioanalytical study was performed in compliance with the agreed upon sample analysis analytical plan, Labcorp Policies and SOPs.

Quality Assurance: A Quality Assurance statement was included indicating that the bioanalytical phase was subject to QA oversight as per QA SOPs.

Monitoring: A monitoring report was not submitted. It was stated that the report was reviewed by Sponsor Representative C. Hagman (Bioanalytical Monitor)

Unblinding for analytical purposes: For the double-blind, randomised, placebo-controlled part of study, only placebo is controlled. All samples received were dosed with inclisiran,

except for the placebo samples which were received and not analysed. The bioanalytical lab and bioanalytical study monitor were not blinded to the inclisiran data.

Analyte: A-120190 (antisense strand of KJX839) and A-122088 (sense strand of KJX839)

Internal standard ALN-60519

CoAs Based on the CoAs provided and the information regarding extension of expiration dates in the bioanalytical report, standards, stock solutions, CC and QC samples were used within established stability.

Instrumental conditions see pre-study validation

Data processing

Calibration model, weighting factors, LLOQ, ULOQ see pre-study validation

Sampling schedule: Day 1 (Baseline and 1st Treatment) 0 hour/Pre-dose (immediately before the first administration of study drug) (Sample ID 101), 4 hours post the first dose (Sample ID 102), 24 hours post the first dose (Sample ID 103)

No. of PK samples: 251 samples received; 144 samples analysed, 55 placebos not analysed, 52 backup samples received.

Sample receipt dates Between 21-May-2021 and 06-Feb-2023.

Duration of analytical data acquisition: 17 Dec 2021 to 16 Feb 2023

Storage conditions -60 to -80°C

No. of accepted analytical runs: 5 (run 2 rejected for A-120190 (LQC failure) & reinjected in run 3)

Stability: It was stated that samples were analysed within established stability: The total duration of sample storage was 729 days (from first sample collection on 17 Feb 2021 to the last sample analysed on 16 Feb 2023). However, the study samples were analysed in multiple subsets which resulted in the analysis of all samples within 303 days of collection which is within established long-term stability at -60 to -80°C for 623 days (A-120190) and 636 days (A-122088) that was reported in [DMPK R2000084-pk-01](#). This reflects all data, including repeat analysis and incurred sample reanalysis evaluations.

In-study validation

8 CC standards (in duplicate) Bias had to be within the range of $\pm 20\%$ at the LLOQ and $\pm 15\%$ at the other concentration levels.

At least 75.0% of the calibration standards must be included in the calibration curve, and at least six non-zero calibration standards must remain in a calibration curve for it to be acceptable

A-120190: Calibration standards met acceptance criteria in accepted runs 1, 3, 4 and 5

A-122088: Calibration standards met acceptance criteria in accepted runs 1, 2, 4 and 5

A-120190: Between-run precision (RSD (%)) ranged from 1.7 to 7.2%
Between-run accuracy (%Bias) ranged from -7.9 to 9.6%

A-122088: Between-run precision (RSD (%)) ranged from 1.7 to 7.2%
Between-run accuracy (%Bias) ranged from -7.9 to 9.6%

4 QC samples (in duplicate) Bias had to be within the range of $\pm 15\%$ for at least 2/3 of the individual QC samples in each run values. A minimum of 3 QC levels with at least 50% of the results at each level fulfilling the acceptance criteria.

A-120190: Between-run precision (RSD (%)) ranged from 4.2 to 10.8%
Between-run accuracy (%Bias) ranged from -10 to 3.2%

A-122088: Between-run precision (RSD (%)) ranged from 3.6 to 12.5%
Between-run accuracy (%Bias) ranged from -6.3 to 14.2%

ISR: 24 incurred samples were identified for ISR evaluation. 3 samples had insufficient sample for reanalysis so that 21 samples were reanalysed with reportable results.

A-120190 results of all 21 samples (100%) met acceptance criteria (%Difference $\leq 16.0\%$).
A-122088 results of 20 samples (95%) met acceptance criteria (%Difference $\leq 16.2\%$).

Reanalysis of study samples: 1 sample was reanalysed for A-122088 due to interference peak in blanks and sample concentration being below 2nd Standard. Original result was found valid and reported.

Reinjection of analytical runs Run 2 did not meet acceptance criteria for A-120190 due to divergence observed in the standard curves and failure of LQCs due to low bias. The run was reinjected in Run 3 using fresh mobile phase and injected on a different instrument and met acceptance criteria. It was concluded that there was no impact on the integrity of the study.

Deviations There were no method or sample analysis analytical plan deviations reported. A facility power outage was reported as deviation allowing unit Probe 116 (-70°C) in which sample delivery group SDG-03-Nov-2021-57 was stored to be out of range (warmer than -50°C) for 3 hours 18 minutes and reaching a maximum recorded temperature of -43.14°C. It was concluded that there was no impact to the study data since the INCLHPP assay has -20°C long-term frozen matrix stability established for at least 623 days for A-120190 and 636 days for A-122088.

KJX839 Conversion

The concentration of KJX839 duplex was determined from the measured A-120190 concentration using an equation. To obtain the duplex concentration all measured A-120190 concentrations were multiplied by the conversion factor.

The concentration of KJX839 duplex was determined from the measured A-122088 using an equation. To obtain the duplex concentration the measured A-122088 concentration was multiplied by the conversion factor.

KJX839 duplex concentrations were reported based on A-120190 (antisense strand) / A-122088 (sense strand) ratio. For any ratio which cannot be calculated, such as antisense or sense is BQL, the concentration of KJX839 is reported as BQL.

No statement on compliance with regulatory guidelines, i.e. Guideline on bioanalytical method validation [EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**] and/or ICH M10 effective date 21/01/2023 was made; however, run acceptance criteria were specified and appear to be overall

compliant with regulatory recommendations. The applicant clarified with the responses to the RSI, that no manual (re) integration took place in the ORION-16 study.

According to the ORION-16 CSR, the most common protocol deviations (reported in 3/141 (2.1%) participants each) were in the category "other", specifically PK sample(s) being taken either before a separate consent signature to the main informed consent form was provided (2 participants (2.2%) in the inclisiran group and 1 participant (2.1%) in the placebo group) or without a separate informed consent (3 participants (3.2%) in the inclisiran group); samples without consent were not used.

In response to a RSI regarding sample disposition, the applicant provided an amended bioanalytical report for the ORION-16 study to correctly reflect the number of samples analysed vs. received. Sample disposition was further clarified in response to a second RSI, explaining the different number of reported sample concentrations between the amended bioanalytical report, the ORION-16 CSR Listing 16.2.6-1.5i and the ORION-16 CSR tables Tables 11-10 and 14.3-9.1i.

As part of concomitant lipid modifying therapies as well as for treatment of AEs, concomitant medications were administered to study participants (see *i.a.* ORION-16 CSR Table 14.3-2.6i). In response to an RSI, the applicant clarified that assay interference by concomitant medication was neither validated nor considered necessary based on the signal (i.e., for inclisiran detection) used for inclisiran being clearly different from any low molecular weight treatment.

According to the run summary provided in Table 5-1 of the bioanalytical report, in run 2, LQCs for analyte A-120190 did not meet acceptance criteria and the run was reinjected in run 3 for quantification of A-120190. The applicant clarified in response to a RSI that the failure was due to a technical cause. According to ICH M10 in cases where the failure is due to an assignable technical cause, samples may be reinjected if reinjection reproducibility has been demonstrated (sufficient on injector stability provided). In response to second RSI, the Applicant substantiated successful validation of reinjection reproducibility.

Of note, because of carryover observed during the pre-study method validation, a recommendation was issued in the method validation report to use special sample ordering and extra carryover blanks as a precaution. In study sample analysis, substantial carryover was reported in all five analytical runs, and substantial interference was detectable in run blanks. According to the report, in each run there were also blanks with acceptable interference. The Applicant's concluded and confirmed this once more in response to an RSI that no sample data was impacted by >5% due to the observed carryover.

Study sample analysis and in-study validation in the ORION-13 study (Bioanalytical report DMPK RCKJX839C12302-pk)

As part of the documentation relating to the ORION-13 study, bioanalytical report ([DMPK RCKJX839C12302-pk](#)), entitled "Determination of A-120190 and A-122088 in human plasma", dated 28 Mar 2024 and issued by CRO Labcorp Early Development Laboratories Inc. was submitted (LabCorp study number 8451542).

Bioanalytical Test Site: Labcorp Early Development Laboratories Inc. 3301 Kinsman Boulevard, Madison, Wisconsin 53704, USA

GCP/GLP: As part of a clinical study, it was stated that the work was conducted in accordance with ICH E6 (R2): Good Clinical Practice, CPMP/ICH/135/95 (June 2017). No formal claim of compliance with GLP regulations was made, although facility is subject to the GLP monitoring programs of US FDA and following laboratory procedures commensurate with International Standards of GLP. It was stated that the bioanalytical study was performed in compliance with the

agreed upon sample analysis analytical plan and with Labcorp Policies and SOPs.

Quality Assurance: A Quality Assurance statement was included indicating that the bioanalytical phase was subject to QA oversight as per QA SOPs.

Monitoring: A monitoring report was not submitted. It was stated that the report was reviewed by Sponsor Representative C. Hagman (Bioanalytical Monitor)

Unblinding for analytical purposes: For the double-blind, randomised, placebo-controlled part of study, only placebo is controlled. All samples received were dosed with inclisiran, except for the placebo samples which were received and not analysed. The bioanalytical lab and bioanalytical study monitor were not blinded to the inclisiran data.

Analyte: A-120190 (antisense strand of KJX839) and A-122088 (sense strand of KJX839)

Internal standard ALN-60519 ()

CoAs Based on the CoAs provided and the information regarding extension of expiration date in the bioanalytical report, standards, stock solutions, CC and QC samples were used within established stability.

Instrumental conditions see pre-study validation

Data processing

Calibration model, weighting factors, LLOQ, ULOQ see pre-study validation

Sampling schedule: Day 1 (Baseline and 1st Treatment) 0 hour/Pre-dose (immediately before the first administration of study drug) (Sample ID 101), 4 hours post the first dose (Sample ID 102), 24 hours post the first dose (Sample ID 103)

No. of PK samples: 38 samples received; 27 samples analysed, 11 placebos not analysed, 0 backup samples received

Sample receipt dates Between 24-Jun-2021 and 26-Jan-2023.

Duration of analytical data acquisition: 27-Jun-2022 to 20-Feb-2023

Storage conditions -60 to -80°C

No. of accepted analytical runs: 2 (run 2 rejected for A-120190 (QC failure) and rejected for A-122088 (Calibration standards failure)). Due to excessive peak tailing and divergent curves for both analytes, Run 2 was reinjected in Run 3 on a system with demonstrated good peak shape and consistent response

Stability: It was stated that samples were analysed within established stability: The total duration of sample storage was 700 days (from first sample collection on 22 March 2021 to the last sample analysed on 20 February 2023). However, the study samples were analysed in multiple subsets

which resulted in the analysis of all samples within 462 days of collection which is within established long-term stability at -60 to -80°C for 623 days (A-120190) and 636 days (A-122088) that was reported in [DMPK R2000084-pk-01](#).

In-study validation

8 CC standards (in duplicate) Bias had to be within the range of $\pm 20\%$ at the LLOQ and $\pm 15\%$ at the other concentration levels.

At least 75.0% of the calibration standards must be included in the calibration curve, and at least six non-zero calibration standards must remain in a calibration curve for it to be acceptable

A-120190: Calibration standards met acceptance criteria in accepted runs 1 and 3

A-122088: Calibration standards met acceptance criteria in accepted runs 1 and 3

A-120190: Between-run precision (RSD (%)) ranged from 2.7 to 7.8%
Between-run accuracy (%Bias) ranged from -8.6 to 10%

A-122088: Between-run precision (RSD (%)) ranged from 2.8 to 8.6%
Between-run accuracy (%Bias) ranged from -6.4 to 12.4%

4 QC samples (in duplicate) Bias had to be within the range of $\pm 15\%$ for at least 2/3 of the individual QC samples in each run values. A minimum of 3 QC levels with at least 50% of the results at each level fulfilling the acceptance criteria.

A-120190: Between-run precision (RSD (%)) ranged from 3.4 to 6.3%
Between-run accuracy (%Bias) ranged from -11.8 to 1.0%

A-122088: Between-run precision (RSD (%)) ranged from 7.4 to 13.5%
Between-run accuracy (%Bias) ranged from -4.7 to 5.0%

ISR: ISR was not performed since the minimum requirement of 20 samples was not met. Only 15 out of the 27 samples analysed for A-120190 and 16 out of the 27 samples analysed for A-122088 have a measurable concentration

Reanalysis of study samples: There was no reanalysis of study samples reported.

Reinjection of analytical runs Analytical run 2 was rejected as QCs failed acceptance criteria for A-120190 and standards failed acceptance criteria for A-122088. Due to excessive peak tailing and divergent curves for both analytes, Run 2 was reinjected in Run 3 on a system with demonstrated good peak shape and consistent response.

Deviations There were no SOP, policy, method or sample analysis analytical plan deviations reported.

KJX839 Conversion

The concentration of KJX839 duplex was determined from the measured A-120190 concentration using the following equation: To obtain the duplex concentration all measured A-120190 concentrations were multiplied by the conversion factor.

The concentration of KJX839 duplex was determined from the measured A-122088 using the following equation: To obtain the duplex concentration the measured A-122088 concentration was multiplied by the conversion factor

KJX839 duplex concentrations were reported based on A-120190 (antisense strand) / A-122088 (sense strand) ratio.. For any ratio which cannot be calculated, such as antisense or sense is BQL, the concentration of KJX839 is reported as BQL.

Protocol deviations listed in the ORION-13 CSR did not impact on the plasma concentration/PK results as deviations concerned participants in the placebo group. In the bioanalytical report, no deviations were reported.

No statement on compliance with regulatory guidelines, i.e. Guideline on bioanalytical method validation [EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**] and/or ICH M10 effective date 21/01/2023 was made; however, run acceptance criteria were specified and appear to be overall compliant with regulatory recommendations. The applicant clarified with the responses to the RSI, that no manual (re) integration took place in the ORION-13 study.

In response to an RSI regarding sample disposition, the applicant provided an amended bioanalytical report for the ORION-13 study to correctly reflect the number of samples analysed vs. received.

As part of concomitant lipid modifying therapies as well as for treatment of AEs, concomitant medications were administered to study participants (see *i.a.* ORION-13 CSR Table 14.3-2.6i). In response to an RSI, the applicant clarified that assay interference by concomitant medication was neither validated nor considered necessary based on the high-resolution mass spectrometry signal (i.e., m/z ratio for inclisiran detection) used for inclisiran being clearly different from any low molecular weight treatment.

According to the run summary provided in Table 5-1 of the bioanalytical report, in run 2, QCs for analyte A-120190 and calibration standards for analyte A-122088 did not meet acceptance criteria and the run was reinjected in run 3 for quantification of A-120190 and A-122088. The applicant clarified in response to a RSI that the failure was due to a technical cause. According to ICH M10 in cases where the failure is due to an assignable technical cause, samples may be reinjected if reinjection reproducibility has been demonstrated (sufficient on injector stability provided). The Applicant substantiated successful validation of reinjection reproducibility.

Of note, because of carryover observed during the pre-study method validation, a recommendation was issued in the method validation report to use special sample ordering and extra carryover blanks as a precaution. In study sample analysis, substantial carryover was reported in all three analytical runs, and substantial interference was detectable in run blanks. According to the report, there were blanks added prior to the study sample in each run which showed acceptable interference ($\leq 20.0\%$ of the mean response of the acceptable LLOQ calibration standards). It was stated and later confirmed that the review confirmed that the carryover observed did not affect the integrity of the data generated as the contribution from one injection to the next injection was $\leq 5.0\%$ of the peak area of the following sample.

PD biomarkers

No information provided.

Immunogenicity

Detection of anti-inclisiran-reactive IgG/IgM antibodies in normal human serum (anti-drug antibodies [ADA] measurement / immunogenicity assessment)

For ADA measurements, a qualitative enzyme-linked immunosorbent assay (ELISA) for the detection of anti-inclisiran reactive immunoglobulin (Ig)G/IgM antibodies in clinical serum samples was developed

by Charles River Laboratories Montreal ULC Senneville Site and was previously validated under study numbers [3000701](#) and [3001805](#).

The method was designed to detect the presence of ADA in human serum in a tiered approach, containing three components: (1) screening assay, which identifies samples as negative or potential positive; (2) confirmatory assay, which assesses specificity of the samples screened as potential positive; and (3) titration assay, which estimates the titer of ADA for the confirmed positive samples.

Method validation reports [3000701](#) and [3001805](#) were assessed previously during the initial marketing authorisation approval of Leqvio. It was concluded that the performance of the assay to detect ADA towards inclisiran is acceptable and has been adequately validated.

As part of sequence 0061 supporting the current variation, method validation report amendment 1 ([DMPK R2100159-ig-01](#)) (Charles River Laboratories Montreal ULC study number [3002412](#)), dated 12 Apr 2023 was submitted.

Report [DMPK R2100159-ig-01](#) presented results of partial validation, with the study plan (amendment 5), CoAs, analytical procedure (AP.3002412.Ab.05) and method validation summary appended to the report.

The experimental phase start date was 18-May-2022, and the experimental phase completion date was 25-Nov-2022.

A compliance statement was included stating that the validation study was performed in accordance with the OECD Principles of GLP and that there were no deviations from these that affected the overall integrity of the study, the results and conclusions.

For the validated method, human serum samples, ADA present in the human serum samples bound to the The detection of inclisiran-bound human anti-inclisiran IgG and/or IgM antibodies present in the test samples was performed using a goat anti-human IgG + IgM (H+L)-horseradish peroxidase (HRP) conjugated secondary antibody. The HRP metabolised the subsequently added tetramethylbenzidine to generate a chromophore, for which the absorbance at 450 nm (A450nm) was determined using a spectrophotometer. The A450nm of the chromophore correlated with the level of human anti-inclisiran IgG/IgM antibodies present in the human samples.

The positive controls (PC) were (i).

The screening assay sensitivity was defined at 489 ng/mL and the low positive control (LPC) set at 600 ng/mL for screening and confirmatory assay. The screening cut point factor (SCPF) was set at 1.37 and the confirmatory cut point (CCP) at 31.03% as summarised in below table.

Summary of validation results for detection of ADA

Method Id	DMPK R2100159-ig
SCPF	1.37
CCP	31.03%
Titer control range	800 - 3200
MRD	1/50
Sensitivity Screening assay	489 ng/mL
Sensitivity Confirmatory assay	625 ng/mL
LPC	600 ng/mL
HPC	20000 ng/mL
Drug Tolerance	Up to 1 µg/mL of inclisiran at 600 ng/mL of positive control in screening and confirmatory assays
Freeze-thaw stability	Up to 12 cycles
Room temperature stability	Up to 51 hours

Source: [DMPK R2100159-ig-01]

Due to the unavailability of for coating that were used in the validated method [DMPK R2100159-ig-01], the ADA method was modified [DMPK R2100159-ig-01]. In the modified ADA method, a was used as the coating plate and direct coating was applied. The screening assay sensitivity was defined at 226 ng/mL as is summarised in the table below.

Summary of cross-validation results for detection of ADA (modified method)

Method Id	DMPK R2100159-ig-01
Same day direct coating	
SCPF	1.37
CCP	31.03
Titer control range	800 - 3200
MRD	1/50
Sensitivity Screening assay	226 ng/mL
Sensitivity Confirmatory assay	156 ng/mL
LPC	600 ng/mL
HPC	20000 ng/mL
Drug Tolerance	Up to 1 µg/mL of inclisiran at 600 ng/mL of positive control in screening and confirmatory assays
Freeze-thaw stability	Up to 12 cycles
Room temperature stability	Up to 51 hours

Source: [DMPK R2100159-ig-01]

The modified method using the showed comparable results to the previous assay using the in 85% of samples tested in the cross-validation [DMPK R2100159-ig-01]. Hence, it was concluded that the methods were successfully cross-validated.

[DMPK R2100159-ig-01](#) method validation results mostly passed acceptance criteria with some exceptions, i.e. overall, 4.1% of the assays (3 out of 74) failed to meet the assay acceptance criteria during the validation.

Despite the observed assay limitations, the assay (original and modified) were considered overall acceptably validated and suitable for ADA measurement in clinical studies ORION-16 and ORION-13. In Part 1 (double-blind part) in ORION-16 and ORION-13 studies, ADA were detected with the original method based on [DMPK R2100159-ig-01]. Due to the unavailability of the in Part 2 (open labelled part) in ORION-16 and ORION-13 studies, ADA were detected with the method based on [DMPK R2100159-ig-01]. As discussed in the validation report assay limitations, the sensitivity values were lower with the modified assay using same day direct coating than using the original coating conditions and results of cross-validation supported an overall greater sensitivity of the modified assay. While a low false positive rate is desirable, it is false negative results that are unacceptable. Since no positive samples would be missed using the same day coating method as correctly pointed out in the validation report, the overall greater sensitivity of the modified assay may be considered acceptable.

ADA study sample analysis and in-study validation in the ORION-16 study (Bioanalytical report [DMPK RCKJX839C12301-ig](#) [Test site Study No. [3002164](#)])

For the analysis of formation of ADA to inclisiran, whole blood study samples were collected in part 1 on Day 1 prior to study drug (inclisiran or placebo) injection (referred to as Day 1 0h) and 4 hours after injection (referred to as Day 1 +4h), as well as on Day 150 and Day 330. Unscheduled samples and Early Termination (ET) samples collected prior to Day 360 (due to unscheduled visits or early termination/premature discontinuation) were also collected and analysed.

In Part 2 (Year 2), samples for the ADA analysis collected on Day 510 and Day 720.

Whole blood study samples from the ORION-16 Clinical Study No. CKJX839C12301 were processed into serum and recovered serum study samples were shipped to the Test Site on dry ice and were stored at the Test Site in a freezer set to maintain -80°C until the end of the study.

The analytical phase experimental start date was 01-Dec-2022 and the analytical phase experimental completion date was 16-Dec-2024.

According to the report, all human serum samples tested in this study phase were analysed within validated bench-top (BT) and freeze-thaw (F/T) stabilities, unless reported as deviation. The long-term storage of study samples at -80°C is supported by the literature (Boridy, et al. 2019).

Deviations were reported relating to a subset of samples undergoing a documented temperature excursion of unknown duration prior to analysis at the Test Site according to the shipping manifest information. Since the results obtained out of stability were not reported and affected profiles were considered to be adequately interpretable without the data from affected samples, it was concluded that these deviations had no impact on the integrity of the overall study data and were considered to have no impact on the ADA results interpretation.

Sample disposition

A total of 827 samples from 141 subjects were analysed, including 551 samples collected during Part 1 (Year 1) and 273 samples collected during Part 2 (Year 2). For 3 samples (001 Day 330, 002 Day 720 and 003 Day 720), the analysis was considered to have been performed outside of the validated BenchTop stability of the sample and reported as deviation and no result is reported (see deviation above).

From the remaining 824 samples analysed in the screening tier, 112 samples from 53 subjects had a mean A450nm value $\geq$ PSCP (plate-specific cut point) and were determined to be potentially positive (The A450nm values obtained for the study samples varied from 0.044 to 0.189 for those that screened negative and from 0.152 to 0.406 for those that screened potentially positive) and were reanalysed in the confirmatory assay. In the confirmatory assay, 12 out of the 112 reanalysed samples were determined to be positive. All confirmed positive samples were collected from 8 different subjects at two of the visits (Day 510 and Day 720). The total incidence of ADA was 5.7% (8 out of 141 subjects).

Table 5: Study sample ADA results grouped by visit (ORION-16)

	Visit/Time point	No. of samples analysed	No. of samples confirmed positive
Collected during Part 1 (Year 1)	Day 1 (0h)	140	0
	Day 1 (+4h)	134	0
	Day 150	136	0
	Day 330	136	0
	Unscheduled	3	0
	ET	2	0
Collected during Part 2 (Year 2)	Day 510	138	6
	Day 720	135	6
	Visit/Time Point	No. of Subjects Analysed	Incidence of ADA in study ^a (%)
All samples	All timepoints	141	5.7

^a % Study subjects with at least one confirmed positive timepoint = (study subjects with at least one confirmed positive timepoint / total number of study subjects in respective category) x 100.
[Source DMPK RCKJX839C12301-ig, Table 7-1]

The false positive rate (FPR) at the screening level was assessed by considering 140 samples collected from 140 subjects prior to injection on Day 1 (Day 1 0h) as baseline samples. 16 out of these were potentially positive in the screening tier and negative in the confirmatory tier. The FPR at the screening level was 11.4 % which was at the higher end of the expected FPR range of 2 to 11% for study sample

testing (Devanarayan V, 2017). Since a confirmatory assay was in place to discriminate between true and false positive, this was considered acceptable. For subject 004, no baseline sample was analysed.

The 12 study samples tested positive in the confirmatory assay were collected from 8 subjects (005, 006, 007, 008, 009, 010, 011 and 012) and were analysed in the titration tier. The titre values (dilution fold) ranged from < 50 (MRD) to 400. The titer values obtained were ≤ 50 (7 samples, 58.3%), 100 (3 samples, 25.0%) or 400 (2 samples, 16.7%; both collected from subject 006).

Since the baseline (Day 1 0h) samples for all 8 of these subjects were all determined to be negative, it was concluded that the presence of a positive Day 510 and/or Day 720 sample in the ADA profile indicated a treatment-related immunogenicity response. Persistent and transient ADA were assessed using the definitions proposed by Shankar et al (2014).

As per clinical protocol, a dosing visit occurred at Day 360 and subjects in the placebo group would have received their first dose of inclisiran at this visit, potentially explaining the greater prevalence of positive samples collected during Part 2 (Year 2) of the clinical study. Since the Part 2 (Year 2) samples were analysed using the same-day coating method, it should be noted that the same-day coating method has a superior sensitivity to the method used for Part 1 samples (refer to Test Site Study No. 3002412). According to the Applicant, the results obtained for the baseline samples (assessed using the coating method) suggest that both coating methods were able to detect ADA appropriately in the samples.

Study sample analysis has been adequately reported. The confirmatory controls from reported assays met the acceptance criteria. The FPR at the screening level was 11.4 %, considerably higher than desirable (preferably 5%); however, the Applicant's reasoning that a confirmatory assay was in place to discriminate between true and false positive may be considered reassuring. During validation (Test Site Study No. 3002412), drug tolerance was established at $\leq 1 \mu\text{g/mL}$ of inclisiran at the sensitivity low positive control (sLPC) level. Therefore, analysis of any study sample with inclisiran concentrations $> 1 \mu\text{g/mL}$ could have yielded false-negative results. The Applicant pointed out that the drug tolerance is highly dependent upon the affinity of the positive control and may not be representative for all study samples.

ADA study sample analysis and in-study validation in the ORION-13 study (Bioanalytical report [DMPK RCKJX839C12302-ig](#) [Test site Study No. [3002165](#)])

For the analysis of formation of ADA to inclisiran, whole blood study samples were collected in part 1 on Day 1 prior to study drug (inclisiran or placebo) injection (referred to as Day 1 0h) and 4 hours after injection (referred to as Day 1 +4h), as well as on Day 150 and Day 330.

In Part 2 (Year 2), samples for the ADA analysis collected on Day 510 and Day 720 (End of Treatment/Study, EOS).

Whole blood study samples from the ORION-13 Clinical Study No. CKJX839C12302 were processed into serum and recovered serum study samples were shipped to the Test Site on dry ice and were stored at the Test Site in a freezer set to maintain -80°C until the end of the study.

The analytical phase experimental start date was 05-Dec-2022 and the analytical phase experimental completion date was 18-Dec-2024.

According to the report, all human serum samples tested in this study phase were analysed within validated bench-top (BT) and freeze-thaw (F/T) stabilities. The long-term storage of study samples at -80°C is supported by the literature (Boridy, et al. 2019).

Besides minor deviations that were captured in the raw data records and not considered to have impacted the overall integrity of the study phase nor the interpretation of the results and conclusions,

one notable deviation from the Laboratory Phase Plan and one notable deviation from the Analytical Procedure were reported. Firstly, wrong assay plates were used to perform two assays (Prod-13 and Prod-14) contrary to the Laboratory Phase Plan, causing assay failure. As expected from this deviation, Prod-13 and Prod-14 failed to meet the run acceptance criteria due to low signals for the positive controls (sLPC, LPC and HPC) and were rejected. Since the results were not reported, this deviation had no impact on the validity of the study phase sample analysis results.

Secondly, wrong stop solution (1N HCl instead of 2N sulfuric acid) was used in two assays (Prod-17 and Prod-18), contrary to the Analytical Procedure. Since the purpose of the stop solution is to inhibit the activity of the peroxidase enzyme with acid (by increasing the concentration of H⁺), no impact on the assay signals would be expected. Consistent with this expectation, Prod-17 and Prod-18 met the run acceptance criteria for the positive and negative controls comparable to other acceptable assays. Moreover, the A450nm signals from the confirmatory (unspiked) and titration (dilution at MRD) produced by the same two study samples were comparable, regardless of the stop solution used. Based on this assessment, this deviation was considered to have no impact on the validity of the study phase sample analysis results and acceptable results from Prod-17 and Prod-18 were reported.

Sample disposition:

A total of 78 samples from 13 subjects were analysed, including 52 samples collected during Part 1 (Year 1) and 26 samples collected during Part 2 (Year 2).

From the 78 samples analysed in the screening tier, 22 samples from 5 subjects had a mean A450nm value $\geq$ PSCP (plate-specific cut point) and were determined to be potentially positive (The A450nm values obtained for the study samples varied from 0.065 to 0.185 for those that screened negative and from 0.140 to 0.391 for those that screened positive) and were reanalysed in the confirmatory assay.

In the confirmatory assay, 6 out of the 22 reanalysed samples were determined to be positive. All confirmed positive samples were collected from the same subject (001), and this subject was positive at all tested time points (Day 1 0h, Day 1 +4h, Day 150, Day 330, Day 510 and Day 720). While the total incidence of ADA was determined to be 7.7% (1 out of 13 subjects), it was noted that subject 001 displayed pre-existing reactivity since the sample collected prior to the first dose administration (Day 1 0h) was positive.

Table 6: Study sample ADA results grouped by visit (ORION-13)

	Visit/Time point	No. of samples analysed	No. of samples confirmed positive
Collected during Part 1 (Year 1)	Day 1 (0h)	13	1
	Day 1 (+4h)	13	1
	Day 150	13	1
	Day 330	13	1
Collected during Part 2 (Year 2)	Day 510	13	1
	Day 720	13	1
	Visit/Time Point	No. of Subjects Analysed	Incidence of ADA in study ^a (%)
All samples	All timepoints	13	7.7

a % Study subjects with at least one confirmed positive timepoint = (study subjects with at least one confirmed positive timepoint / total number of study subjects in respective category) x 100.

The false positive rate (FPR) at the screening level was assessed by considering 13 samples collected from 13 subjects prior to injection on Day 1 as baseline samples. Each of these baseline samples was analysed using the coating method. From 13 pre-dose baseline samples, 4 were potentially positive in the screening tier and 1 of these 4 was additionally positive in the confirmatory tier (true positive). The FPR at the screening level was determined to be 25.0% (3 confirmed negative samples/12 baseline samples with overall negative status), which was higher than the expected FPR range of 2 to 11% for study sample testing (Devanarayan et al. 2017). Given the low number of samples (13) used for the

calculation, this calculated FPR may not be a reliable estimate of the FPR of the assay for the study population. Moreover, since a confirmatory assay was in place to discriminate between true and false positive, the observed FPR was considered acceptable.

The 6 samples collected from 1 subject that confirmed positive were reanalysed in the titration assay.

For all 6 study samples collected from 1 subject analysed in the titration tier, the titer values (dilution fold) ranged from < 50 (MRD) to 100. Since all of the titer values from post-treatment samples were comparable (within ± 1 two-fold dilution) to the pre-dose sample collected on Day 1, it was concluded that the immunogenicity response displayed by subject 001 was not treatment-related and was likely due to the presence of pre-existing cross-reactive antibodies.

Study sample analysis has been adequately reported. The confirmatory controls from reported assays met the acceptance criteria. The FPR at the screening level was calculated to be 25.0 %, substantially higher than desirable (preferably 5%). As pointed out by the Applicant, this may have been caused by the low number of samples in the calculation. Furthermore, the Applicant's reasoning that a confirmatory assay was in place to discriminate between true and false positive may be considered reassuring. During validation (Test Site Study No. 3002412), drug tolerance was established at ≤ 1 $\mu\text{g/mL}$ of inclisiran at the sensitivity low positive control (sLPC) level. Therefore, analysis of any study sample with inclisiran concentrations > 1 $\mu\text{g/mL}$ could have yielded false-negative results. The Applicant pointed out that the drug tolerance is highly dependent upon the affinity of the positive control and may not be representative for all study samples.

Pharmacokinetic data analysis

The evaluation of inclisiran concentrations was an exploratory endpoint for both the ORION-16 and ORION-13 studies.

Inclisiran PK parameters using noncompartmental analysis were not calculated as only sparse PK sampling was conducted at the Day 1 visit for these studies: i.e., 0 hours (pre-dose -immediately before the first administration of study drug), 4 hours post first dose, and 24 hours post first dose, respectively). Concentrations below the LLOQ were reported as zero and missing data was labelled as such in the Bioanalytical Data Report.

Inclisiran concentration-time data was summarised using descriptive statistics by sampling time point. Summary descriptive statistics included mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV; arithmetic and geometric), median, minimum, and maximum and including the frequency (n, %) of concentrations below the LLOQ (reported as zero). The PK analysis set was used for this analysis. In ORION-16 and ORION-13, inclisiran plasma concentrations were measured only after the first dose; thus, only inter-subject, and not intra-subject, variability was assessed.

A population PK analysis was conducted to calculate inclisiran PK parameters.

Population pharmacokinetic analysis

The popPK analysis was based on data from: four global adult studies (ALN-PCSSC-001, ORION-6, ORION-7, ORION-12), one China PKPD study (ORION-14), one Japan bridging study in ASCVD, ASCVD-risk equivalents or patients with HeFH (ORION-15), and two adolescent studies in HoFH (ORION-13) and HeFH (ORION--16). Since hepatic and renal impairment is not relevant for this analysis given the young patient populations, only subjects with normal hepatic and renal function were included from the ORION-6 and ORION-7 studies in the PK analysis. A total of 60 adolescents

(aged 12-17 years) and 173 adults had evaluable PK and were included in the popPK analysis. Distribution of age and weight in the available dataset is depicted in **Table 7**.

Available samples in adolescents were sparse samples from ORION-13 and ORION-16 with three sampling time points: pre-dose, 4h and 24h post-dose. Dosing ORION-16 and ORION-13 was: Inclisiran sodium 300 mg SC administered as a single SC injection on Day 1, Day 90, Day 270. Part 2: Inclisiran sodium 300 mg SC administered as a single SC injection on Day 360 (if switching from placebo in Part 1), Day 450 and Day 630. Participants on inclisiran in part 1 receive Placebo on Day 360.

During popPK analysis, missing covariates were imputed as median. In the popPK analysis, inclisiran plasma concentration data below the LLOQ (BLQ) was handled using the M3 censoring method as described in Beal, 2001. Multivariate linear models were fit to log transformed NCA parameters, including continuous covariates as log transformed. All covariate relationships were fit simultaneously, and covariates with p-value less than 0.001 were considered for testing in the population PK analysis. Covariate effects with relative standard error (RSE) less than 30% (p-value less than 0.001) were retained in the final model. Model diagnostics of empirical bayes estimates vs covariate values were also examined to assess plausibility of additional covariate effects. A sensitivity analysis was performed by fitting the final popPK model on adult data only to determine the effects of including adolescent data into the model fitting. Population PK analyses were performed using the software.

Table 7: Distribution of body weight and age across PK dataset

Category	Adolescent	Adult	All
Body weight (kg)			
< 40	6	.	6
≥ 40, < 50	13	3	16
≥ 50, < 60	15	20	35
≥ 60, < 70	13	42	55
≥ 70, < 80	10	46	56
≥ 80	3	62	65
Age (years)			
≥ 12, < 15	29	.	29
≥ 15, < 18	31	.	31
≥ 18, < 40	.	45	45
≥ 40, < 50	.	32	32
≥ 50, < 60	.	55	55
≥ 60	.	41	41
Total	60	173	233

Note: Only participants with PK data are summarized; "Adolescent" includes patients from both ORION-16 and ORION-13; "Adult" includes participants from ALN-PCSSC-001, ORION-6, ORION-7, ORION-12, ORION-14 and ORION-15; Renal and hepatic impaired patients from ORION-6 and ORION-7 are excluded.

Source: TASK7102_O13-16_popPK_year_1_DBL/results/001_weight_age_summary.csv

Generated by: TASK7102_O13-16_popPK_year_1_DBL/scripts/001_explore_data.R

The base adult and adolescent popPK model was a one compartment model with simultaneous first and zero order absorption and first order elimination. Covariate exploration on adult NCA parameters, and adult and adolescent 4h and 24h concentration, revealed body weight as a significant covariate on almost all parameters, including 4h concentration, C_{max} , AUC, CL/F and V_z/F . The final popPK model includes body weight as a covariate on clearance and volume with an estimated exponent. Model parameter estimates from base and final model are reported in Table 8, with RSE (%) given in brackets. The final popPK model was used to obtain post-hoc estimated popPK parameters, and popPK simulated individual PK profiles for the patients in ORION-13 and ORION-16. These individual PK profiles were used to calculate individual NCA PK parameters, including C_{max} , T_{max} , AUC_{0-24h}, $T_{1/2}$ and AUC_{inf}.

Table 8: Parameter estimates for base and final popPK models

Parameter	Base Adult + Adolescent Model (run003)	Final Adult + Adolescent Model (run004)	Sensitivity Adult Model (run002)
CL (clearance, L/h)	27.1 (2.38)	28.2 (2.11)	27.6 (2.3)
V (volume, L)	170 (4.91)	185 (4.07)	181 (4.33)
KA (first order absorption rate, 1/h)	2.69 (9.11)	2.93 (10.1)	2.99 (9.87)
F1 (fraction first order)	0.35 (3.77)	0.35 (4.11)	0.329 (4.41)
Tk0 (duration zero order, h)	12.1 (3.95)	12.5 (3.54)	12.8 (3.68)
Residual errors			
Additive error	3.97 (9.98)	3.91 (10.1)	3.86 (10.3)
Proportional error	0.183 (1.31)	0.182 (1.34)	0.183 (1.36)
Between subject variability			
bsv_Ka	0.636 (25.1)	0.683 (26.6)	0.625 (27.3)
cor_Ka_CL	0.0909 (34.8)	0.105 (29.5)	0.107 (30.3)
bsv_CL	0.0975 (11.6)	0.0687 (12.9)	0.0682 (14.3)
cor_Ka_V1	0.189 (31.3)	0.209 (24.9)	0.192 (28.2)
cor_CL_V1	0.136 (14.8)	0.0769 (17.8)	0.0736 (20.6)
bsv_V1	0.318 (14.1)	0.204 (14.4)	0.193 (16.9)
bsv_Tk0	0.146 (11.9)	0.118 (13)	0.129 (12.7)
bsv_F1	0.22 (27.1)	0.265 (22.6)	0.277 (25.2)
Covariate effects			
WT on CL	-	0.842 (11.2)	0.873 (12.8)
WT on V	-	1.73 (9.23)	1.65 (12.1)

Source: TASK7102_O13-16_popPK_year_1_DBL/results/KJX_03_ParaSumm_run010.html

Generated by: TASK7102_O13-16_popPK_year_1_DBL/scripts/KJX_03_ParaSumm.R

The methods used for model development are considered standard. Covariate analyses used low p-values ($p < 0.001$). Estimated exponents for body weight relation to clearance was 0.842 and for volume 1.73 for the combined adolescent and adult dataset. These values deviate from the empirical exponents of 0.75 for clearance and 1 for volume. But since the dataset with $n=60$ adolescents in the age of 12-17 years and $n=173$ adults is considered sufficient to estimate the exponent and model performance overall appears adequate (see below), this is considered acceptable.

Evaluation and qualification of models

Precision of final model parameters are given in **Table 8** above. VPCs from the final popPK model for dose-normalised in-clinical concentrations in adults and adolescents, stratified by body weight and age categories are given in **Figure 1** and **Figure 2**, respectively.

Figure 1: Visual Predictive Check of dose-normalised concentration stratified by body weight categories from the Final Adult + Adolescent popPK Model (run004), Linear scale

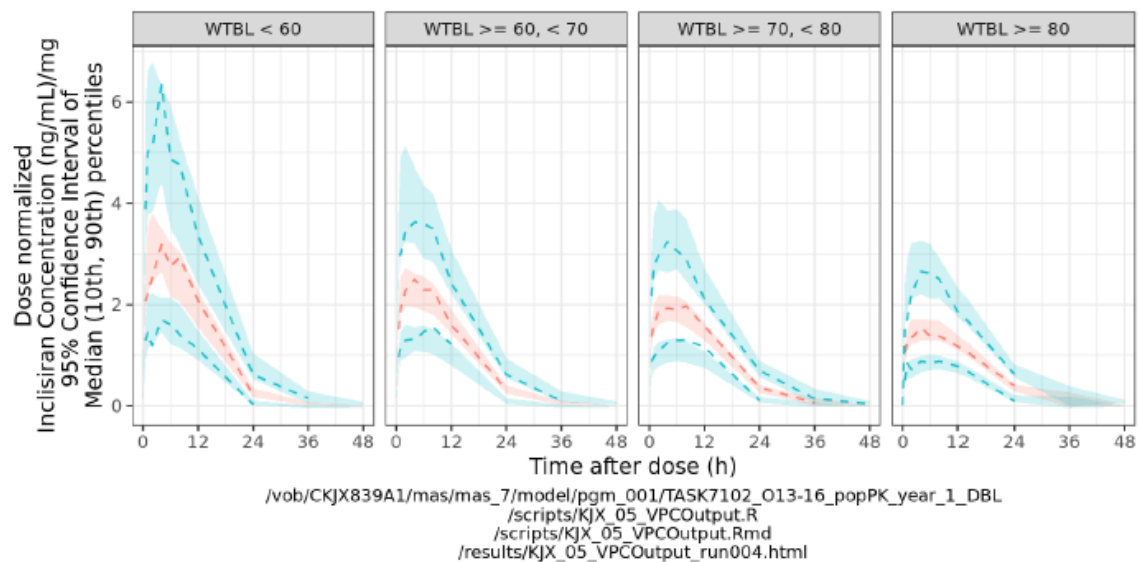
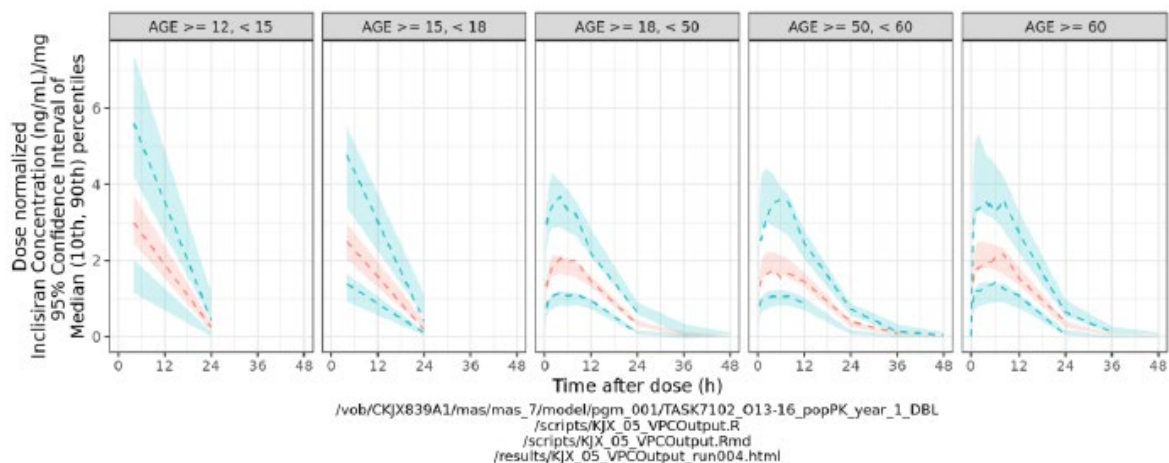


Figure 2: Visual Predictive Check of dose-normalised concentration stratified by age categories from the Final Adult + Adolescent popPK Model (run004), Linear scale



The Applicant did not submit the complete CSRs for the ORION-14 and ORION-15 studies but instead provided the respective bioanalytical reports. Since data of these studies were included in the PopPK analysis, it needs to be shown that the results of the analytical methods for determination of inclisiran concentrations are comparable. If different analytical methods and/or CROs have been involved, a cross-validation would be needed and should be reported. The additional explanation was provided. Method INCLHPP applied to study sample analysis in studies ORION-16 and -13 was not directly cross-validated to original QPS method 319-1418. Instead, method comparison is to rely on indirect chain comparison only. According to weighted Deming regression, LabCorp Madison duplex assay results are generally higher than those at QPS with difference increasing with concentration. Based on the Bland-Altman Plot of mean percentage difference, Labcorp Madison duplex results are lower than those for QPS in the lower concentration range (i.e. at LQC (30ng/mL) and LMQC (400ng/mL)), and higher in the higher concentration range (i.e. at MQC (5000ng/mL) and HQC (8000ng/mL)). In absence of a direct cross-validation, stronger bias than revealed for the Labcorp duplex assay vs. the QPS duplex assay cannot be ruled out for the Labcorp Madison single strand assay. However, given that most

samples reported in the ORON-16 and -13 studies had a measured concentration below 2000 ng/mL, the impact on PK data may still be acceptable.

The model purpose is to describe the concentration-time curve in adolescents and adults, to evaluate similarity of exposure between adults and adolescents and finally to define whether dosing in adolescents was adequate. For this purpose, the depicted VPCs are not considered meaningful. Observed concentrations should be depicted in addition (according to Bergstrand et al. 2011). Additionally, pcVPCs (based on non-dose-normalised concentrations) should be provided instead of VPCs with dose-normalised concentrations. Further data concerning this was provided and was considered acceptable. From the initially presented results, it could not be decided whether the proposed dose (300mg sc) is adequate for the entire group of adolescents or whether a lower body weight cut-off would be needed. Therefore, individual and predicted exposure metrics were asked to be shown with age and body weight on a continuous scale. In addition, boxplots of exposure (C_{max} , C_{min} , and AUC) for patients below and above 40, 45 and 50 kg were asked to be shown and the need for a lower weight cut-off discussed (depiction according to EMA paediatric Q&A).

For the final popPK model, pcVPCs (based on non-dose-normalised concentrations) instead of VPCs with dose-normalised concentrations should be provided with observed concentrations depicted in addition (according to Bergstrand et al. 2011). Additionally, boxplots of exposure (for C_{max} , C_{min} , and AUC) for patients below and above 40, 45 and 50 kg should be shown (for depiction see EMA paediatric Q&A) and the need for a lower weight cut-off discussed. The requested pcVPC was reported and is considered acceptable. The requested plots comparing exposure (C_{max} and AUC) for different weight bands compared to adult exposure were also reported.

The responses provided revealed that exposures were much higher (3-fold for C_{max} and AUC) in adolescents compared to adults after administration of same dose (300mg). This led to the question about adequacy of the dosing regimen for adolescent patients. In response to the 2nd RSI, the MAH argued mainly with the benign safety profile of inclisiran, with no SAEs considered related to study drug, no new safety signals in the adolescent studies and neither in younger patients (6-12 years, with lower weights but same dose (300mg) down to 23 kg), and no sign of accumulation (also not in the liver). Therefore, the proposed dosing regimen was considered acceptable.

2.3.3. Pharmacokinetics

Data on dose proportionality, PK (absorption, distribution and protein binding, metabolism, excretion) of inclisiran in adults, inclisiran PK in adult special populations and in vitro enzyme/transporter DDI assessments were reviewed as part of the initial registration.

Special populations

Pharmacokinetics of inclisiran in adolescents (≥ 12 to < 18 years of age)

The evaluation of inclisiran concentrations in plasma was an exploratory endpoint for both the ORION-16 and ORION-13 studies. For both studies, a detailed description of the study design, methods and primary, secondary and other explorative endpoints is presented in section Clinical Efficacy, subsection: Main studies.

Inclisiran PK parameters using noncompartmental analysis were not calculated as only sparse PK sampling was conducted at the Day 1 visit for these studies: i.e., 0 hours (pre-dose -immediately before the first administration of study drug), 4 hours post first dose, and 24 hours post first dose, respectively).

Inclisiran concentration-time data was summarised using descriptive statistics.

To assess whether inclisiran concentrations at these timepoints would be different from adults, concentrations at 4 and 24 hours are compared to those measured in adults at the same timepoints. Furthermore, due to the sparse PK sampling in ORION-16 and ORION-13 a population PK model was established based on adult and adolescent data to obtain individual PK parameters for adolescents in both studies. For this purpose, the final popPK model was used to obtain post-hoc estimated popPK parameters, and popPK simulated individual PK profiles for the patients in ORION-13 and ORION-16. These individual PK profiles were used to calculate individual NCA PK parameters, including C_{max} , T_{max} , AUC_{0-24h} , $T_{1/2}$, and AUC_{inf} . The individual PK parameters came from [KJX839 Population PK Model].

ORION-16 (HeFH)

After a single s.c. administration of inclisiran sodium 300 mg, variability in inclisiran plasma concentrations was low to moderate and overall higher than in the adult population. The highest inclisiran concentrations for each subject were at 4 hours after s.c. administration. At 24 hours post-dose, inclisiran concentrations declined to either substantially lower levels or were below the LLOQ (<10 ng/mL).

Inclisiran mean plasma concentration-time profile is shown in the figure below. Summary statistics for plasma concentration-time data following a single s.c. administration of inclisiran sodium 300 mg are presented in the table underneath.

Figure 3: Mean (+/-SD) plasma concentration-time profile following single sc administration of inclisiran – Part 1 Primary Analysis PK Analysis set (ORION-16)

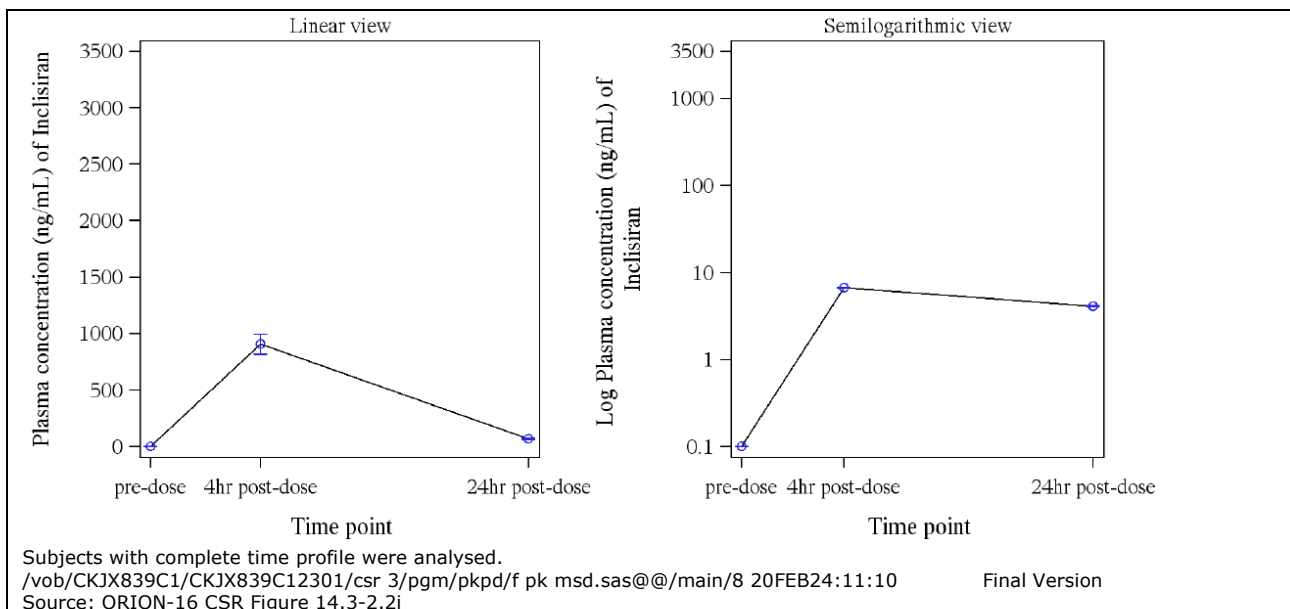


Table 9: Pharmacokinetics of inclisiran: Summary statistics of plasma concentration (ng/mL)-time data following a single s.c. administration of inclisiran – Part 1 Primary Analysis (PK Analysis set) (ORION-16)

Treatment		Pre-dose	4hr Post-dose	24hr Post-dose
Inclisiran N=51	n	40	40	40
	Mean	0.0	905.0	65.7
	SD	0.00	564.93	41.13
	CV% mean		62.4	62.6
	Geo-mean		769.1	60.7
	CV% geo-mean		62.1	64.1
	Median	0.0	699.5	58.2
	Min	0.0	225.0	0.0
	Max	0.0	3010.0	143.0
	Participants with LLOQ <10, n (%)	40 (100)	0	3 (7.5)

-CV% = coefficient of variation (%)=SD/mean*100; CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

-LLOQ=lower limit of quantification.

-N=number of participants in PK analysis set.

-Participants with complete time profile were analysed.

Source: ORION-16 CSR; Table 11-10 and Table 14.3-9.1i

The range of inclisiran concentrations at the 4- and 24-hour timepoints shown in the above table substantially overlap with concentrations at 4 hours (range: 371 to 1071 ng/mL, n=4) and 24 hours (12 to 206 ng/mL, n=4) reported for adults co-administered inclisiran sodium 300 mg and a statin [PK Report ALN-PCSSC-001-Table 15.1.1.1.5].

From population PK modelling of adolescent PK data that importantly provides individual PK parameters, inclisiran mean (SD) C_{max} , AUC_{0-24hr} , and AUC_{inf} is 953 (524) ng/mL, 12300 (4640) ng*hr/mL and 12800 (4490) ng*hr/mL, respectively for ORION-16 (n=51) and 1270 (480) ng/mL, 14400 (2720) ng*hr/mL and 14700 (2670) ng*hr/mL, respectively, for ORION-13 (n=9) [KJX839 Population PK Report, Table 7 7]. For adults co-administered inclisiran sodium 300 mg and a statin, after a single inclisiran sodium 300 mg s.c. dose C_{max} , AUC_{0-24hr} , and AUC_{inf} is 928 (375) ng/mL, 12286 (4404) ng*hr/mL and 13414 (1748) ng*hr/mL, respectively [PK Report ALN-PCSSC 001 Table 15.2.1.1.5].

ORION-13 (HoFH)

After s.c. administration of inclisiran sodium 300 mg, variability in inclisiran plasma concentrations was low in adolescents aged 12 to <18 years with HoFH and LDL-C >130 mg/dL (3.4 mmol/L) on stable, individualised, optimal standard of care (SoC) background lipid-lowering therapy including maximally tolerated statin treatment, at the investigator's discretion. The highest inclisiran concentrations for each participant were at 4 hours after s.c. administration. At 24 hours post-dose, inclisiran concentrations declined to either substantially lower levels or were below the LLOQ (<10 ng/mL).

Inclisiran mean plasma concentration-time profile is shown in the figure below. Summary statistics for plasma concentration-time data following a single s.c. administration of inclisiran sodium 300 mg are presented in the table underneath.

Figure 4: Mean (+/-SD) plasma concentration-time profile following single sc administration of inclisiran – Part 1 Primary Analysis PK Analysis set (ORION-13)

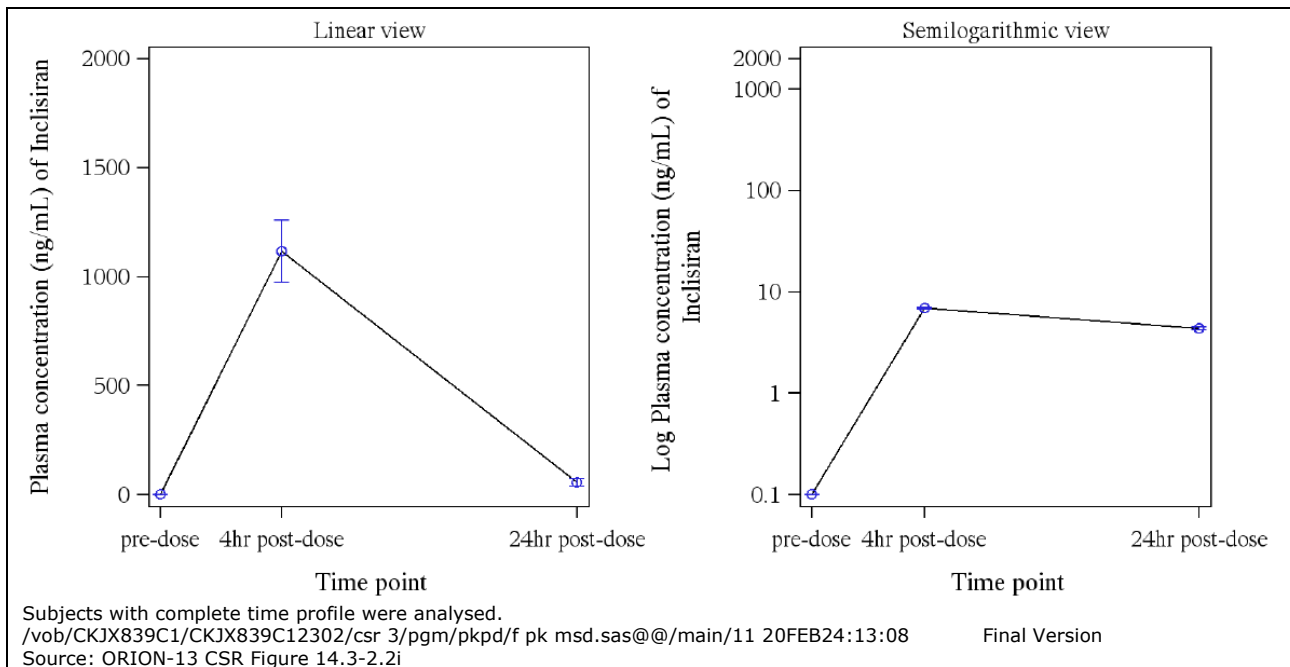


Table 10: Pharmacokinetics of inclisiran: Summary statistics of plasma concentration (ng/mL)-time data following a single s.c. administration of inclisiran – Part 1 Primary Analysis (PK Analysis set)

Treatment		Pre-dose	4hr Post-dose	24hr Post-dose
Inclisiran N=9	n	9	9	9
	Mean	0.0	1118.2	56.9
	SD	0.00	427.75	50.79
	CV% mean		38.3	89.3
	Geo-mean		1042.4	79.6
	CV% geo-mean		42.9	42.7
	Median	0.0	1090.0	59.2
	Min	0.0	461.0	0.0
	Max	0.0	1930.0	141.0
	Participants with LLOQ <10, n (%)	9 (100)	0	3 (33.3)

-CV% mean = coefficient of variation (%)=sd/mean*100; CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

-LLOQ-lower limit of quantification.

-N=number of participants in PK analysis set.

-Participants with complete time profile were analysed.

Source: ORION-13 CSR, Table 11-10, Table 14.3-9.1i

The range of inclisiran concentrations at the 4- and 24-hour timepoints shown in the table above substantially overlap with concentrations at 4 hours (range: 371 to 1071 ng/mL, n=4) and 24 hours (12 to 206 ng/mL, n=4) reported for adults co-administered inclisiran sodium 300 mg and a statin [PK Report ALN-PCSSC-001-Table 15.1.1.1.5].

From the population PK modelling of adolescent PK data that importantly provides individual PK parameters, inclisiran mean (SD) C_{max} , AUC_{0-24hr} , and AUC_{inf} is 953 (524) ng/mL, 12300 (4640) ng*hr/mL and 12800 (4490) ng*hr/mL, respectively for ORION-16 (n=51) and 1270 (480) ng/mL, 14400 (2720) ng*hr/mL and 14700 (2670) ng*hr/mL, respectively, for ORION-13 (n=9) [KJX839 Population PK Report, Table 7 6]. For adults co-administered inclisiran sodium 300 mg and a statin, after a single inclisiran sodium 300 mg s.c. dose, C_{max} , AUC_{0-24hr} , and AUC_{inf} was 928 (375) ng/mL, 12286 (4404) ng*hr/mL and 13414 (1748) ng*hr/mL, respectively [PK Report ALN-PCSSC 001 Table 15.2.1.1.5].

To ease direct comparison, the relevant excerpt from PK Report ALN-PCSSC-001-Table 15.1.1.1.5 referred to by the Applicant is included in the following, showing plasma concentrations reported for adults co-administered inclisiran sodium 300 mg and a statin at corresponding time points 0.00, 4.00 and 24.00:

Individual and Summary Plasma Concentrations of ALN-60212 Following 300 mg ALN-PCSSC –MD Arm with Statin Medication (Day 0)

Treatment = 300 mg ALN-PCSSC (Statin_Medication = On)			
Plasma ALN-60212			
Concentration (ng/mL) over Nominal Time (h)			
Subject	0.00	4.00	24.00
015	BQL <(10.0)	1070.909	26.333
016	BQL <(10.0)	982.564	41.683
017	BQL <(10.0)	1016.818	12.419
018	BQL <(10.0)	370.843	206.081
N	4	4	4
Mean	0.0000	860.2835	71.6290
SD	0.00000	328.31422	90.42797
Min	0.000	370.843	12.419
Median	0.000	999.691	34.008
Max	0.000	1070.909	206.081
CV%	NA	38.2	126.2

BQL <(10.0) = Below limit of quantification

NA = Not Applicable

[Source ALN-PCSSC-001 – 16.1.13 - 13.7 Pharmacokinetic Report (ALNY-PCS-116) table 15.1.1.1.5]

ORION-16 (HeFH): Conclusions on PK/measured plasma concentration in adolescents (12 to <18 years) with a genetic and/or clinical diagnosis of HeFH and LDL-C >130 mg/dL (3.4 mmol/L) on optimal SoC lipid-lowering therapy are at present considered preliminary. While it is agreed that plasma concentrations as reported in the ORION-16 study in n=40 adolescents (12 to <18 years) with a genetic and/or clinical diagnosis of HeFH and LDL-C >130 mg/dL (3.4 mmol/L) on optimal SoC lipid-lowering therapy overlap with the plasma concentrations reported in n=4 adults co-administered inclisiran sodium 300 mg and a statin in early PK study ALN-PCSSC-001, it should be noted that besides the very low number of only n=4 adults on whom the comparison is to rely, the highest concentration determined in the paediatric population at 4 hours postdose is 3010ng/mL. Furthermore, based on population PK modelling, exposures are overall higher in the paediatric population than in the adult population. Of note, different methods and different contract facilities were involved in the quantification of inclisiran in plasma in the two studies and methods were not directly cross-validated. Indirect method comparison has to rely on an additionally established assay not yet used for study sample analysis having to serve as "bridge". Proportional and fixed bias was revealed in the indirect cross validations. Since most concentrations in the ORION-16 study were below 2000 ng/mL, the impact on PK may be considered overall acceptable (see section on bioanalytics).

Of note, regarding the ORION-16 protocol Amendment 2, dated 17-Feb-2023, it was stated that the purpose of the amendment was to add an interim analysis (IA) for the PK data collected on Day 1, to update a PK extrapolation to paediatrics, i.e., to further refine the extrapolation from adult PK data with adolescent PK data, covering a lower range of body weights and ages. The updated PK extrapolation was seen critical as part of developing a dose selection strategy for planned future paediatric studies in younger children (<12 years). The PK IA was performed by a separate team (not involved in any other study activities) before the Part 1/Year 1 database lock, when the study was unblinded as per protocol. No further information on the results of the IA, incl. the updated PK extrapolation could be located.

ORION-13 (HoFH): The Applicant's conclusion that plasma concentrations as reported in the ORION-13 study in n=9 adolescents (12 to <18 years) with a diagnosis of HoFH and LDL-C > 130 mg/dL (3.4 mmol/L) on optimal SoC lipid-lowering therapy substantially overlap with the plasma concentrations reported in n=4 adults co-administered inclisiran sodium 300 mg and a statin in early PK study ALN-

PCSSC-001 could not be fully followed. While minimum plasma concentration reported in the adolescent ORION-13 study population is within the range of concentrations reported in the adult ALN-PCSSC-001 study population, the maximum concentration reported is almost doubled, and higher values are reported also for mean and median. Uncertainty regarding the informative value of the comparison pertains to the low number of patients for whom plasma concentration information is available, i.e. only n=9 adolescents from study ORION-13 and n=4 adults from study ALN-PCSSC-001. As noted for the ORION-16 study above, different methods and different contract facilities were involved in the quantification of inclisiran in plasma in the two studies compared. As noted above, only indirect cross-validation is available. Similarly to the ORION-16 study, regarding the ORION-13 protocol Amendment 2, dated 17-Feb-2023, it was stated that the purpose of the amendment was to add an interim analysis (IA) for the PK data collected on Day 1, to update a PK extrapolation to paediatrics, i.e., to further refine the extrapolation from adult PK data with adolescent PK data, covering a lower range of body weights and ages. The updated PK extrapolation was seen critical as part of developing a dose selection strategy for planned future paediatric studies in younger children (<12 years). The PK IA was performed by a separate team (not involved in any other study activities) before the Part 1/Year 1 database lock, when the study was unblinded as per protocol.

2.3.4. Discussion on clinical pharmacology

In ORION-16 and in ORION-13 Studies, PK samples were collected pre-dose (immediately before the first administration of study drug), 4- and 24-hours after the first dose. Inclisiran was quantified using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method with the Lower Limit of Quantification (LLOQ) of 10 ng/mL. In both studies, the highest inclisiran concentrations were observed at 4 hours after s.c. administration. At 24 hours post-dose, inclisiran concentrations declined to either lower levels or below the LLOQ.

Validation Report Quantitative determination of A-120190 and A-122088 in human plasma by LC-MS/MS from 25-Aug-2022 and Method validation report Amendment No. 1 from 19-Oct-2022 have been submitted, as were the respective bioanalytical reports. The acceptance criteria provided are in line with the Guideline on bioanalytical method validation [EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**]. The method can be considered adequate for determination of A-120190 and A-122088 in human plasma and with acceptable performance in both studies.

To support conclusions on inclisiran PK/plasma concentration data reported in the ORION-16 and ORION-13 studies as regards their comparability with earlier PK data reported in adults in the PK studies supporting the initial marketing authorisation of Leqvio, as well as with recent inclisiran PK data in Japanese and Chinese subjects, and as regards extrapolation efforts, these are hampered by the fact that the bioanalytical sites and the bioanalytical methods used for quantification of inclisiran in the paediatric vs. adult populations differ and methods were not directly cross-validated. Instead, method comparisons are to rely on chains of separate cross-validations involving further assays that were not yet used for study sample analysis to serve as “bridges”. Proportional and fixed bias were revealed in statistical analyses for some of the cross-validations. Overall, results from the LabCorp Madison site are generally higher than those at the original QPS site with difference increasing with concentration. Based on Bland-Altman Plot of mean percentage difference, while the overall mean is higher, Labcorp Madison results are lower than those for QPS in the lower concentration range (i.e. at LQC (30ng/mL) and LMQC (400ng/mL)) and higher in the higher concentration range (i.e. at MQC (5000ng/mL) and HQC (8000ng/mL)).

In absence of direct cross-validations, stronger bias than revealed in the indirect comparisons cannot be ruled out. However, given that most samples reported in the ORON-16 and -13 studies had a measured concentration below 2000 ng/mL, the impact on PK data was considered acceptable.

A population PK analysis was performed to describe inclisiran exposure over time in adults and adolescents and to calculate individual PK parameters for adolescents in ORION-13 and ORION-16. Based on the analysis that showed that although PK was significantly correlated with body weight, the body weight distribution and the concentrations in adolescents and adults overlapped, no dose adjustment was considered necessary for adolescents.

2.3.5. Conclusions on clinical pharmacology

Overall, with the limitations noted, the provided clinical pharmacology data package can be considered acceptable. Slight amendment of the SmPC to reflect that inclisiran plasma concentrations were higher in paediatric patients than those measured in adults has been agreed with the Applicant.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

N/A

2.4.2. Main studies

ORION-13 (CKJX839C12302; EudraCT No.: 2020-002755-38): "A Two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in adolescents (12 to less than 18 years) with homozygous familial hypercholesterolemia (HoFH) and elevated LDL-cholesterol"

Study ORION-13 evaluated the safety, tolerability, and efficacy of inclisiran in adolescents from 12 to less than 18 years of age with homozygous familial hypercholesterolemia (HoFH) and elevated low-density lipoprotein cholesterol (LDL-C). It is part of the inclisiran paediatric program as agreed with the European Medicines Agency (EMA) in the paediatric investigation plan (PIP; EMEA-002214-PIP01-17-M02, P/0322/2023) and intended to support the registration of inclisiran in adolescents with HoFH.

The study was conducted in two-parts, a double-blind inclisiran versus placebo part (Year 1), followed by an open-label inclisiran part (Year 2), as a randomised, multicentre study in adolescents with HoFH and LDL-C >130 mg/dL (3.4 mmol/L) on stable, individualised, optimal standard of care (SoC) background lipid-lowering therapy including maximally tolerated statin treatment, at the investigator's discretion.

To explore the pharmacokinetics (PK) of inclisiran in adolescents with HoFH, the study also included PK and pharmacogenetic assessments. PK assessment was based on sparse PK sampling (i.e. 3 samples at the Day 1 visit; pre-dose immediately before the first administration of study drug, 4-, and 24-hours after first dose; see section Pharmacokinetics). Optional pharmacogenetic analyses included analyses for potential mutations in the LDLR, ApoB, PCSK9, and LDLR adaptor protein 1 (LDLRAP1) genes.

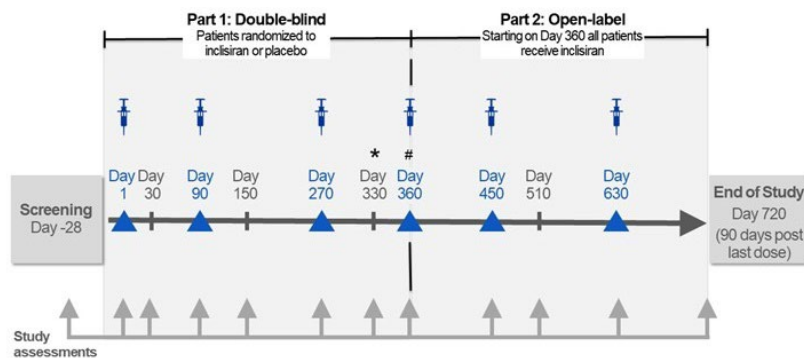
The study design is summarised in the following table.

Table 11: Summary of study design

Two-part, randomised, multicentre, international Phase III study. The study had two sequential parts:

- Part 1/Year 1: 12 months double-blind, parallel group period, in which participants were randomised in a 2:1 ratio to receive either inclisiran sodium 300 mg 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.

ORION-13 Study Design



* Primary endpoint assessed at Day 330.

"Switch Day": Participants randomised to placebo in Part 1 started to receive inclisiran on Day 360. Participants randomised to inclisiran in Part 1 received placebo on Day 360 only to maintain the blind for Part 1.

[Study ORION-13-Figure 9-1]

Methods

Study participants

The study population consisted of adolescents (male or female; ≥ 12 to <18 years at screening) with a genetically confirmed diagnosis of HoFH (excluding LDLR null/null genotypes) and on a maximally tolerated dose of statin (at investigator's discretion) with or without other lipid lowering therapy (e.g., ezetimibe).

Key inclusion criteria were:

- HoFH diagnosed by genetic confirmation excluding LDLR null/null genotypes,
- fasting LDL-C >130 mg/dL (3.4 mmol/L) at screening,
- on maximally tolerated dose of statin (Investigator's discretion) with or without other lipid-lowering therapy (e.g., ezetimibe),
- participants on lipid-lowering therapies (such as statin and/or e.g., ezetimibe) should have been on stable dose ≥ 30 days before screening with no planned medication or dose changes during study participation,
- participants on documented regimen of LDL-apheresis were allowed to continue apheresis during study if needed (schedule not allowed to change during double-blind period),
- estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m² at screening.

Key exclusion criteria were:

- documented evidence of a null (negative) mutation in both LDLR alleles,
- previous treatment (≤ 90 days of screening) with monoclonal antibodies towards PCSK9,
- history of poor response to therapy with any monoclonal antibody directed towards PCSK9,
- treatment with mipomersen or lomitapide (≤ 5 months of screening),

- active liver disease or unexplained, confirmed ALT or AST elevation $>3 \times \text{ULN}$, or total bilirubin elevation $>2 \times \text{ULN}$ (except Gilbert's syndrome) at screening,
- pregnant or nursing females,
- HeFH
- recent or planned use of other investigational medicinal products or devices,
- secondary hypercholesterolemia (e.g., hypothyroidism or nephrotic syndrome),
- major cardiovascular AEs ≤ 1 month prior to randomisation.

The study included male and female adolescents from ≥ 12 to <18 years of age with a genetic confirmation of HoFH, excluding LDLR null/null genotypes, and an LDL-C >130 mg/dL who were on a maximally tolerated dose of an HMG-CoA reductase inhibitor (statin) with or without other lipid lowering therapy (excluding PCSK9 inhibitors, mipomersen, and lomitapide).

Patients with heterozygous familial hypercholesterolemia (HeFH) or secondary hypercholesterolemia were excluded.

Treatments

In part 1 (year 1), participants received either commercially available inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 mL solution (batch numbers 2040834, 2040329, 2041729) or a placebo formulation to the active drug formulation (batch numbers 2041390, 2040833, 2041156); during part 2 (year 2), all participants received inclisiran (batch numbers 2040329, 2040921, 2041729, 2047184).

Placebo was supplied as sterile normal saline (0.9% sodium chloride in water for injection) and administered as a 1.5 mL s.c. injection to match the dose in the inclisiran arm; the placebo pre-filled syringes were blinded and were identical in appearance to their active counterparts.

During Part 1, participants received either inclisiran at the licensed standard dose and posology for adults or placebo. During Part 2, all participants received standard dose inclisiran.

Objectives, outcomes, endpoints

During the double-blind Part 1 (year 1) of the study, the primary efficacy and safety data comparing inclisiran to placebo were collected. The open-label single arm Part 2 (year 2) of the study collected longer-term data on inclisiran with a focus on longer-term safety.

Objectives and endpoints of study ORION-16 are summarised in the table below.

Table 12: Summary of objectives and endpoints of study ORION-13

Objectives	Endpoints
Primary objective	Endpoint for primary objective
• The primary objective is to evaluate the effect of inclisiran compared to placebo on reducing low density lipoprotein cholesterol (LDL-C) [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with homozygous familial hypercholesterolaemia (HoFH) and elevated LDL-C	• Percentage change in LDL-C from baseline to Day 330 (Year 1)

Objectives	Endpoints
Secondary objectives	Endpoints for secondary objectives
Evaluate the effect of inclisiran compared to placebo on reducing LDL-C [time-adjusted percent change] over Year 1	Time-adjusted percent change in LDL-C from baseline after Day 90 and up to 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	Percent change and absolute change in LDL-C, apolipoprotein B (Apo B), lipoprotein (a) [Lp(a)], non-high density lipoprotein cholesterol (non-HDL-C), total cholesterol, triglycerides, high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo A1) and PCSK9 from baseline to each assessment time up to Day 720 (Year 2)
Evaluate the safety and tolerability of inclisiran compared to placebo (for Year 1) and long-term (up to Day 720), in adolescents (aged 12 to < 18 years) with HoFH	Incidence, severity, and relationship to study drug of treatment-emergent adverse events (AEs) and serious adverse events (SAEs); vital signs; laboratory parameters; anti-drug antibodies (ADA) measurement; growth (height, weight, body mass index (BMI)); pubertal development (steroid hormones and Tanner staging)
Exploratory objectives	Endpoints for exploratory objectives
Explore the effect of inclisiran compared to placebo (at Day 330) and long-term (at Day 720) on the individual responsiveness of participants	Individual responsiveness of participants defined through on treatment LDL-C levels of <50 mg/dL, <70 mg/dL, <100 mg/dL and <130 mg/dL at Day 330 (Year 1) and Day 720 (Year 2)
Explore the effect of inclisiran compared to placebo (at Day 330) and long-term (at Day 720) on achieving at least 10% or 20% LDL-C reduction	≥10% or ≥20% LDL-C reduction from baseline at Day 330 (Year 1) and Day 720 (Year 2)
Explore the effect of inclisiran compared to placebo on the response of LDL-C reduction by underlying causal mutations of HoFH at Day 330 (Year 1)	Percentage change and absolute change in LDL-C from baseline to Day 330 (Year 1), by type of underlying causal mutation
Explore the effect of inclisiran on the frequency of LDL-apheresis treatment at Day 720 (Year 2) (in participants receiving apheresis)	Reduced frequency of LDL-apheresis treatment at Day 720 (Year 2) compared to baseline
Explore the effect of inclisiran compared to placebo (at Day 330) and long-term (at Day 720) on the carotid intima-media thickness (cIMT)	Change in cIMT from baseline to Day 330 (Year 1) and Day 720 (Year 2)
Explore (sparse) pharmacokinetics (PK) of inclisiran in adolescents with HoFH	Evaluation of inclisiran concentrations at 4 and 24 hours after the first dose

For the primary efficacy assessment beta quantification LDL-C, i.e., LDL-C directly measured using ultracentrifugation, was used; if a beta quantification LDL-C was missing, calculated LDL-C could be used instead.

Participants were in a fasted state for all efficacy laboratory assessments. From randomisation (Day 1) until Day 360, the results were blinded to participants, investigator staff, persons performing the assessments, and the clinical trial team.

In addition, carotid intima-media thickness (cIMT) was measured locally at Day 1 (baseline), Day 330 (Year 1), and Day 720 (EoS) by ultrasonography. This assessment was exploratory / hypothesis-generating in nature.

PK assessment was based on sparse PK sampling (i.e. 3 samples at the Day 1 visit; pre-dose immediately before the first administration of study drug, 4-, and 24-hours after first dose). Concentration-time data were summarised using descriptive statistics. (see sections 8.2.1 Methods and 8.2.2 Pharmacokinetics)

All participants were invited to optional pharmacogenetic analyses of the underlying causal mutation(s) of their HoFH. Samples were analysed for potential mutations in the LDLR, ApoB, PCSK9, and LDLRAP1 genes.

The key safety assessments consisted of monitoring and recording of all adverse events (AEs), laboratory evaluations (haematology, biochemistry, urinalysis, pregnancy tests), anti-drug antibody (ADA) measurement, vital signs, growth (height, weight, body mass index [BMI]), and pubertal development (sex hormones, Tanner staging). Other safety evaluations were physical examinations, neurological evaluations, and electrocardiograms (ECGs).

The primary endpoint was the percentage change in LDL-C from baseline to the end of the double-blind treatment period at day 330 (year 1).

Secondary endpoints included time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, absolute changes in LDL-C and other lipid parameters during Part 1, as well as assessments from baseline to the end of the open-label Part 2, i.e. day 720.

Exploratory endpoints included individual responsiveness of participants, changes in LDL-C by type of underlying causal mutation, change in carotid intima-media thickness (cIMT), reduced frequency of LDL-apheresis treatment at Day 720 (Year 2) compared to baseline, and evaluation of inclisiran pharmacokinetics (PK) based on sparse data.

The endpoints are considered to be in line with previous inclisiran studies in adults.

Sample size

There was no formal sample size calculation. The sample size for this study was selected based on feasibility; the planned sample size was approximately 12 adolescent participants. In Part 1 of the study, 13 eligible participants (9 inclisiran, 4 placebo) were enrolled and analysed. All 13 randomised participants entered Study Part 2 and were analysed.

Randomisation and blinding (masking)

Part 1 of the study was randomised, double-blind and placebo-controlled. Participants, investigator staff, persons performing the assessments, and the clinical trial team were blinded to the identity of the treatment from the time of randomisation until at least database lock for all Part 1 (year 1) data. Exceptions were the independent statistician and programmer to prepare interim analysis reports for the DMC, and the PK analyst to avoid unnecessary analysis of placebo samples; in addition, a PK interim analysis (IA) team had access to unblinded individual-level PK/baseline data in order to update a PK extrapolation to paediatrics before the Part 1 database lock to support early planning of a dose

selection strategy for paediatric studies in younger children. Part 2 of the study had a single-arm, open-label design.

After baseline visit (Day 1), participants were randomised by interactive response technology in a 2:1 ratio to receive double-blind s.c. injections of inclisiran sodium 300 mg or placebo in Part 1 (year 1) of the study (days 1, 90, 270). On day 360 ("switch day"), participants randomised to placebo in Part 1 received inclisiran and participants randomised to inclisiran in Part 1 received placebo. This dose remained blinded in order to maintain the blind for Part 1 of the study. Subsequently, all participants received open-label s.c. injections of inclisiran sodium 300 mg in Part 2 (year 2).

Investigational and control drugs were supplied by the MAH as single-use pre-filled syringes for s.c. injection. Placebo was supplied as sterile normal saline (0.9% sodium chloride in water for injection) and administered as a 1.5 mL s.c. injection to match the dose in the inclisiran arm. The placebo pre-filled syringes were blinded and were identical in appearance to their active counterparts.

Statistical methods

Efficacy and safety analyses of Part 1 data were performed after all participants completed the Day 360 visit or discontinued prior to the Day 360 visit; analyses of Part 2 data were performed after all participants completed the Day 720 (EoS) visit or discontinued prior to the Day 720 visit. In cases where the dosing time at Day 360 did not allow to determine whether data belonged to Part 1 or 2, the data were considered to belong to Part 1.

The following data sets were analysed. The Screened Set (SCR) included all participants who provided study informed consent. The Randomised Set (RAN) consisted of all participants who received a randomisation number, regardless of whether double-blind treatment was received or not. The Full Analysis Set (FAS) consisted of all randomised participants with the exception of those mis-randomised participants who did not receive study drug; mis-randomised participants were defined as those who were not qualified for randomization but were inadvertently randomised into the study. According to the intent to treat principle, participants were analysed according to the treatment they were assigned to during the randomisation procedure. The FAS was used in analyses for the primary, secondary, and exploratory efficacy objectives in Part 1 of the study. The Safety Set (SAF) included all participants who received at least 1 dose of study treatment. Participants were analysed according to the study treatment received. This was the primary population for the safety analyses in Part 1. The SAF allowed the inclusion of nonrandomised participants who received double-blind treatment in error. The PK analysis Set included all randomised participants who had at least 1 PK measurement. Participants were analysed according to the treatment they received. This was the primary population for the PK analyses. The Open-label Phase Analysis Set (OAS) included all participants who entered Part 2 of the study and received at least 1 dose of study treatment in Part 2. The OAS was used to analyse data from participants who entered Part 2.

For the primary endpoint percentage change in LDL-C from pre-dose baseline measurement to Day 330, summary statistics to characterise change from baseline in LDL-C by treatment group and the difference between treatment groups along with 95% confidence interval (CI) at the Day 330 time point were used. The CI was constructed assuming Students t-distribution and equal variance between the 2 samples. No formal hypothesis testing was planned. No remaining intercurrent events were expected. The primary endpoint did not have missing data imputed. Only data from the Day 330 visit time point and baseline data needed to evaluate change from baseline in LDL-C were included in the primary analysis. No sensitivity analyses were planned. As a supplementary analysis, the main analysis, after excluding the participant receiving LDL-apheresis during the study, was repeated.

Summary statistics by treatment group and treatment difference along with 95% CI was provided. No subgroup analysis was performed.

For the secondary endpoints time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 330 (year 1), defined as the average of percent changes from baseline to Days 150, 270, and 330, percent and absolute change in LDL-C, Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, HDL-C, VLDL-C, Apo A1, and PCSK9 from baseline to each assessment time up to Day 720 (Year 2), and incidence, severity, and relationship to study drug of treatment-emergent AEs and SAEs; vital signs; laboratory parameters; ADA measurement; growth (height, weight, BMI); pubertal development (sex hormones and Tanner staging) descriptive summaries by treatment group were presented.

Additionally, the mean treatment difference and associated 95% CI was provided for time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, for absolute change in LDL-C at Day 330, and for percentage change in Apo B, Lp(a), non-HDL-C, total cholesterol, and PCSK9 at Day 330. To construct the CI for the time-adjusted percent change analysis, the patient-level averages assuming Students t-distribution and equal variance were used, as for the primary analysis. No formal hypothesis testing was performed.

For exploratory variables, frequencies and percentages of participants in the categories LDL-C <50 mg/dL, <70 mg/dL, <100 mg/dL, and <130 mg/dL, as well as reductions of $\geq 10\%$ and $\geq 20\%$ LDL-C from baseline were summarised by treatment group at Day 330 (Year 1) and Day 720 (Year 2). In addition, as supportive analyses, $>15\%$ LDL-C reduction from baseline was summarised by treatment group at Day 330 and Day 720, and $\geq 30\%$ LDL-C reduction from baseline at Day 720. For participants receiving LDL-apheresis, the number and percentage of participants with a reduced frequency of LDL-apheresis was presented by treatment group at Day 720. Summary statistics for LDL-C percent and absolute change from baseline were provided by treatment group in subgroups defined by underlying genetic mutation(s). Values of cIMT were summarised at each time point by treatment group. Change in cIMT from baseline to Day 330 (Year 1) and to Day 720 (Year 2) were summarised by treatment group.

As regards PK analyses, inclisiran plasma concentration data were listed by treatment, participant, and sampling time point using descriptive statistics (see section Pharmacokinetic data analysis).

An interim analysis on PK data was performed to update a PK extrapolation to paediatrics (i.e., to further refine the extrapolation from adult PK data with adolescent PK data) as part of developing a dose selection strategy for planned future paediatric studies in younger children <12 years of age.

For safety analyses, the number and percentage of participants who had treatment-emergent AEs, treatment-emergent SAEs, injection site reactions, and treatment-emergent events related to other safety topics (including cardiac / hepatic / hypersensitivity / musculoskeletal / neurological / renal / psychiatric / new onset or worsening of diabetes) were summarised. For laboratory data and vital signs, absolute values and change from baseline were summarised. The number and percentage of participants with categorical criteria were summarised. In addition, the number and percentage of participants with newly occurring notable abnormalities for selected laboratory parameters and vital signs were summarised. The number and percentage of participants with treatment-induced transient and persistent ADA and no treatment-induced ADA were summarised. Shift from baseline in Tanner stage was summarised by sex, treatment, and visit. Shift in menarche status from baseline was summarised by visit and treatment group.

Adequate statistical methods were applied. Due to the small sample size, only summary statistics were provided. No formal hypothesis testing was planned.

Results

Participant flow, numbers analysed, and recruitment

Study ORION-13 was started on 16 February 2021 (first participant first visit) and completed 18 November 2024 (last participant last visit); the CSR version 1.0 is dated 05 March 2025.

A total of 20 participants were screened and 13 were enrolled and randomised, 9 in the inclisiran and 4 in the placebo group. All 13 participants completed Part 1, entered Part 2, and were analysed. The planned full study duration was 748 days.

All 13 participants randomised, 9 in the inclisiran and 4 in the placebo group, completed Part 1 and Part 2, and were analysed.

Conduct of the study

The study protocol was amended twice. Key features of each amendment are given in the table below. There were no other changes to the study conduct.

Table 13: Protocol amendments

Version and date	Summary of key changes
Amendment 1, 01-Oct-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 randomised.
Amendment 2, 17-Feb-2023	The purpose of Amendment 2 was to add an IA for the PK data collected on Day 1, to update a PK extrapolation to paediatrics, i.e., to further refine the extrapolation from adult PK data with adolescent PK data, covering a lower range of body weights and ages. The updated PK extrapolation was critical as part of developing a dose selection strategy for planned future paediatric studies in younger children (<12 years). The PK IA was performed by a separate team (not involved in any other study activities) before the Part 1/Year 1 database lock, when the study was unblinded as per protocol. This amendment was issued after completion of recruitment.

There were no changes to the planned protocol specified analysis. In an earlier synoptic CSR, which provided results of the Part 1/Year 1 analysis of the study, screening values were used for weight and height baseline calculations, while in the present final CSR, for reasons of consistency, the baseline values (i.e., last measurement collected on or prior to the first dose of double-blind treatment) were used.

The changes in the planned conduct of the study are not considered to have influenced the outcome of study ORION-13.

Baseline data

Demographic and baseline characteristics were overall comparable between the treatment groups. Approximately two thirds of the randomised participants were female (9/13; 69.2%) and the mean age was 14.8 years (range 12 to 17 years). Most participants were White (11/13; 84.6%) and the remaining 2/13 (15.4%) participants Asian, 1 in per group. The mean (±SD) BMI was 20.8 (±3.9) kg/m². Mean (±SD) baseline LDL-C and PCSK9 levels of study participants were 272.2 (±111.2) mg/dL

and 501.4 (± 102.3) ng/mL, respectively. All (100%) participants received statin treatment and 11/13 (84.6%) were treated additionally with ezetimibe with or without other lipid lowering therapies; 1 participant in the placebo group was on LDL-apheresis. All participants had HoFH, which was diagnosed genetically as required per protocol. There were no important differences in genotypes between treatment groups, with most participants having either a LDLR defective/defective or LDLR null/defective genotype, as expected.

No participants had a medical history of pre-diabetes, type 1 diabetes, type 2 diabetes, hypertension, coronary heart disease, cerebrovascular disease, peripheral artery disease, or chronic heart failure. However, 1 (1/13; 7.7%) participant in the inclisiran group met the fasting plasma glucose (FPG) laboratory criteria for pre-diabetes; no participants met the corresponding laboratory criteria for diabetes. All participants had never smoked or used e-liquids. One (1/13; 7.7%) participant in the placebo group had a current . No participants in either treatment group had partial or complete statin intolerance. Overall, 4/13 (30.8%) participants were treated with an anti-PCSK9 monoclonal antibody, evolocumab or alirocumab, as a prior medication, 2/9 (22.2%) in the inclisiran and 2/4 (50.0%) in the placebo group; treatment had ended >90 days before the screening visit as required per protocol.

During the double-blind Part 1, 10/13 (76.9%) participants had been taking at least 1 concomitant medication, 7/9 (77.8%) in the inclisiran and 3/4 (75.0%) in the placebo group. The most common drug classes used were anilides, corticosteroids, COVID-19 vaccines, and oral bivalent iron preparations (all 30.8%). There was 1 change in lipid modifying therapy (LMT) from rosuvastatin 20 mg to atorvastatin 20 mg in the placebo group. During the open-label Part 2, 9/13 (69.2%) participants had been taking at least 1 concomitant medication, 6/9 (66.7%) in the inclisiran-inclisiran and 3/4 (75.0%) in the placebo-inclisiran group. The most common drug classes used were anilides and propionic acid derivatives (each 30.8%) and ascorbic acid plain and oral bivalent iron preparations (each 23.1%). The only new or changed LMT during Part 2 was a change from atorvastatin 40 mg to rosuvastatin 40 mg.

In Part 1, 2/13 (15.4%) participants reported at least 1 protocol deviation, both in the placebo group. The protocol deviations concerned 2 changes in apheresis schedule / duration and a change in the type of background statin medication (rosuvastatin 20 mg to atorvastatin 20 mg). There were no protocol deviations during Part 2.

As regards duration of study treatment exposure, in Part 1 as well as in Part 2, all (100%) participants were administered all 3 doses of study drug (inclisiran or placebo). Mean duration on study and mean duration of exposure to study treatment in Part 1 were both 360.6 days in the inclisiran and 364.0 days in the placebo group and both 358.5 days in Part 2, with similar durations in the inclisiran-inclisiran and placebo-inclisiran groups. In Part 1 and Part 2 combined, the mean duration on study and the mean duration of exposure to study treatment were both 719.1 days, with similar durations in the inclisiran-inclisiran and placebo-inclisiran groups. The overall patient years of exposure to study treatment was 25.6, 17.7 in the inclisiran-inclisiran and 7.9 in the placebo-inclisiran group. Dose modifications and dose interruptions were not permitted and did not occur.

Demographic and baseline characteristics were comparable between treatment groups. Approximately two thirds of the randomised participants were female (9/13; 69.2%) and the mean age was 14.8 years (range 12 to 17 years). One (1) participant in the placebo group was on LDL-apheresis. All participants had HoFH diagnosed genetically and there were no important differences in genotypes between groups.

Outcomes and estimation

Primary analysis

The mean percent change in LDL-C from baseline to Day 330 was -21.6% in the inclisiran and +11.7% in the placebo group, with a mean between-group difference (95% CI) of -33.25% (-59.17, -7.34). While formal hypothesis testing was not planned, the 95% CI indicates nominal statistical significance. For further details see table below.

A supplementary analysis excluding participants (n=1) on LDL-apheresis treatment yielded consistent results, with a mean between-group difference (95% CI) of -37.72% (-67.37, -8.08).

Table 14: Primary Efficacy Endpoint: Percentage change in LDL-C from baseline to Day 330- Part 1 Primary Analysis (Full Analysis Set)

	Inclisiran N=9	Placebo N=4
Percentage Change from Baseline to Day 330		
n	9	4
Mean ± SD	-21.6 ± 13.36	11.7 ± 30.52
Median	-20.9	3.6
Q1, Q3	-30.9, -14.5	-8.6, 32.0
Min, Max	-39.7, -1.9	-15.4, 54.9
Mean difference from Placebo (95% CI)	-33.25 (-59.17, -7.34)	

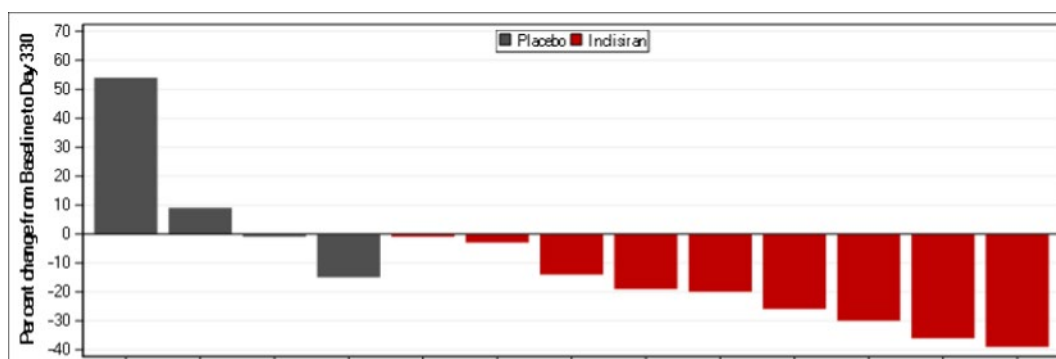
-Baseline is defined as the last measurement collected before the first dose of double-blind treatment.

-Q1, Q3: Quartile 1, Quartile 3

Source: [Study ORION-13 - Table 14.2-1.1i]

A waterfall plot of individual percentage changes in LDL-C from baseline to Day 330 by participant is provided in the figure below. While of variable magnitude, all participants in the inclisiran group showed a reduction in LDL-C, with the highest change being -39.7%. The response in the placebo group was less consistent; one participant showed a large increase in LDL-C (54.9%), while another participant showed a decrease (-15.4%). LDL-C reductions greater than 15% are considered a clinically relevant improvement with a PCSK9 directed therapy according to the 2023 EAS consensus statement update on HoFH (Cuchel et al., 2023). Two thirds (66.7%) of the participants in the inclisiran group achieved a >15% reduction in LDL-C from baseline to Day 330 and more than half (55.6%) had a ≥20% improvement in LDL-C.

Figure 5: Waterfall plot for LDL-C lowering effect at Day 330- Part 1 Primary Analysis (Full Analysis Set)



[Study ORION-13 - Figure 11-1]

For study ORION-13 no formal hypothesis testing was planned. The mean percent change in LDL-C from baseline to Day 330 was -21.6% in the inclisiran and +11.7% in the placebo group (mean between-group difference [95% CI] -33.25% [-59.17, -7.34]). A supplementary analysis excluding the participant (n=1) on LDL-apheresis showed consistent results.

A waterfall plot of individual percentage changes in LDL-C from baseline to Day 330 by participant showed a variable magnitude; all participants in the inclisiran group showed a reduction in LDL-C albeit with significant differences in magnitude, while response in the placebo group was less consistent with an increase in LDL-C of 54.9%, as well as a decrease of -15.4%.

Two thirds (66.7%) of the participants in the inclisiran group achieved a >15% and more than half (55.6%) a ≥20% reduction in LDL-C from baseline to Day 330.

Secondary analyses

In line with the primary efficacy endpoint, the mean time-adjusted percent change in LDL-C (after Day 90 up to Day 330) was -21.0% in the inclisiran and 13.0% in the placebo group, with a between-group difference (95% CI) of -33.97% (-67.54, -0.39) (see table below). A supplementary analysis excluding the participant on apheresis showed consistent results with the primary analysis.

Table 15: Secondary efficacy endpoint – Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 330- Part 1 Primary Analysis (Full Analysis Set)

	Inclisiran N=9	Placebo N=4
Time adjusted percentage change in LDL-C from Baseline after Day 90 and up to Day 330		
n	9	4
Mean ± SD	-21.0 ± 15.11	13.0 ± 41.88
Median	-17.9	1.4
Mean difference from Placebo (95% CI)	-33.97 (-67.54, -0.39)	

-Baseline is defined as the last measurement collected before the first dose of double-blind treatment.
Source: Table 14.2-2.1i

During the double-blind Part 1, the percentage changes from baseline in LDL-C were largely consistent across visits, with only isolated outliers. The participant in the placebo group treated with LDL-apheresis, showed some visit-to-visit fluctuation. Improvements consistent with the primary efficacy endpoint were seen for absolute change in LDL-C and percent change in ApoB, non-HDL-C, and total cholesterol; the mean between-group differences (95% CI) for change from baseline to Day 330 were -74.64 mg/dL (-150.93, -1.66), -23.03% (-40.13, -5.93), -32.69% (-59.81, -5.56), and -27.79% (-51.88, -3.71), respectively. Inclisiran also decreased VLDL-C; mean (±SD) percent change from baseline at Day 330 was -29.0 (±49.96%) in the inclisiran and 2.0 (±113.44%) in the placebo group. A reduction in Lp(a) was not seen and only small variable effects were observed for triglycerides, HDL-C, and Apo A1. Marked reductions in PCSK9 levels indicated effective target engagement with inclisiran; the mean percent change in PCSK9 from baseline to Day 330 was -65.3% in the inclisiran group and -5.1% in the placebo group, with a between-group difference (95% CI) of -60.20% (-79.76, -40.65). Please see also table below.

Table 16: Secondary efficacy endpoints- Absolute change in LDL-C and percentage change in Apo B, non-HDL-C, total cholesterol, PCSK9, from baseline to Day 330- Part 1 Primary Analysis (Full Analysis Set)

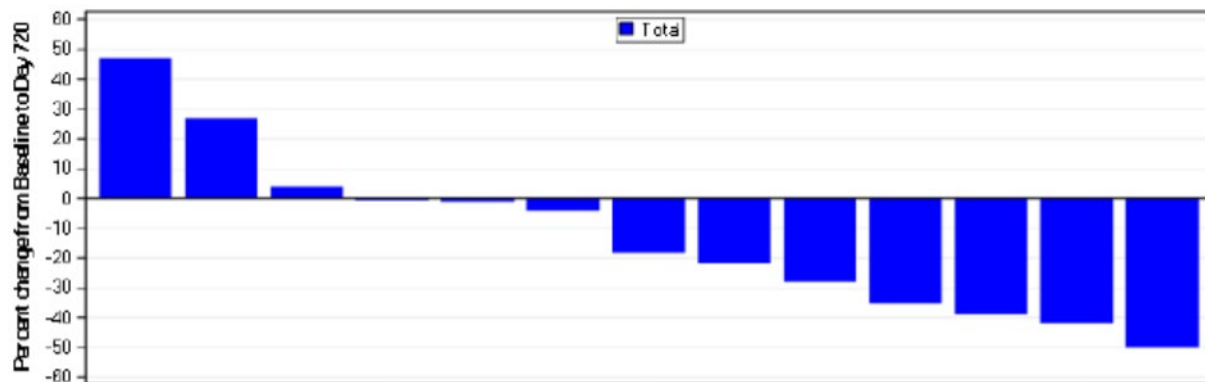
	Inclisiran N=9	Placebo N=4
LDL-C – Absolute Change (mg/dL) from BL to Day 330		
n	9	4
Mean ± SD	-62.9 ± 52.35	11.8 ± 69.94
Median	-51.0	8.0
Mean difference from Placebo (95% CI)	-74.64 (-150.93, 1.66)	
Apo B – Percentage Change from BL to Day 330		
n	9	4
Mean ± SD	-18.5 ± 10.47	4.5 ± 17.91
Median	-19.1	4.1
Mean difference from Placebo (95% CI)	-23.03 (-40.13, -5.93)	
Lp(a) – Percent Change from BL to Day 330		
n	9	4
Mean ± SD	-0.3 ± 21.27	-16.5 ± 27.29
Median	0.0	-22.2
Mean difference from Placebo (95% CI)	16.25 (-14.26, 46.76)	
Non-HDL-C – Percentage Change from BL to Day 330		
n	9	4
Mean ± SD	-23.3 ± 10.99	9.4 ± 34.93
Median	-22.3	-3.4
Mean difference from Placebo (95% CI)	-32.69 (-59.81, -5.56)	
Total Cholesterol – Percentage Change from BL to Day 330		
n	9	4
Mean ± SD	-19.1 ± 10.30	8.7 ± 30.54
Median	-18.2	-1.9
Mean difference from Placebo (95% CI)	-27.79 (-51.88, -3.71)	
PCSK9 – Percentage Change from BL to Day 330		
n	9	4
Mean ± SD	-65.3 ± 12.51	-5.1 ± 19.60
Median	-59.4	-13.0
Mean difference from Placebo (95% CI)	-60.20 (-79.76, -40.65)	

-Baseline (BL) is defined as the last measurement collected before the first dose of double-blind treatment.
Source: [ORON-13 CSR - Table 14.2-2.3i]

During the open-label Part 2, the mean (±SD) percent change in LDL-C from baseline to Day 720 was -12.6 (±28.5%) overall, -8.4 (±31.6%) in the inclisiran-inclisiran and -22.2 (±19.9%) in the placebo-inclisiran group. In a supplementary analysis excluding the participant on LDL-apheresis (placebo-inclisiran group), the mean (±SD) percentage change in LDL-C from baseline to Day 720 was -14.1 (±29.23%) overall, -8.4 (±31.61%) in the inclisiran-inclisiran and -31.1 (±10.82%) in the placebo-inclisiran group. The lower extent of the overall mean change compared to Part 1 and the difference between treatments groups were driven by 2 participants in the inclisiran-inclisiran group who had large increases in LDL-C (+27.3% and +47.4%, respectively). A waterfall plot of percentage change in

LDL-C from baseline to Day 720 by participant is provided in the figure below. While of variable magnitude, 10/13 participants showed a decrease in LDL-C at Day 720, with the highest change being –50.3% (inclisiran-inclisiran group). In 3/13 participants, LDL-C increased at Day 720, with 2 of the participants showing large increases of +27.3% and +47.4% (see above).

Figure 6: Waterfall plot for LDL-C lowering effect at Day 720- Part 2 Analysis (Open-label phase analysis Set)



Source: Figure 14.2-1.1iib

The table below shows changes in LDL-C in the 13 study participants at Day 330 (Part 1 endpoint double-blind period) and Day 720 (Part 2 endpoint open-label period), respectively. In the inclisiran-inclisiran group (n=9), 4 participants showed similar or larger decreases in LDL-C at Day 720 compared to Day 330, indicating sustained efficacy over the 2-year treatment period. In addition, 1 participant showed a small reduction in LDL-C at both timepoints, while the remaining 4 participants showed either a smaller decrease or an increase in LDL-C at Day 720 compared to Day 330; these participants also showed larger variations in percentage change in LDL-C between visits in Part 2, with decreases of up to –28.9% at visits other than Day 720. In the placebo-inclisiran group (n=4), 2 participants with increases in LDL-C at Day 330 showed decreases at Day 720; 1 participant who previously showed a decrease in LDL-C at Day 330 more than doubled this decrease at Day 720 and 1 participant treated with LDL-apheresis showed no meaningful change between Day 330 and Day 720. However, the latter participant had reductions in LDL-C of –14.4% to –18.6% between Day 450 and Day 630 before LDL-C increased at Day 720 (+4.5%).

Table 17: LDL-C lowering at Day 330 (Part 1, primary endpoint, double-blind period) and Day 720 (Part 2, end of open-label period)

Participant ID	Day 330 Inclisiran N=9	Day 330 Placebo N=4	Day 720 Inclisiran-Inclisiran Placebo-Inclisiran N=13
Percentage change from baseline to Day 330/Day 720			
002	-19.4		-22.4
003	-36.6		-42.1
004	-26.5		-50.3
005	-30.9		-28.5
006	-3.6		-1.8
007	-39.7		-0.6
008	-20.9		-4.3
009	-1.9		+27.3
010	-14.5		+47.4
011		+9.0	-18.9
012		+54.9	-35.2
013		-15.4	-39.4
014		-1.7	+4.5

Source: Table 14.2-2.5ia and Table 14.2-2.5iib

The mean ($\pm$ SD) absolute change in LDL-C from baseline at Day 720 was -39.8 (± 96.59) mg/dL overall, -27.3 (± 105.25) mg/dL in the inclisiran-inclisiran and -67.8 (± 79.20) mg/dL in the placebo-inclisiran group. The mean ($\pm$ SD) percent changes in ApoB, non-HDL-C, and total cholesterol were overall -7.3% (± 29.36) (-3.2% [± 32.89] inclisiran-inclisiran, -16.7% [± 19.86] placebo-inclisiran), -13.0% (± 23.65) (-9.1% [± 26.27] inclisiran-inclisiran, -21.8% [± 15.75] placebo-inclisiran), and -9.6% ($\pm 20.86\%$) (-7.0% [± 23.60] inclisiran-inclisiran, -15.4% [± 13.81] placebo-inclisiran), respectively. Supplementary analyses excluding the participant on apheresis showed consistent, though numerically somewhat higher reductions. Consistent lowering of PCSK9 levels was seen with inclisiran across visits; the mean ($\pm$ SD) change in PCSK9 from baseline to Day 720 was -64.1% (± 12.12) overall (-65.0% [± 13.25] inclisiran-inclisiran, -62.0% [± 10.59] placebo-inclisiran). A supplementary analysis excluding the participant on apheresis showed consistent results. During treatment with inclisiran, all participants showed consistent lowering of PCSK9 across all visits. The mean ($\pm$ SD) percent changes in Lp(a) and VLDL-C from baseline at Day 720 overall were -8.8% (± 22.03) (-8.8% [± 19.16] inclisiran-inclisiran, -8.6% [± 31.02] placebo-inclisiran) and -1.4% (± 69.03) ($+4.9\%$ [± 77.47] inclisiran-inclisiran, -15.6% [± 51.66] placebo-inclisiran), respectively. Overall, the mean percent changes in HDL-C and ApoA1 from baseline at Day 720 were $+13.9\%$ (± 18.81) ($+9.1\%$ [± 12.49] inclisiran-inclisiran, $+24.9\%$ [± 27.72] placebo-inclisiran) and $+6.5\%$ (± 10.10) ($+2.5\%$ [± 9.31] inclisiran-inclisiran, $+15.5\%$ [± 4.39] placebo-inclisiran), respectively. Only a small, variable effect was seen for triglycerides.

In line with the primary endpoint, the mean time-adjusted percent change in LDL-C (after Day 90 up to Day 330) was -21.0% in the inclisiran and 13.0% in the placebo group (between-group difference [95% CI] -33.97% [-67.54 , -0.39]). A supplementary analysis excluding the participant on apheresis showed consistent results. The percentage changes from baseline in LDL-C in Part 1 were largely consistent across visits, with isolated outliers; the participant in the placebo group treated with LDL-apheresis showed some visit-to-visit fluctuation. Reductions were seen for absolute change in LDL-C and percent change in ApoB, non-HDL-C, VLDL-C, and total cholesterol. No reduction was seen in

Lp(a) and only small variable effects for triglycerides, HDL-C, and Apo A1. As regards Part 2, there was a lower extent of the overall mean change in LDL-C compared to Part 1; the difference between treatments groups was driven by 2 participants in the inclisiran-inclisiran group who had increases in LDL-C of +27.3% and +47.4%, respectively. A waterfall plot of percentage change in LDL-C from baseline to Day 720 showed a variable magnitude; 10/13 participants had a decrease in LDL-C at Day 720, while in 3/13 participants, LDL-C increased at Day 720. In a comparison of changes in LDL-C between Day 330 (Part 1) and Day 720 (Part 2), 4 participants in the inclisiran-inclisiran group (n=9) showed similar or larger decreases in LDL-C at Day 720 compared to Day 330, 1 participant showed a small reduction in LDL-C at both timepoints, and 4 participants showed either a smaller decrease or an increase in LDL-C at Day 720 compared to Day 330. In the placebo-inclisiran group (n=4), 2 participants with increases in LDL-C at Day 330 showed decreases at Day 720, 1 participant with a decrease in LDL-C at Day 330 more than double of this decrease at Day 720, and 1 participant on LDL-apheresis no meaningful change between Day 330 and Day 720.

Ancillary analyses

Exploratory endpoints

As regards individual responsiveness of participants, during the double-blind period 6/9 (66.7%) participants in the inclisiran vs. 1/4 (25.0%) in the placebo group achieved a >15% reduction in LDL-C from baseline to Day 330, and 5/9 (55.6%) in the inclisiran vs. no participant in the placebo group achieved a $\geq 20\%$ reduction. A $\geq 30\%$ reduction in LDL-C was achieved by 3/9 (33.3%) inclisiran-treated participants. A more than 15% LDL-C reduction was described by the 2023 European Atherosclerosis Society (EAS) consensus statement update on HoFH as being a clinically relevant improvement with a PCSK9-directed therapy (Cuchel et al 2023). However, consistent with the high mean baseline LDL-C levels (inclisiran: 265.0 mg/dL, placebo: 288.3 mg/dL), only 1 participant in the inclisiran group reached the pre-specified LDL-C threshold of <130 mg/dL and no participant a LDL-C <100 mg/dL. Results are summarised in the table below.

Table 18: Individual responsiveness of participants as measured by reaching levels or percentage reduction of LDL-C at Day 330- Part 1 Primary Analysis (Full Analysis Set)

	Inclisiran	Placebo
	N=9	N=4
Responsiveness criteria at Day 330*	n/m (%)	n/m (%)
Number of participants with $\geq 10\%$ reduction in LDL-C from BL	7/9 (77.8)	1/4 (25.0)
Number of participants with > 15% reduction in LDL-C from BL	6/9 (66.7)	1/4 (25.0)
Number of participants with $\geq 20\%$ reduction in LDL-C from BL	5/9 (55.6)	0
Number of participants reaching LDL-C < 130 mg/dL	1/9 (11.1)	0
Number of participants reaching LDL-C < 100 mg/dL	0	0

-BL=baseline

*Participants can be counted in multiple categories.

-Participants who are having data at day 330 are included in denominator.

-Percentages are based out of n.

Source: Table 14.2-4.1i

During Part 2, 7/13 (53.8%) participants achieved a >15% reduction in LDL-C from baseline to Day 720, 4/9 (44.4%) in the inclisiran-inclisiran and 3/4 (75.0%) in the placebo-inclisiran group. A $\geq 20\%$ reduction in LDL-C was achieved by 6/13 participants (46.2%), 4/9 (44.4%) in the inclisiran-inclisiran and 2/4 (50.0%) in the placebo-inclisiran group. A $\geq 30\%$ reduction in LDL-C was seen in 4/13 (30.8%) participants, 2/9 (22.2%) in the inclisiran-inclisiran and 2/4 (50.0%) in the placebo-inclisiran group. Only 2 participants reached the pre-specified LDL-C threshold of <130 mg/dL (1 participant per

group) and 1 participant (inclisiran-inclisiran group) achieved an LDL-C <100 mg/dL. No participant reached an LDL-C below 70 mg/dL.

Table 19: Individual responsiveness of participants as measured by reaching levels or percentage reduction of LDL-C at Day 720- Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran	Placebo- Inclisiran	Total
	N=9	N=4	N=13
Responsiveness criteria at Day 720*	n/m (%)	n/m (%)	n/m (%)
Number of participants with ≥ 10% reduction in LDL-C from BL	4/9 (44.4)	3/4 (75.0)	7/13 (53.8)
Number of participants with > 15% reduction in LDL-C from BL	4/9 (44.4)	3/4 (75.0)	7/13 (53.8)
Number of participants with ≥ 20% reduction in LDL-C from BL	4/9 (44.4)	2/4 (50.0)	6/13 (46.2)
Number of participants with ≥ 30% reduction in LDL-C from BL	2/9 (22.2)	2/4 (50.0)	4/13 (30.8)
Number of participants reaching LDL-C < 130 mg/dL	1/9 (11.1)	1/4 (25.0)	2/13 (15.4)
Number of participants reaching LDL-C < 100 mg/dL	1/9 (11.1)	0	1/13 (7.7)

-BL=baseline

*Participants can be counted in multiple categories.

-Participants who are having data at Day 720 are included in denominator.

-Percentages are based out of n.

Source: Table 14.2-4.1ii

An exploratory analysis of LDL-C response by genotype included only participants with adjudicated central laboratory genetic results (n=12/13). During Part 1, consistent LDL-C lowering was seen with inclisiran across the included genetic variant groups. For the 2 main genotypes, compound heterozygous LDLR defective/defective and compound heterozygous LDLR null/defective, the LDL-C reductions with inclisiran were -20.5% (n=4) and -18.1% (n=4), respectively. See also table below.

Table 20: Summary of LDL-C by genetic variant group on Day 330- Part 1 Primary Analysis (Full Analysis Set)

Genotype	Statistics	Inclisiran		Placebo	
		Base (mg/dL)	% Change	Base (mg/dL)	% Change
Compound heterozygous LDLR defective/defective (N=4/1)					
	n	4	4	1	1
	Mean (SD)	240.8 (110.37)	-20.5 (11.99)	233.0 (NA)	9.0 (NA)
Compound heterozygous LDLR null/defective (N=4/1)					
	n	4	4	1	1
	Mean (SD)	312.0 (130.78)	-18.1 (14.35)	291.0 (NA)	-1.7 (NA)
Double heterozygous LDLR/ApoB (N=0/1)					
	n			1	1
	Mean (SD)	NA	NA	182.0 (NA)	54.9 (NA)
Homozygous LDLRAP1 (N=1/0)					
	n	1	1		
	Mean (SD)	174.0 (NA)	-39.7 (NA)	NA	NA

-Base = Baseline, % change = Percentage change from baseline to Day 330.

-Baseline is defined as the last measurement collected before the first dose of double-blind treatment

-At each time point, only participants with a value at both Baseline and that time point are included.

-Genetic variant group from central laboratory data has been used for analysis.

Source: Table 14.2-3.1i

For the open-label Part 2, a subgroup analysis of percent changes in LDL-C from baseline at Day 720 by genotype was not specified in the protocol as an exploratory endpoint but was added for

completeness in the SAP. For the compound heterozygous LDLR defective/defective subgroup (n=5), the mean ($\pm$ SD) change in LDL-C overall was -20.7% (± 19.79) (-21.2% [± 22.81] inclisiran-inclisiran [n=4], -18.9% placebo-inclisiran group [n=1]). For the compound heterozygous LDLR null/defective subgroup (n=5), the mean ($\pm$ SD) change in LDL-C was $+2.9\%$ (± 36.21) overall ($+2.5\%$ [± 41.79] inclisiran-inclisiran [n=4], $+4.5\%$ placebo-inclisiran [n=1]); changes in LDL-C ranged from -42.1% to $+47.4\%$ and the 2 participants with large increases in LDL-C (see also above) are both part of this subgroup (014, 009).

Carotid intima media thickness (cIMT) was measured as an exploratory endpoint at Day 1 (baseline), Day 330 (Year 1), and Day 720 (Year 2) by ultrasonography, using local machines; right and left common carotid arteries were assessed. No effect on changes from baseline to Day 330 in cIMT was seen in either treatment group. The mean ($\pm$ SD) baseline cIMT for the average of right and left cIMT was 0.492 mm (± 0.097) in the inclisiran and 0.486 mm (± 0.070) in the placebo group. At Day 330, the mean ($\pm$ SD) changes from baseline were -0.005 mm ± 0.067 in the inclisiran and -0.033 mm (± 0.034) in placebo group. At Day 720 (Part 2), the mean ($\pm$ SD) change from baseline was 0.053 mm (± 0.112) overall, 0.049 mm (± 0.098) in the inclisiran-inclisiran and 0.063 mm (± 0.176) in the placebo-inclisiran group.

As regards frequency of LDL-apheresis, only 1/13 (7.7%) participant in the placebo-inclisiran group (1/4; 25%) was treated with LDL-apheresis; thus no relevant analysis is feasible. The frequency of LDL-apheresis for this participant remained unchanged at "every 2 weeks" over the course of the study, except for occasionally longer periods caused by exceptional circumstances (e.g., vacation).

Pharmacokinetic results

An exploratory endpoint for this study was the evaluation of inclisiran concentrations. For pharmacokinetic results, see section Pharmacokinetics above.

As regards exploratory results, 6/9 (66.7%) participants in the inclisiran versus 1/4 (25.0%) in the placebo group achieved a $>15\%$ reduction in LDL-C from baseline to Day 330, 5/9 (55.6%) versus none, respectively a $\geq 20\%$, and 3/9 (33.3%) versus none a $\geq 30\%$ reduction. However, only 1 participant in the inclisiran group reached the pre-specified LDL-C threshold of <130 mg/dL and none an LDL-C <100 mg/dL. During Part 2, 7/13 (53.8%) participants achieved a $>15\%$ reduction in LDL-C from baseline to Day 720, 6/13 (46.2%) a $\geq 20\%$, and 4/13 (30.8%) a $\geq 30\%$ reduction. Only 2 participants reached the pre-specified LDL-C threshold of <130 mg/dL, 1 participant an LDL-C <100 mg/dL, and no participant an LDL-C below 70 mg/dL. Consistent LDL-C lowering was seen across the included genetic variants. No clinically relevant effect of inclisiran on carotid intima media thickness (cIMT) was seen. Since only 1 participant was treated with LDL-apheresis, no relevant analysis is feasible in this regard.

ORION-16 (CKJX839C12301, EudraCT No.: 2020-002757-18): "Two part (double-blind inclisiran versus placebo [Year 1] followed by openlabel inclisiran [Year 2]) randomised 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"

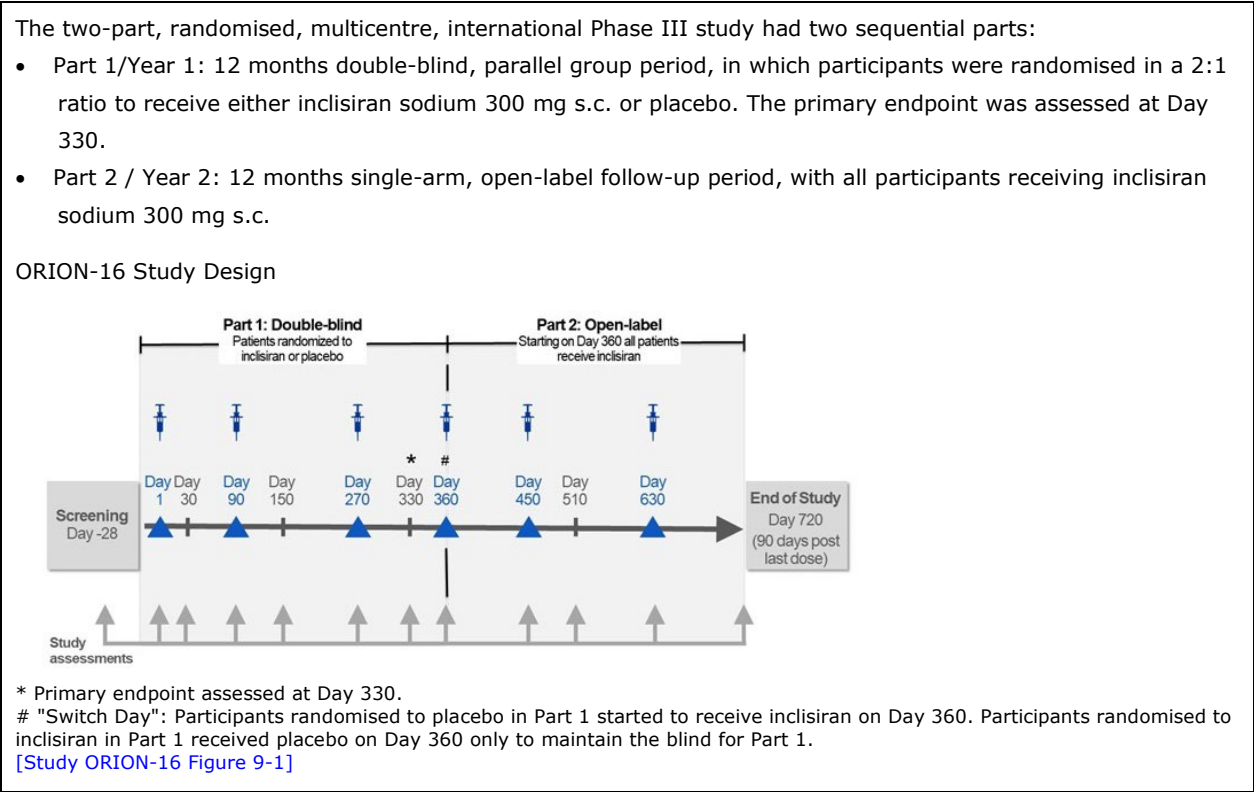
Study ORION-16 evaluated safety, tolerability, and efficacy of inclisiran in adolescents from 12 to less than 18 years of age with heterozygous familial hypercholesterolemia (HeFH) and elevated low-density

lipoprotein cholesterol (LDL-C). It is part of the inclisiran paediatric program as agreed with European Medicines Agency (EMA) in the paediatric investigation plan (PIP; EMEA-002214-PIP01-17-M02, P/0322/2023) and intended to support the registration of inclisiran in adolescents with HeFH. Study ORION-16 also included pharmacokinetic (PK) and pharmacogenetic assessments; PK assessment was based on sparse PK sampling (i.e. 3 samples at the Day 1 visit; pre-dose immediately before the first administration of study drug, 4-, and 24-hours after first dose; see section Pharmacokinetics.

The study was conducted in two-parts, a double-blind, inclisiran versus placebo part (Year 1) followed by an open-label inclisiran part (Year 2). It was a randomised, multicentre Phase III study in adolescents aged 12 to <18 years with HeFH and elevated LDL-C (>130 mg/dL; 3.4 mmol/L) on stable, individualised, optimal standard of care (SoC) background lipid-lowering therapy including maximally tolerated statin treatment, at the Investigator’s discretion.

According to the data provided, study ORION-16 was conducted in compliance with Good Clinical Practice (GCP). The study design is summarised in the following table.

Table 21: Summary of study design



The completed paediatric study ORION-16 (CKJX839C12301) is part of post-authorisation measures for Leqvio (inclisiran) and was intended to investigate the use of inclisiran in adolescents from 12 to less than 18 years of age with heterozygous familial hypercholesterolemia (HeFH) and elevated LDL-cholesterol. Currently, inclisiran is only licensed in adults, including patients with HeFH, from 18 years of age onwards. The study has been submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study ORION-16 was conducted as a two-part, multicentre, randomised study; Part 1 (year 1) investigated inclisiran versus placebo in a double-blind setting, while in Part 2 (year2) all participants received open-label inclisiran.

Methods

Study participants

The study population consisted of adolescents (male or female; 12 to <18 years) with a genetic or clinical diagnosis of HeFH and LDL-C >130 mg/dL (3.4 mmol/L) and being on a maximally tolerated dose of statin (at investigator's discretion) with or without other lipid lowering therapy (e.g., ezetimibe).

Key inclusion criteria were:

- HeFH diagnosed either by genetic testing or on phenotypic criteria (according to the EAS Consensus Panel),
- fasting LDL-C >130 mg/dL (3.4 mmol/L) at screening,
- on maximally tolerated dose of statin (Investigator's discretion) with or without other lipid-lowering therapy (e.g. ezetimibe),
- participants on lipid-lowering therapies (such as statin and/or e.g. ezetimibe) should have been on a stable dose for ≥ 30 days before screening with no planned medication or dose changes during study participation,
- fasting triglycerides <400 mg/dL (4.5 mmol/L) at screening, and
- eGFR >30 mL/min/1.73 m² at screening.

Key exclusion criteria were:

- previous treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9,
- active liver disease or unexplained, confirmed ALT, AST elevation >3x ULN, or total bilirubin elevation >2x ULN (except patients with Gilbert's syndrome),
- pregnant or nursing females,
- HoFH,
- recent and/or planned use of other investigational medicinal products or devices,
- secondary hypercholesterolemia, e.g. hypothyroidism or nephrotic syndrome, and
- major adverse cardiovascular events within 3 months prior to randomization.

The study included male and female adolescents from 12 to less than 18 years of age with a genetic or clinical diagnosis of HeFH and an LDL-C >130 mg/dL who were on a maximally tolerated dose of an HMG-CoA reductase inhibitor (statin) with or without other lipid lowering therapy (excluding PCSK9 inhibitors). Patients with homozygous familial hypercholesterolemia (HoFH) or secondary hypercholesterolemia were excluded.

Treatments

During Part 1 (year 1) participants received either investigational drug inclisiran sodium 300 mg (equivalent to 284 mg inclisiran) in 1.5 ml solution (batch numbers 2040329, 2040834, 2040921, 2046470) or reference drug placebo formulation to this active drug formulation (batch numbers 2040833, 2041156, 2041335, 2043088) for s.c. injection.

In Part 2 (year 2) all participants received Inclisiran sodium 300 mg (batch numbers 2040329, 2040979, 2041729, 2047184).

During Part 1, participants received either inclisiran at the licensed standard dose and posology for adults or placebo. During Part 2, all participants received standard dose inclisiran.

Objectives / outcomes / endpoints

During the double-blind Part 1 (year 1) of the study, the primary efficacy and safety data comparing inclisiran to placebo were collected. The open-label single arm Part 2 (year 2) of the study allowed the collection of longer-term data on inclisiran, with a focus on longer-term safety.

Objectives and endpoints of study ORION-16 are summarised in the table below.

Table 22: Summary of objectives and endpoints of study ORION-16

	Objective	Endpoint
Primary	To demonstrate superiority of inclisiran compared to placebo in reducing LDL-C [percent change] at Day 330 (Year 1) in adolescents (aged 12 to <18 years) with HeFH and elevated LDL-C	Percentage change in LDL-C from baseline to Day 330 (Year 1)
Secondary	- 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 Apo B, Lp(a), 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 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	- Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1) - Absolute change in LDL-C from baseline to Day 330 (Year 1) - Percent change in Apo B, Lp(a), non-HDL-C, and total cholesterol from baseline to Day 330 (Year 1) - Percent change and absolute change in LDL-C, Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, HDL-C, VLDL-C, ApoA1 and PCSK9 from baseline to each assessment time up to Day 720 (Year 2) - Incidence, severity and relationship to study drug of treatment-emergent AEs and SAEs; vital signs; laboratory parameters; ADA measurement; growth (height, weight, BMI); pubertal development (steroid hormones and Tanner staging)
Exploratory	- Explore the effect of inclisiran compared to placebo (at Day 330) and long-term (at Day 720) on the individual responsiveness of participants - Explore the effect of inclisiran compared to placebo (at Day 330) and long-term (at Day 720) on achieving at least 50% LDL-C reduction	- Individual responsiveness of participants defined through on treatment LDL-C levels of <50 mg/dL, <70 mg/dL, <100 mg/dL and <130 mg/dL at Day 330 (Year 1) and Day 720 (Year 2) ≥50% LDL-C reduction from baseline at Day 330 (Year 1) and Day 720 (Year 2)

	Objective	Endpoint
	- Explore the effect of inclisiran compared to placebo on the response of LDL-C reduction by underlying causal mutations of HeFH at Day 330 (Year 1) - Explore the effect of inclisiran compared to placebo (at Day 330) and long-term (at Day 720) on the carotid intima-media thickness (cIMT) - Explore (sparse) PK of inclisiran in adolescents with HeFH (subgroup of 12 - 15 participants)	- Percentage change and absolute change in LDL-C from baseline to Day 330 (Year 1), by type of underlying causal mutation - Change in cIMT from baseline to Day 330 (Year 1) and Day 720 (Year 2) - Evaluation of inclisiran concentrations at 4 and 24 hours after the first dose

For the primary efficacy assessment reflexive LDL-C was used for analysis, i.e., Friedewald formula to calculate LDL-C levels in a first step, and in those cases where the formula is not valid (i.e., triglycerides >400 mg/dL, calculated LDL <40 mg/dL), in a second step, ultracentrifugation to measure LDL-C directly.

Participants were in a fasted state for all efficacy laboratory assessments. From randomisation (Day 1) until Day 360, the results were blinded to participants, investigator staff, persons performing the assessments, and the clinical trial team, except for bioanalytical analysis related to PK which was conducted in an unblinded manner.

In addition, carotid intima-media thickness (cIMT) was measured locally by ultrasonography and was exploratory / hypothesis-generating in nature.

All participants were invited to optional pharmacogenetic analyses of the underlying causal mutation(s) of their HeFH. Samples were analysed for potential mutations in the LDL receptor (LDLR), ApoB, PCSK9, and LDLR adaptor protein 1 (LDLRAP1) genes.

The key safety assessments consisted of monitoring and recording of all adverse events (AEs), laboratory evaluations (haematology, biochemistry, urinalysis, pregnancy tests), anti-drug antibody (ADA) measurement, vital signs, growth (height, weight, body mass index [BMI]), and pubertal development (sex hormones, Tanner staging). Other safety evaluations were physical examinations, neurological evaluations, and electrocardiograms (ECGs).

The primary endpoint was the percentage change in LDL-C from baseline to the end of the double-blind treatment period at day 330 (year 1).

Secondary endpoints included absolute change in LDL-C and other lipid parameters during Part 1 as well as assessments from baseline to the end of the open-label Part 2, i.e. day 720.

Exploratory endpoints included individual responsiveness of participants, changes in LDL-C by type of underlying causal mutation, change in carotid intima-media thickness (cIMT), and evaluation of inclisiran pharmacokinetics (PK) based on sparse data.

The endpoints are considered to be in line with previous adult inclisiran studies.

Sample size

Sample size was calculated based on detecting a reduction of at least 30% in the inclisiran compared to the placebo group in percent change of LDL-C from baseline to Day 330. The primary efficacy

variable was assumed to have a standard deviation of 30% in the control group and 20% in the inclisiran group. These assumptions were based on observed results from adult inclisiran studies.

The initial planned sample size was approximately 150 adolescents; this was adjusted to at least 102 participants in protocol amendment 1 dated 28-Oct-2022. A sample size of at least 102 participants provided more than 90% power to detect a 30% reduction at significance level of 0.025 (one-sided test) in a 2:1 (inclisiran vs. placebo) randomisation ratio.

The initial planned sample size of 150 adolescents was significantly reduced to at least 102 participants in a protocol amendment in October 2022. A sample size of ≥ 102 participants allowed only for detecting a $\geq 30\%$ reduction in LDL-C in the chosen setting.

Randomisation and blinding (masking)

Part 1 of the study was double-blind and placebo-controlled. Participants, investigator staff, persons performing the assessments, and the clinical trial team were blinded to the identity of the treatment from the time of randomisation until at least database lock for all Part 1 (year 1) data. Exceptions were the independent statistician and programmer to prepare interim analysis reports for the DMC, and the PK analyst to avoid unnecessary analysis of placebo samples; in addition, a PK interim analysis (IA) team had access to unblinded individual-level PK/baseline data in order to update a PK extrapolation to paediatrics before the Part 1 database lock to support early planning of a dose selection strategy for paediatric studies in younger children. Part 2 of the study had a single-arm, open-label design.

After baseline visit (Day 1), participants were randomised by interactive response technology in a 2:1 ratio to receive double-blind s.c. injections of inclisiran sodium 300 mg or placebo in Part 1 (year 1) of the study (days 1, 90, 270). On day 360 ("switch day"), participants randomised to placebo in Part 1 received inclisiran and participants randomised to inclisiran in Part 1 received placebo. This dose remained blinded in order to maintain the blind for Part 1 of the study. Subsequently, all participants received open-label s.c. injections of inclisiran sodium 300 mg in Part 2 (year 2).

Investigational and control drugs were supplied by the MAH as single-use pre-filled syringes for s.c. injection. Placebo was supplied as sterile normal saline (0.9% sodium chloride in water for injection) and administered as a 1.5 mL s.c. injection to match the dose in the inclisiran arm. The placebo pre-filled syringes were blinded and were identical in appearance to their active counterparts.

Part 1 was conducted randomised, double-blind, and placebo-controlled. In Part 2, all participants received open-label inclisiran.

Statistical methods

Efficacy and safety analyses of Part 1 data were performed after all participants completed the Day 360 visit or discontinued prior to the Day 360 visit; analyses of Part 2 data were performed after all participants completed the Day 720 (EoS) visit or discontinued prior to the Day 720 visit. In cases where the dosing time at Day 360 did not allow to determine whether data belonged to Part 1 or 2, the data were considered to belong to Part 1.

The following data sets were analysed. The Screened Set (SCR) included all participants who provided study informed consent. The Randomised Set (RAN) consisted of all participants who received a randomisation number, regardless of whether double-blind treatment was received or not. The Full Analysis Set (FAS) consisted of all randomised participants with the exception of those mis-randomised participants who did not receive study drug; mis-randomised participants were defined as those who were not qualified for randomization but were inadvertently randomised into the study. According to

the intent to treat principle, participants were analysed according to the treatment they were assigned to during the randomisation procedure. The FAS was used in analyses for the primary, secondary, and exploratory efficacy objectives in Part 1 of the study. The Safety Set (SAF) included all participants who received at least 1 dose of study treatment. Participants were analysed according to the study treatment received. This was the primary population for the safety analyses in Part 1. The SAF allowed the inclusion of nonrandomised participants who received double-blind treatment in error. The PK analysis Set included all randomised participants who had at least 1 PK measurement. Participants were analysed according to the treatment they received. This was the primary population for the PK analyses. The Open-label Phase Analysis Set (OAS) included all participants who entered Part 2 of the study and received at least 1 dose of study treatment in Part 2. The OAS was used to analyse data from participants who entered Part 2.

For the primary endpoint percentage change in LDL-C from pre-dose baseline measurement to Day 330, the primary null hypothesis (H_0) was the difference (inclisiran minus placebo) in the LS mean percentage change from baseline to the Day 330 visit in LDL-C = 0 and the alternative hypothesis (H_a) the difference in the LS mean percentage change from baseline to the Day 330 visit in LDL-C < 0. The primary objective would be achieved if the null hypothesis is rejected at a significance level of 0.025 (one-sided test). The primary endpoint was analysed using an analysis of covariance (ANCOVA) model, in which the response variable was the LDL-C percentage change from baseline to Day 330. The model included the fixed effects of treatment group and baseline age group (≥ 12 -<15 or ≥ 15 -<18 years of age), with baseline LDL-C as a covariate. No remaining intercurrent events were expected. Multiple imputation was used to impute missing data based on a washout model which is a modified control-based pattern-mixture-model. The wash-out model imputed the missing values for participants in the inclisiran group with data from participants with similar background characteristics in the placebo group, under the assumption of missing not at random (MNAR) unless the participants with missing values completed the first 3 doses and had data available after Day 330. For participants who completed the first 3 doses of inclisiran and had data available after Day 330, and participants in the placebo group (regardless of how many doses taken), the missing values were imputed under the assumption of missing at random (MAR). A total of 100 imputed datasets were created. The ANCOVA model was fit to each imputed dataset, and results were combined using Rubin's combination rules. For sensitivity analyses of the primary endpoint a linear mixed-effect model for repeated measures (MMRM) analysis without multiple imputation (under an implicit assumption of MAR), a MMRM analysis on the imputed datasets, and multiple imputation will be based on a control-based pattern mixture model (under the assumption of MNAR), and an ANCOVA using the washout model including the following fixed effects: baseline concomitant lipid-modifying therapies, baseline age group, region, and a treatment-by region interaction were performed. Supplementary analyses included LDL-C percent change from baseline to Day 330 by subgroups gender, age group (≥ 12 to <15, ≥ 15 to <18 years of age), race, ethnicity, BMI, region, baseline statin use, baseline LDL-C, and baseline PCSK9. The MMRM model was used to evaluate the difference between inclisiran and placebo groups in each subgroup.

The key secondary endpoints time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 330 (year 1), defined as the average of percent changes from baseline to Days 150, 270, and 330 and absolute change in LDL-C and percentage change in Apo B, Lp(a), non-HDL-C, and total cholesterol from baseline to Day 330 (year 1) were analysed using the same ANCOVA with multiple imputation using wash-out model, except the time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330; the latter was analysed using a MMRM model with a control-based pattern mixture model for missing value imputation. A hierarchical testing strategy was applied to control the family-wise type I error rate at the one-sided significance level of $\alpha = 0.025$ to assess the superiority of inclisiran over placebo; hypotheses were tested in the order listed above. For sensitivity analysis a MMRM analysis without multiple imputation that assumed missing data are MAR

was performed and MMRM analysis using control-based pattern mixture model for missing value imputation was performed for other key secondary endpoints. Supplementary analyses of the key secondary endpoints were performed in subgroups as specified for the primary analysis. The MMRM model (using control-based pattern mixture model for missing value imputation) was used to evaluate the difference between inclisiran and placebo groups in each subgroup. Another supplementary analysis for Lp(a) was applied in log-transformed scale using the same MMRM without multiple imputation specified above.

Other secondary efficacy endpoints included the percent change and absolute change from baseline throughout the time course up to Day 720 (year 2) of LDL-C, Apo B, Lp(a), non-HDL-C, total cholesterol, triglycerides, HDL-C, VLDL-C, Apo A1, and PCSK9. Descriptive summaries by treatment group were provided for these endpoints.

For exploratory variables LDL-C <50 mg/dL, <70 mg/dL, <100 mg/dL, and <130 mg/dL, as well as $\geq 50\%$ LDL-C reduction from baseline, frequencies and percentages of participants were summarised by treatment group at Day 330 (year 1) and Day 720 (year 2). In addition, reductions of $\geq 20\%$ and $\geq 30\%$ LDL-C from baseline were summarised at Day 720 (year 2) as supportive analyses. Summary statistics for LDL-C percent and absolute change from baseline were provided by treatment group in subgroups defined by underlying genetic mutation(s). Furthermore, values of cIMT were summarised at each time point by treatment group. Change in cIMT from baseline to Day 330 (year 1) and Day 720 (year 2) were summarised by treatment group.

As regards PK analyses, inclisiran plasma concentration data were listed by treatment, participant, and sampling time point. Descriptive summary statistics were provided by sampling time point, including the frequency (n, %) of concentrations below the LLOQ; these were reported as zero. Summary descriptive statistics included mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV; arithmetic and geometric), median, minimum, and maximum. An interim analysis (IA) on PK data was performed to update a PK extrapolation to paediatrics (i.e., to further refine the extrapolation from adult PK data with adolescent PK data) as part of developing a dose selection strategy for planned future paediatric studies in younger children <12 years of age.

As regards safety, the number and percentage of participants who had treatment-emergent adverse events (AEs), treatment-emergent serious AEs (SAEs), injection site reactions, and treatment-emergent events related to other safety topics (including cardiac, hepatic, hypersensitivity, musculoskeletal, neurological, renal, psychiatric, new onset or worsening of diabetes) were summarised. For laboratory data and vital signs, absolute values and change from baseline were summarised. The number and percentage of participants with categorical criteria were summarised. In addition, the number and percentage of participants with newly occurring notable abnormalities for selected laboratory parameters and vital signs were summarised. The number and percentage of participants with treatment-induced transient and persistent anti-drug antibodies (ADA) and no treatment-induced ADA were summarised. Shift from baseline in Tanner stage was summarised by sex, treatment, and visit. Shift in menarche status from baseline was summarised by visit and treatment group. Subgroup analyses by gender, age group (≥ 12 to <15 and ≥ 15 to <18 years of age), race, and BMI were performed for all treatment-emergent AEs and separately for injection site reactions. IA for safety monitoring were planned at regular intervals. IA before unblinding for the analysis of Part 1 of the study were performed by an independent statistician/programmer not involved in the trial conduct. The interim results were reviewed by the independent data monitoring committee (DMC).

The CHMP concluded that the statistical methods applied were adequate.

Results

Participant flow, numbers analysed, and recruitment

Study ORION-16 was started on 27 January 2021 (first participant first visit) and completed on 27 November 2024 (last participant last visit); the CSR version 1.0 is dated 14 March 2025.

A total of 141 participants were enrolled, 93 in the inclisiran and 48 in the placebo group. The were randomised from 51 study centres in 26 countries (Argentina 1, Brazil 3, Canada 1, Czech Republic 2, France 3, Germany 2, Greece 1, Hungary 1, Israel 2, Italy 4, Jordan 1, Lebanon 1, Malaysia 1, Netherlands 2, Norway 1, Poland 2, Russian Federation 2, Slovakia 1, Slovenia 1, South Africa 3, Spain 4, Switzerland 1, Taiwan 1, Turkey 4, United Kingdom 1, United States of America 5).

Of the 141 randomised participants, 98.6% (139/141) completed Part 1, 97.8% (91/93) in the inclisiran and 100% (48/48) in the placebo group. The reasons for the two discontinuations were participant/guardian decision (change of mind regarding study participation) and physician decision (following discontinuation of study drug due to mild AEs of nausea and vertigo). All 139 participants who completed Part 1 entered and completed Part 2, i.e., 91 participants in the inclisiran-inclisiran and 48 in the placebo-inclisiran group.

Of the 141 participants randomised, 139 completed Part 1 and entered and completed Part 2.

Conduct of the study

The study protocol was amended twice. Key features of each amendment are given in the table below. There were no other changes to the study conduct.

Table 23: Protocol amendments

Version and date	Summary of key changes
Amendment 1, 28-Oct-2022	To reduce the sample size of the study from approximately 150 participants to a minimum of 102 participants; the revised sample size was based on a review of existing evidence. The revised sample size of at least 102 participants provides more than 90% power to assess the primary efficacy endpoint, under conservative assumptions of a 30% between-group difference and standard deviations of 30/40% for the inclisiran and placebo groups. However, the actual enrolment was 141 participants, which increased the statistical power for the primary efficacy endpoint and contributed additional safety data.
Amendment 2, 17-Feb-2023	To add an interim analysis for the PK data collected on Day 1, to update a PK extrapolation to paediatrics, i.e., to further refine the extrapolation from adult PK data with adolescent PK data, covering a lower range of body weights and ages. The updated PK extrapolation was critical as part of developing a dose selection strategy for planned future paediatric studies in younger children (<12 years). The PK IA was performed by a separate team not involved in any other study activities before the Part 1 (year 1) database lock, when the study was unblinded as per protocol.

As regards changes in planned analyses, after the Part 1 (year 1) database lock, an analysis of percentage change in PCSK9 from baseline to Day 330 using an ANCOVA model was added with treatment as fixed effect and baseline PCSK9 and baseline age group as covariates; only descriptive summary statistics by treatment and visit was pre-specified for PCSK9.

After the Part 2 (year 2) database lock, an implausible increase in Lp(a) at Day 720 was observed for participant C12301- 013 (inclisiran-inclisiran group), which had a large impact on the mean percent

change from baseline for this parameter. The Lp(a) value for this participant was 17 nmol/L at Day 1 and consistently low at subsequent visits but markedly higher (337 nmol/L) at Day 720, corresponding to an 1882.4% increase from baseline (Listing 16.2.6-1.2ii). This result was not plausible given that Lp(a) levels are largely genetically determined. An analytical error at the central laboratory was excluded as a potential reason for the unusual value at Day 720; however, it was noticed that participant C12301- 014 (inclisiran-inclisiran group), who had the Day 720 visit at the same investigational site on the same day as participant C12301- 013, showed an atypical decrease in Lp(a) at Day 720. The Lp(a) value for this participant was 355 nmol/L at Day 1 and consistently high at subsequent visits but only 16 nmol/L at Day 720 (Listing 16.2.6-1.2ii). Hence, the most plausible explanation for the observed outlier values at Day 720 is a sample mix-up between the two participants C12301- 013 and C12301- 014. There is no evidence to suggest sample mix-ups at any other time points for these two participants. A post-hoc sensitivity analysis, excluding participants C12301- 013 and C12301- 014 from the OAS, was therefore performed. As a conservative approach, absolute and percent mean changes from baseline at Day 720 were analysed for all lipid/lipoprotein secondary endpoint parameters, i.e., Lp(a), LDL-C, Apo B, non-HDL-C, total cholesterol, HDL-C, ApoA1, VLDL-C, and triglycerides. For all other lipid/lipoprotein parameters, including LDL-C, results of the sensitivity analysis were consistent with the primary analysis, with no clinically meaningful differences.

With amendment 1 in October 2022, the sample size of the study was significantly reduced (from 150 to ≥ 102 participants). Nevertheless, 141 participants were enrolled. Amendment 2 in February 2023 added an interim analysis for the PK data collected on Day 1. The changes in the planned conduct of the study are not considered to have influenced the outcome of study ORION-16.

Baseline data

Overall, demographic and baseline characteristics were comparable between the treatment groups. Approximately half of the randomised participants were female (53.2%; 75/141) and the mean age was 15.1 years (range 12 to 17 years). The majority of participants (90.8%; 128/141) were white, with all participants of other races being in the inclisiran group. The mean ($\pm$ SD) BMI was 22.7 $\pm$ 4.88 kg/m². Mean ($\pm$ SD) baseline LDL-C and PCSK9 levels of study participants were 183.1 $\pm$ 48.67 mg/dL and 376.4 $\pm$ 157.39 ng/mL, respectively. Overall, 92.9% (131/141) of participants (96.8% inclisiran, 85.4% placebo) received statin treatment. About one fourth of participants (24.8%; 35/141) were treated with other lipid-lowering treatments, mostly ezetimibe (23.4%; 33/141), with a similar proportion in both groups. All participants had HeFH, diagnosed either clinically by EAS Consensus Panel criteria or clinically and genetically; the majority of participants (95.7%, 135/141) had a genetic diagnosis of HeFH, including LDLR null (negative) mutations (51.1%; 72/141) and LDLR defective mutations (39.7%; 56/141) as the most prevalent variants. There were no important differences in genotypes between treatment groups.

In Part 1, 12.1% (17/141) of participants reported at least one protocol deviation, 16.1% (15/93) in the inclisiran and 4.2% (2/48) in the placebo group. The most common protocol deviations (>6 participants) were PK sample(s) being taken either before a separate consent signature to the main informed consent form was provided or without a separate informed consent; samples without consent were not used. Three (3) protocol deviations were related to changes in concomitant lipid-lowering treatment, a change from pravastatin to ezetimibe during the screening period, a prolonged interruption of atorvastatin and ezetimibe before Day 330 visit in the inclisiran, and an increase of the rosuvastatin dose in the placebo group. In Part 2, 1.4% (2/139) of participants reported at least one protocol deviation, all (2.2%; 2/91) in the inclisiran-inclisiran group. The first protocol deviation was receipt of study treatment twice within <60 days (i.e., 53 days), which did not cause any AEs and the

second concerned accidental unblinding by site in interactive response technology of the Part 1 treatment assignment at the EoS/Day 720 visit.

During Part 1, the mean duration on study and of exposure to study treatment were 357.9 days in the inclisiran and 362.9 days in the placebo group. For Part 2, the mean duration on study and the mean duration of exposure to study treatment were 361.1 days and 360.6 days, respectively, with similar durations in the inclisiran-inclisiran and placebo-inclisiran groups. Over the entire study duration (Part 1 and 2), 97.9% (138/141) of participants were administered all 6 doses of study drug. The mean duration on study was 714.6 days and the mean duration of exposure to study treatment 714.1 days, with similar durations in the inclisiran-inclisiran and placebo-inclisiran groups. The overall patient years of exposure to study treatment was 275.6, 180.5 in the inclisiran-inclisiran and 95.1 in the placebo inclisiran group.

Demographic and baseline characteristics were comparable between treatment groups. Approximately half of the participants were female and the mean age was 15.1 years (range 12 to 17 years). The majority of participants had a genetic diagnosis of HeFH and there were no important differences in genotypes between treatment groups.

Outcomes and estimation

Primary analysis

The LDL-C LS mean percent change (95% CI) from baseline to Day 330 was -27.14% (-32.04, -22.24) in the inclisiran and 1.40% (-3.97, 6.78) in the placebo group, with a between-group difference (95% CI) of -28.54% (-35.81, -21.27; $p < 0.0001$). The study met its primary objective of demonstrating superiority of inclisiran compared to placebo in reducing LDL-C in adolescents with HeFH; it showed a clinically relevant and statistically significant reduction in LDL C with inclisiran.

Table 24: Primary Efficacy Endpoint – Percent Change in LDL-C from baseline to Day 330 (Part 1, Full Analysis Set)

Inclisiran N=93 PCHG LS Mean (95% CI)	Placebo N=48 PCHG LS Mean (95% CI)	Difference between Inclisiran and Placebo	
		LS Mean (95% CI)	One-sided p-value
-27.14 (-32.04, -22.24)	1.40 (-3.97, 6.78)	-28.54 (-35.81, -21.27)	<.0001

-PCHG=Percentage Change from baseline.

-A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. ANCOVA, assuming unequal variance for treatment group, on each of the 100 datasets was performed by including fixed effects for treatment and baseline LDL-C and baseline age group as a covariate. Treatment effects from the 100 analyses were combined using Rubin's Method.

Source: [Study ORION-16 - Table 14.2-1.1i]

The primary analysis used a pre-specified multiple imputation washout model/ANCOVA. Three (3) pre-specified sensitivity analyses with respect to handling missing data were performed, a linear-MMRM without multiple imputation, a MMRM analysis using a control-based pattern mixture model (PMM), and ANCOVA using the multiple imputation washout model including the fixed effects baseline concomitant lipid-modifying therapies, baseline age group, region, and treatment by-region interaction.

Results were consistent with the primary analysis independent of the sensitivity analysis used. The between-group differences (95% CI) for LS mean change in LDL-C were -29.10% (-36.88, -21.32), -28.69% (-36.44, -20.93), and -32.15% (-42.42, -21.87), respectively (all p-values <0.0001).

Subgroup analyses by age group, gender, race, ethnicity, BMI, region, baseline statin use, baseline LDL-C, and PCSK9 showed clinically relevant and nominally statistically significant placebo-adjusted percentage changes in LDL-C from baseline to Day 330 except for region = other. In addition, consistent reductions in LDL-C were seen across subgroups in the inclisiran group, while some larger

variability was observed with placebo, in line with the smaller numbers in this group. The non-White race subgroups had few participants only in the inclisiran group and none in the placebo group, thus preventing the pre-specified model-based analysis. Similarly, the ethnicity subgroup “other” consisted of only 3 participants and the model-based analysis could therefore not be performed.

Study ORION-16 met the primary objective of demonstrating superiority of inclisiran compared to placebo in reducing LDL-C in adolescents with HeFH on maximally tolerated statin treatment. The effect of a between-group difference (95% CI) of -28.54% (-35.81, -21.27; $p < 0.0001$) between inclisiran and placebo is considered clinically relevant. Results of sensitivity and subgroup analyses were consistent with the primary analysis.

Secondary analyses

Concerning key secondary efficacy endpoints, relevant improvements were seen for time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, consistent with the primary efficacy endpoint. The LS mean percent change was -26.04% in the inclisiran and 3.26% in the placebo group, with a between-group difference (95% CI) of -29.30% (-36.24, -22.36; $p < 0.0001$).

Table 25: Key secondary efficacy endpoint - Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 330 (Part 1, Full Analysis Set)

Inclisiran N=93 PCHG LS Mean (95% CI)	Placebo N=48 PCHG LS Mean (95% CI)	Difference between Inclisiran and Placebo	
		LS Mean (95% CI)	One-sided p-value
-26.04 (-30.11, -21.98)	3.26 (-2.37, 8.89)	-29.30 (-36.24, -22.36)	<.0001

-PCHG=Percentage change from baseline.

* A control-based PMM was used for missing data imputation with 100 total imputed datasets. A MMRM on each of the 100 datasets was performed by including fixed effects for treatment, visit (Day 150, 270, and 330), interaction between treatment and visit, and baseline LDL-C and baseline age group as a covariate. A linear combination of the estimated means after Day 90 and up to Day 330 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.

Source: [Study ORION-16 - Table 14.2-2.1i]

Relevant improvements were also seen for absolute change in LDL-C, and percent change in Apo B, non-HDL-C, and total cholesterol; the LS mean between-group differences (95% CI) for change from baseline to Day 330 were -49.99 mg/dL (-63.18, -36.81), -25.70% (-31.68, -19.73), -26.80% (-33.63, -19.97) and -19.20% (-24.65, -13.75), respectively (all p-values <0.0001).

For Lp(a), using the primary analysis method (ANCOVA), the LS mean between-group difference (95% CI) for change from baseline to Day 330 was -6.18% (-17.48, 5.12; p-value 0.1419). The supplementary analysis, using log transformation to account for the skewed distribution of this parameter, showed a ratio of geometric means inclisiran / placebo (95% CI) of 0.90 (0.80,1.00) in favour of inclisiran (p-value 0.0212).

Given the hierarchical nature of testing for the key secondary endpoints and the non-significant result for Lp(a) using the primary analysis method, time-adjusted percentage change in LDL-C, absolute change in LDL-C, and percentage change in Apo B are considered statistically significant, whereas the other results are considered exploratory.

Table 26: Other key secondary efficacy endpoints (Part 1, Full Analysis Set)

		Difference between Inclisiran and Placebo	
Inclisiran N=93	Placebo N=48		
LS Mean CHG (95% CI)	LS Mean CHG (95% CI)	LS Mean (95% CI)	One-sided p-value
LDL-C– Absolute change (mg/dL) from BL to Day 330			
-50.54 (-59.22, -41.86)	-0.55 (-10.48, 9.38)	-49.99 (-63.18, -36.81)	<.0001
Apo B – Percentage change from BL to Day 330			
-21.46 (-25.59, -17.33)	4.24 (-0.07, 8.56)	-25.70 (-31.68, -19.73)	<.0001
Lp(a) – Percentage change from BL to Day 330			
-5.04 (-14.21, 4.13)	1.14 (-5.48, 7.77)	-6.18 (-17.48, 5.12)	0.1419
Non-HDL-C – Percentage change from BL to Day 330			
-25.04 (-29.68, -20.41)	1.76 (-3.25,6.77)	-26.80 (-33.63, -19.97)	<.0001
Total Cholesterol – Percentage change from BL to Day 330			
-18.72 (-22.48, -14.96)	0.48 (-3.46, 4.42)	-19.20 (-24.65, -13.75)	<.0001
-CHG=Change from baseline, BL=Baseline -A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. ANCOVA, assuming unequal variance for treatment group, on each of the 100 datasets was performed by including fixed effects for baseline LDL-C and baseline age group as a covariate. Treatment effects from the 100 analyses were combined using Rubin's Method. -Given the hierarchical nature of testing for the key secondary endpoints and the non-significant result for Lp(a), the p-values <0.0001 for absolute change in LDL-C and Apo B should be considered significant, whereas the other p-values <0.0001 should be considered exploratory. Source: [Study ORION-16 - Table 14.2-2.3i, Table 14.2-2.5i, Table 14.2-2.6i, Table 14.2-2.8i, and Table 14.2-2.9i]			

Pre-specified sensitivity analyses for the key secondary endpoints used MMRM with control-based PMM for missing value imputation, except for the time-adjusted percent change in LDL-C, for which MMRM without multiple imputation (that assumes missing data as MAR) was utilised. Results of the sensitivity analyses were consistent with the primary analysis.

Subgroup results for the key secondary endpoints (time-adjusted percent change in LDL-C, absolute change in LDL-C, percent change in Apo B, non-HDL-C, total cholesterol) were consistent with subgroup results for the primary efficacy endpoint. More variability was seen for percent change in Lp(a).

As regards other secondary efficacy results, PCSK9 was reduced vs. baseline by -71.2% at Day 330 and by -76.3% in the inclisiran versus the placebo group. Reductions in LDL-C were observed by the first assessment at Day 90 and reached a maximum at Day 150 in the inclisiran group, which was mostly sustained over the remaining Part 1 treatment period (i.e., up to Day 360). In inclisiran-treated participants, clinically meaningful reductions in LDL-C were observed irrespective of their genetic variant group. Results for Apo B, Lp(a), non-HDL-C, and total cholesterol were also consistent across visits in Part 1. Modest improvements were observed in HDL-C and ApoA1, while no effect was seen on triglycerides and VLDL-C.

During the open-label Part 2 period, a consistent, clinically relevant reduction in LDL-C was observed with inclisiran, sustained over 2 years of treatment. The mean percent change in LDL-C ($\pm$ SD) from baseline to Day 720 was -33.7% ($\pm$ 24.0) (-32.3% [$\pm$ 24.8] inclisiran-inclisiran group, -36.4% [$\pm$ 22.3] placebo-inclisiran group). Improvements were also seen in ApoB, non-HDL-C, and total cholesterol. PCSK9 levels were reduced from baseline at Day 720 by -71.6% ($\pm$ 13.4) (-71.4% [$\pm$ 13.4] inclisiran-inclisiran, -72.2% [$\pm$ 13.5] placebo-inclisiran).

As regards key secondary efficacy endpoints, in Part 1 of the study, relevant reductions were seen for time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330; the between-group difference in mean percent change was -29.30% (-36.24, -22.36; $p < 0.0001$).

Relevant reductions were also seen for absolute change in LDL-C, and percent change in Apo B, non-HDL-C, and total cholesterol (all p-values <0.0001), while results for Lp(a) were not statistically significant (p-value 0.1419) and, given the hierarchical testing of the key secondary endpoints, further results are to be considered exploratory.

Results of pre-specified sensitivity and subgroup analyses for the key secondary endpoints were consistent with the primary analysis.

During the open-label Part 2, consistent reductions were seen in LDL-C, sustained over 2 years of treatment. The mean percent change in LDL-C ($\pm$ SD) from baseline to Day 720 was -33.7% (± 24.0).

Ancillary analyses

Exploratory endpoints

As regards exploratory results, number and percentage of participants reaching individual response criteria of LDL-C thresholds or percent LDL-C reductions at Day 330 are summarised in the table below. The proportion of participants reaching the recommended LDL-C target for adolescents and children of <130 mg/dL was 56.7% (51/90) in inclisiran versus 12.5% (6/48) in placebo treated participants; 27.8% (25/90) of participants in the inclisiran versus no participants in the placebo group reached a LDL-C of <100 mg/dL. Lower LDL-C thresholds were only reached by few participants in the inclisiran group. A $\geq 50\%$ reduction in LDL-C was reached by 16 participants in the inclisiran (17.8%, 16/90) and no participants in the placebo group.

Table 27: Individual responsiveness of participants as measured by reaching levels or percentage reduction of LDL-C at Day 330 – Part 1 Primary Analysis (Full Analysis Set)

	Inclisiran	Placebo
	N=93	N=48
Responsiveness criteria at Day 330*	n/m (%)	n/m (%)
Number of participants reaching LDL-C < 130 mg/dL	51/90 (56.7)	6/48 (12.5)
Number of participants reaching LDL-C < 100 mg/dL	25/90 (27.8)	0/48 (0.0)
Number of participants with $\geq 50\%$ reduction in LDL-C from BL	16/90 (17.8)	0/48 (0.0)

BL = baseline

* Participants can be counted in multiple categories

Participants who are having data at Day 330 are included in denominator

Percentage is based on n

Source: Table 14.2-4.1i

Results for the open-label Part 2 period at Day 720 are summarised in the table below. The proportion of participants reaching the recommended LDL-C target for adolescents and children of <130 mg/dL was 64.7% (90/139) overall, 62.6% (57/91) in the inclisiran-inclisiran, and 68.8% (33/48) in the placebo-inclisiran group; 38.1% (53/139) reached an LDL-C of <100 mg/dL. Lower LDL-C thresholds were reached by only a limited number of participants ($\leq 11.5\%$ overall). A $\geq 20\%$ reduction in LDL-C was reached by 75.5% (105/139) and $\geq 30\%$ by 61.2% (85/139) of participants. A $\geq 50\%$ reduction in LDL-C was reached by 23.7% (33/139) of participants, 23.1% (21/91) in the inclisiran-inclisiran and 25.0% (12/48) in the placebo-inclisiran group.

Table 28: Individual responsiveness of participants as measured by reaching levels or percentage reduction of LDL-C at Day 720 – Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran	Placebo- Inclisiran	Total
	N=91	N=48	N=139
Responsiveness criteria at Day 720*	n/m (%)	n/m (%)	n/m (%)
Number of participants reaching LDL-C < 130 mg/dL	57/91 (62.6)	33/48 (68.8)	90/139 (64.7)
Number of participants reaching LDL-C < 100 mg/dL	35/91 (38.5)	18/48 (37.5)	53/139 (38.1)
Number of participants with ≥20% reduction in LDL-C from BL	67/91 (73.6)	38/48 (79.2)	105/139 (75.5)
Number of participants with ≥30% reduction in LDL-C from BL	53/91 (58.2)	32/48 (66.7)	85/139 (61.2)
Number of participants with ≥50% reduction in LDL-C from BL	21/91 (23.1)	12/48 (25.0)	33/139 (23.7)

BL = baseline

*Participants can be counted in multiple categories

Participants who are having data at Day 720 are included in denominator

Percentages are based out of m

Source: Table 14.2-4.1ii

LDL-C response by genotype subgroup analysis included only participants with adjudicated central laboratory genetic results (n=125/141). In the double-blind Part 1 period, consistent LDL-C lowering was seen with inclisiran across the included genetic variant groups; for the two main genotypes, LDLR null (negative) and LDLR defective, LDL-C reductions with inclisiran were –25.1% (n=45) and –31.0% (n=28), respectively. For the open-label Part 2 period, this analysis was not specified in the protocol as an exploratory endpoint but was added for completeness in the SAP. As for Part 1, consistent LDL-C lowering was seen with inclisiran across the included genetic variant groups. In the LDLR null (negative) group, LDL-C reductions were –32.7% overall (n=68; –30.0% inclisiran-inclisiran, –38.3% placebo-inclisiran) and in the LDLR defective group, reductions were –36.9% overall (n=47; –35.4% inclisiran-inclisiran, –38.9% placebo-inclisiran group).

The exploratory endpoint carotid intima media thickness (cIMT; right and left common carotid arteries) was measured at Day 1 (baseline), Day 330 (Year 1), and Day 720 (Year 2) by ultrasonography, using local machines. During the double-blind Part 1, mean cIMT (right, left, and average of right and left) at baseline and Day 330 were measured and changes from baseline to Day 330 in both treatment groups provided. No effect on cIMT was seen with inclisiran treatment following 1 year of treatment. The mean (±SD) baseline cIMT for the average of right and left cIMT was 0.482 ±0.081 mm in the inclisiran and 0.498 ±0.076 mm in the placebo group. At Day 330, the mean (±SD) changes from baseline were –0.003 ±0.056 mm in the inclisiran and –0.007 ±0.073 mm in placebo group. Changes from baseline to Day 720 (EoS; Part 2) in mean cIMT were –0.015 ±0.071 mm overall and –0.010 ±0.068 mm in the inclisiran-inclisiran and –0.026 ±0.078 mm in the placebo-inclisiran group.

Pharmacokinetic results

An exploratory endpoint for this study was the evaluation of inclisiran concentrations. For pharmacokinetic results, see section Pharmacokinetics.

As regards exploratory results, 56.7% (51/90) in the inclisiran versus 12.5% (6/48) in placebo group reached an LDL-C <130 mg/dL and 27.8% (25/90) versus none, respectively, an LDL-C <100 mg/dL. A ≥50% reduction in LDL-C was reached by 16/90 (17.8%) in the inclisiran and none in the placebo group. During the open-label Part 2, 90/139 (64.7%) participants reached an LDL-C <130 mg/dL and 53/139 (38.1%) an LDL-C <100 mg/dL. A ≥20% reduction in LDL-C was reached by 105/139 (75.5%), ≥30% by 85/139 (61.2%), and ≥50% by 33/139 (23.7%) participants. Consistent LDL-C lowering was seen with inclisiran across the included genetic variant groups in Part 1. For the open-

label Part 2, such an analysis was not specified in the protocol but added for completeness in the SAP; as for Part 1, consistent LDL-C lowering was seen across the included genetic variant groups. No clinically relevant effect of inclisiran on carotid intima media thickness (cIMT) was seen during Part 1 or 2.

2.4.3. Discussion on clinical efficacy

Assessment of paediatric data on clinical efficacy

Inclisiran was first approved in the EU on 09 December 2020 under the proprietary name of Leqvio and is currently only licensed in adults, including patients with heterozygous, but not with homozygous familial hypercholesterolaemia, from 18 years of age onwards.

The completed paediatric studies ORION-13 (CKJX839C12302) and ORION-16 (CKJX839C12301) are part of agreed PIP for inclisiran and were intended to investigate the use of inclisiran in adolescents from ≥ 12 to < 18 years of age with homozygous (HoFH; ORION-13) or heterozygous (HeFH; ORION-16) familial hypercholesterolaemia and elevated LDL-cholesterol.

Both were conducted as two-part, multicentre, randomised studies; Part 1 (year 1) investigated inclisiran versus placebo in a double-blind setting, while in Part 2 (year 2) all participants received open-label inclisiran.

Homozygous familial hypercholesterolaemia (HoFH) / Study ORION-13

Inclisiran is not licensed in adults with HoFH. In the phase III, two-part (double-blind placebo-controlled / open-label), multicentre study ORION-5 (MDCO-PCS-17-02) in adult patients with HoFH, inclisiran treatment did not reduce LDL-C levels despite substantial lowering of PCSK9 levels (Raal et al., 2024)⁹.

The paediatric study ORION-13 included 13 male and female adolescents, 9 in the inclisiran and 4 in the placebo group, with a genetic confirmation of HoFH, excluding LDLR null/null genotypes, and an LDL-C > 130 mg/dL who were on a maximally tolerated dose of an HMG-CoA reductase inhibitor (statin) with or without other lipid lowering therapy. One (1) participant in the placebo group was on LDL-apheresis.

For study ORION-13 no formal hypothesis testing was planned and none was performed.

All participants completed both parts of the study and were analysed.

In Part 1, the mean percent change in LDL-C from baseline to Day 330 was -21.6% in the inclisiran and $+11.7\%$ in the placebo group (mean between-group difference [95% CI] -33.25% [-59.17 , -7.34]). However, a waterfall plot of individual percentage changes in LDL-C from baseline to Day 330 by participant showed a variable magnitude; all participants in the inclisiran group showed a reduction in LDL-C albeit with significant differences in magnitude, while response in the placebo group was less consistent with an increase in LDL-C of 54.9% as well as a decrease of -15.4% . Two thirds (66.7%) of the participants in the inclisiran group achieved a $> 15\%$ and more than half (55.6%) a $\geq 20\%$ reduction in LDL-C from baseline to Day 330. In line with the primary endpoint, the mean time-adjusted percent change in LDL-C (after Day 90 up to Day 330) was -21.0% in the inclisiran and 13.0% in the placebo group (between-group difference [95% CI] -33.97% [-67.54 , -0.39]).

⁹ Raal F, Durst R, Bi R, Talloczy Z, Maheux P, Lesogor A, Kastelein JJP; ORION-5 Study Investigators. Efficacy, Safety, and Tolerability of Inclisiran in Patients With Homozygous Familial Hypercholesterolemia: Results From the ORION-5 Randomised Clinical Trial. *Circulation*. 2024 Jan 30;149(5):354-362. doi: 10.1161/CIRCULATIONAHA.122.063460. Epub 2023 Oct 18. PMID: 37850379; PMCID: PMC10815002.

The percentage changes from baseline in LDL-C in Part 1 were largely consistent across visits, but there were outliers. Reductions were seen for absolute change in LDL-C and percent change in ApoB, non-HDL-C, VLDL-C, and total cholesterol. No reduction was seen in Lp(a) and only small variable effects for triglycerides, HDL-C, and Apo A1. Supplementary analyses excluding the participant (n=1) on LDL-apheresis showed consistent results.

In Part 2, the extent of the overall mean change in LDL-C was lower compared to Part 1 (difference driven by 2 participants in inclisiran-inclisiran group with LDL-C of +27.3% and +47.4%, respectively). A waterfall plot of percentage change in LDL-C from baseline to Day 720 showed a variable magnitude; 10/13 participants had a decrease in LDL-C at Day 720, while in 3/13 participants, LDL-C increased at Day 720.

As regards exploratory results, in Part 1, only 1 participant in the inclisiran group reached the pre-specified LDL-C threshold of <130 mg/dL and none an LDL-C <100 mg/dL. In Part 2, 2 participants reached the pre-specified LDL-C threshold of <130 mg/dL, 1 participant an LDL-C <100 mg/dL, and no participant an LDL-C below 70 mg/dL. Consistent LDL-C lowering was seen across the included genetic variants. No clinically relevant effect of inclisiran on carotid intima media thickness (cIMT) was seen. Since only 1 participant was treated with LDL-apheresis, no relevant analysis is feasible.

While the observed reductions in LDL-C and other lipid parameters in study ORION-13 are acknowledged, the very low number of participants and the exploratory design of the study (including the absence of formal hypothesis testing) preclude robust conclusions regarding efficacy in this population. Furthermore, inclisiran is currently not approved in adults with HoFH, as study ORION-5 in adult patients with HoFH failed to demonstrate a relevant effect of inclisiran in this patient population, thereby limiting transferability of the data.

Within current application the MAH submitted a variation application under category C.I.6 of the variation classification Guideline with the scope to include C.I.6: "Extension of indication to include the treatment of paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia (HoFH) for LEQVIO based on the final results from study CKJX839C12302 (ORION-13). ORION-13 is a two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicentre study to evaluate safety, tolerability, and efficacy of inclisiran in paediatric patients (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol. "

Based on the assessment of the data contained in the application, the CHMP is of the view that the following changes to the MA should be introduced "Update to sections 5.1 and 5.2 of the SmPC to include the treatment of paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia (HoFH) based on the final results from study CKJX839C12302 (ORION-13). ORION-13 is a two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicentre study to evaluate safety, tolerability, and efficacy of inclisiran in paediatric patients (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol." These changes fall under category C.4 of the variation classification Guideline.

During the procedure, the MAH announced that it no longer wishes to pursue the proposed indication in paediatric patients aged 12 to <18 years with homozygous familial hypercholesterolaemia (HoFH). In reply to the Request for Supplementary Information, the MAH updated the electronic Application Form and the product information accordingly.

The CHMP considered that the results of paediatric study ORION-13 are adequately reflected in sections 4.8, 5.1 and 5.2 of the SmPC.

Heterozygous familial hypercholesterolaemia (HeFH) / Study ORION-16

Study ORION-16 in adolescents with HeFH included 141 participants and 139 of them completed Part 1 and Part 2. The majority of participants had a genetic diagnosis of HeFH.

The study met the primary endpoint of superiority of inclisiran compared to placebo in reducing LDL-C in adolescents with HeFH on maximally tolerated statin treatment. The between-group difference (95% CI) of -28.54% (-35.81, -21.27; $p < 0.0001$) between inclisiran and placebo is considered clinically relevant. Furthermore, in Part 1 relevant reductions were seen for key secondary efficacy endpoints (time-adjusted percent change in LDL-C from baseline after Day 90 up to Day 330 between-group difference mean percent change -29.30% [-36.24, -22.36; $p < 0.0001$]; absolute change in LDL-C, percent change in Apo B, non-HDL-C, total cholesterol all $p < 0.0001$). Results for Lp(a) were not statistically significant. Results of pre-specified sensitivity and subgroup analyses were consistent with the primary analysis and during Part 2, consistent reductions in LDL-C were seen.

For the exploratory endpoints concerning individual responsiveness of participants, relevant effects of inclisiran versus placebo were seen in the percentage of participants reaching an LDL-C < 130 mg/dL and < 100 mg/dL as well as a $\geq 50\%$ reduction in LDL-C. Consistent LDL-C lowering was seen with inclisiran across the included genetic variant groups in Part 1. No clinically relevant effect of inclisiran on cIMT was seen.

Overall, it can be agreed that clinically meaningful effects were shown in HeFH participants in Study Orion-16. However, interpretation of the provided data is limited by the low number of participants included in study Orion 16 (141 participants, 93 inclisiran, 48 placebo) as well as by the open-label uncontrolled design of Part 2.

Furthermore, the applicant was asked to reconsider dose finding in adolescents. The applicant did not provide a different body weight limit for the dose of 300mg in the paediatric population but proposed to retain the proposed dosing strategy focussing on the benign safety profile of inclisiran. The applicant argued that kidney and liver function were considered mature by 2 years of age and above that age were expected to be equivalent to adults, citing a publication by Boven 2013. Overall, due to the good safety profile of inclisiran, the proposed and studied dosing regimen is considered acceptable.

Thus, it is noted that subjects were on maximally tolerated dose of statins with or without other lipid-lowering therapy. The Applicant was asked to clarify if any of the subjects reduced the dose of concurrently taken statins or other lipid-lowering agents during the Study. The applicant clarified that during Part 1 of study ORION-16, where type and dose of lipid-lowering therapy was not to be altered, none of the participants in either group reduced the dose of concomitant background statin or other lipid-lowering therapy, while during the open-label Part 2, dose reductions in concomitant background statin / lipid-lowering medications were reported for 3/139 (2.2%) participants. It was agreed that these changes are not considered to have significantly influenced efficacy of inclisiran in trial ORION-16.

Furthermore, the overall number of protocol deviations in the Study was considered quite high - overall, 12.1% (17/141) of participants reported at least one protocol deviation, 16.1% (15/93) in the inclisiran group and 4.2% (2/48) in the placebo group. The Applicant was asked to comment on possible reasons for the reported disproportion of protocol deviations between the inclisiran and placebo groups during Part 1 of the Study (OC). The applicant responded that protocol deviations occurred only in the category "other" (12.9% [12/93] inclisiran, 2.1% [1/48] placebo); only 1 of these deviations in the inclisiran group occurred during the treatment period, the other 11 deviations occurred before participants received the first dose of inclisiran, either related to the separate consents required for the optional pharmacogenomics or PK assessments, or related to Interactive Response Technology (IRT) procedures, including randomisation calls before the actual randomisation visit. It

was concluded that the observed imbalance in protocol deviations between both groups are not considered to have possibly affected conclusions on efficacy or safety in study ORION-16.

In addition, it is noted that after the Part 2/Year 2 database lock, an implausible increase in Lp(a) at Day 720 was observed for one participant (inclisiran-inclisiran group) and that another participant (inclisiran-inclisiran group), who had the Day 720 visit at the same investigational site on the same day, showed an atypical decrease in Lp(a) at Day 720. The Applicant assumed that the possible reason was a sample mix-up between both participants and has implemented precautionary measures to prevent such cases in two studies with younger children.

2.4.4. Conclusions on the clinical efficacy

As regards the use of inclisiran in adolescents ≥ 12 years of age with heterozygous familial hypercholesterolaemia (Study ORION-16), the efficacy data provided from this study together with the available efficacy data from the use of inclisiran in the adult population with heterozygous familial hypercholesterolaemia, are, in general, considered to support the proposed relevant change to the indication (in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH): in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated).

As regards the use of inclisiran in paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia (HoFH) in combination with other lipid-lowering therapies (Study ORION-13), the available efficacy data were considered insufficient to support the proposed indication. During the procedure, the applicant announced that it no longer wishes to pursue the proposed HoFH indication. However, a concise summary of study ORION-13 was reflected in sections 4.8, 5.1 and 5.2 of the SmPC with corresponding change of scope from C.I.6 to variation category C.4 of the Variation Classification Guideline.

2.5. Clinical safety

Introduction

The safety of inclisiran in adults has been characterised and assessed from the Phase III development program, consisting of three pivotal Phase III studies (ORION-9 / ORION-10 / ORION-11) with 18-months duration, including data from 1833 adults with ASCVD, ASCVD risk equivalents, and/or HeFH exposed to inclisiran on top of maximally tolerated statin therapy, and from two extension studies (ORION-3, extension to Phase II study ORION-1; ORION-8, extension to Phase III studies ORION-9 / -10 / -11 and to ORION-3).

Data from these studies indicate a favourable safety profile in adults. A higher incidence of injection site reactions is an identified common adverse drug reaction (ADR) of inclisiran (8.2% inclisiran, 1.8% placebo). These injection site ADRs were mild or moderate in severity, transient, and resolved without sequelae. The most frequently ADRs at the injection site were injection site reaction (3.1%), injection site pain (2.2%), injection site erythema (1.6%), and injection site rash (0.7%). There were more frequent elevations of serum hepatic transaminases between >1x the upper limit of normal (ULN) and ≤3x ULN in patients on inclisiran (ALT: 19.7%, AST: 17.2%) than on placebo (ALT: 13.6%, AST: 11.1%); these elevations did not progress to >3x ULN, were asymptomatic, and not associated with adverse reactions or other evidence of liver dysfunction. In patients tested for anti-drug antibodies in the pivotal trials, confirmed positivity was detected in 1.8% prior to dosing and 4.9% during the 18 months of treatment with inclisiran; no clinically significant differences in the clinical efficacy, safety, or pharmacodynamic profiles of inclisiran were observed in the patients who tested positive for anti-inclisiran antibodies. No overall differences in safety were observed between these elderly and younger patients. Inclisiran is not associated with an increased risk for renal dysfunction, hypersensitivity, or neurologic events / neurocognitive disorders, and there was no difference from placebo in new onset or worsening of diabetes.

So far, more than 30,000 patients have been exposed to inclisiran in completed and ongoing clinical trials and the exposure to inclisiran from post-marketing experience was 368,582 patient treatment years as of 31 December 2024 (PSUR 01 January 2024 to 31 December 2024).

For the current application, the existing safety data in adults have been complemented by safety data from the use of inclisiran in the treatment of adolescents from 12 to less than 18 years of age with heterozygous (HeFH) and with homozygous familial hypercholesterolemia (HoFH). These safety data are from the two pivotal adolescent clinical studies CKJX839C12302 (ORION-13) for HoFH and CKJX839C12301 (ORION-16) for HeFH. Furthermore, safety data from the clinical study CKJX839A12302 (ORION-5) in adults with HoFH have been included in the submission as supportive data. Also, supportive safety data from the ongoing extension study CKJX839C12001B (VICTORION-PEDS-OLE) in participants who have completed ORION-13 or ORION-16 have been provided.

Safety results for both pivotal studies in this application have been presented separately by the applicant, arguing that HoFH and HeFH are different disease manifestations in severity, prevalence, and treatment modalities and that the sample size of study ORION-13 (HoFH) was very small (n = 13).

Patient exposure

Studies ORION-13 (HoFH) and ORION-16 (HeFH) both had a 1 year double-blind inclisiran versus placebo (2:1) Part 1, followed by a 1 year open-label inclisiran Part 2. Participants were on a maximally tolerated dose of statin at the investigator's discretion, and study ORION-13 (HoFH) included 13 and ORION-16 (HeFH) 141 participants. For demographic and baseline characteristics of studies ORION-13 and ORION-16 please see Clinical efficacy section, above.

The design of study ORION-5 (HoFH) used for supportive safety information, differed compared to studies ORION-13 and ORION-16 as Part 1 covered only 6 months double-blind inclisiran versus placebo, followed by an 18 months open-label inclisiran Part 2. Study ORION-5 included 56 adult participants ≥ 18 years of age, with a genetic and/or clinical diagnosis of HoFH and fasting LDL-C ≥ 130 mg/dL (3.4 mmol/L). Demographic and baseline characteristics were overall comparable between the treatment groups; 60.7% were female, the median age was 41.0 years (range 22-70 years), the mean BMI 26.2 kg/m², the median baseline eGFR 95.5 mL/min/1.73 m², and 85.7% of participants were white. All participants used high intensity statins, 33.9% statins only, 66.1% other lipid-lowering therapy (mostly ezetimibe), and 35.7% were on LDL-apheresis. Overall, 67.9% had a history of ASCVD, all of whom had prior or current CHD, 5.4% had diabetes mellitus, 37.5% had hypertension, and 89.3% had a prior or current history of tendon xanthomas. Participants were categorised in the genotype groups homozygous LDLR, compound heterozygous LDLR, other genetic types, and double null alleles for LDLR; 13/56 (23.2%) had double null alleles for LDLR (LDLR null/null genotype), 10/37 (27.0%) in the inclisiran and 3/19 (15.8%) in the placebo group. All participants had at least 1 concomitant medication at Day 1 of the study; the most common drug classes in addition to LMTs were antithrombotic agents (71.4%), beta blocking agents (57.1%), and plain ACE inhibitors (28.6%).

VICTORION-PEDS-OLE is an ongoing open-label, single arm, multicentre extension study in participants with HoFH or HeFH who have completed studies ORION-13 or ORION-16 and derived a benefit in the investigator's judgement. The purpose of the study is to provide continued access to treatment with inclisiran and to evaluate longer-term safety and tolerability. Selected safety data (deaths, SAEs, AEs leading to study drug discontinuation, pregnancy) with a data cut-off date of 02 January 2025 have been provided as supportive. Approximately half of the enrolled participants are female (55.2%, 69/125). The mean age of participants was 17.1 years at time of entry into the study (40.8% ≥ 18 years of age).

ORION-13 HoFH

In the double-blind Part 1, the mean duration on study was identical to the mean duration of exposure to study treatment in both treatment groups and they were comparable between groups (360.6 days inclisiran, 364.0 days placebo).

During the open-label Part 2, the mean duration on study and the mean duration of exposure to study treatment were both 358.5 days overall, with comparable durations in the inclisiran-inclisiran and placebo-inclisiran groups.

Over the entire study duration, all participants were administered all 6 scheduled study doses of study drug. Overall, the mean duration on study and the mean duration of exposure to study treatment were both 719.1 days with comparable durations in the inclisiran-inclisiran and the placebo-inclisiran group. Patient years of exposure to study treatment were 25.6 overall, 17.7 in the inclisiran-inclisiran, and 7.9 in the placebo-inclisiran group.

ORION-16 HeFH

In the double-blind Part 1 study period, the mean duration on study was identical to the mean duration of exposure to study treatment in both treatment groups and they were comparable between both groups (357.9 days inclisiran, 362.9 days placebo).

During the open-label Part 2, the mean duration on study was 361.1 days and the mean duration of exposure to study treatment 360.6 days overall, with comparable durations in the inclisiran-inclisiran and placebo-inclisiran groups.

Over the entire study duration, 97.9% (138/141) of participants were administered all 6 scheduled doses of study drug, 96.8% (90/93) in the inclisiran-inclisiran and 100% (48/48) in the placebo-inclisiran group. The mean duration on study was 714.6 days and the mean duration of exposure to study treatment 714.1 days overall, with comparable durations in the inclisiran-inclisiran and placebo-inclisiran groups. The overall patient years of exposure to study treatment were 275.6, 180.5 in the inclisiran-inclisiran and 95.1 in the placebo-inclisiran group.

Supportive safety data

ORION-5 (adult HoFH)

In the 6 month double-blind Part 1, 94.6% of participants in the inclisiran and 100% in the placebo group received both scheduled doses (Day 1, Day 90). The subject year exposure to inclisiran was 18.6.

In the open-label Part 2, 82.4% in the inclisiran-inclisiran and 89.5% in the placebo-inclisiran group received all scheduled doses of study medication. The subject year exposure to inclisiran was 65.5 in the inclisiran-inclisiran and 29.2 in the placebo-inclisiran group.

Overall, 94.6% (53/56) completed Part 1; reasons for discontinuation prior to Day 180 were withdrawal of consent (2 participants) and other (1 participant), all in the inclisiran group. Of the 53 participants entering Part 2, 47 (88.7%) completed Part 2; reasons for discontinuation included death (3 participants) and withdrawal of consent (2 participants) in the inclisiran-inclisiran and "other" (1 participant) in the placebo-inclisiran group.

VICTORION-PEDS-OLE

From studies ORION-13 and ORION-16, 9/13 and 116/139 participants, respectively, were enrolled. At the time of the data cut-off, no participants had completed the study and 23.2% (29/125; 33.3% [3/9] ORION-13, 22.4% [26/116] ORION-16) discontinued from the study. The primary reason for discontinuation was post-study access to treatment (19.2%, 24/125), which occurred in line with the corresponding protocol stopping criteria (applicable after 1 year) for participants reaching the local legal age and inclisiran being commercially available in the adult population. In addition, 5 participants discontinued from the study due to a subject or guardian decision. Study treatment disposition was identical to study disposition, except that 7 additional participants were marked as having discontinued study treatment due to post-study access to treatment; since the early exit visits for these participants had not taken place at the time of the data cut-off date, this was not yet reflected in the study discontinuation count.

The mean duration on study and mean duration of exposure was 230.6 ±174.0 days and 230.4 ±173.8 days, respectively. The patient years of exposure to inclisiran in VICTORION-PEDS-OLE was 78.9, and the cumulative patient-year exposure to inclisiran over the feeder studies and VICTORION-PEDS-OLE was 284.3.

Adverse events

ORION-13 HoFH

During Part 1, 7/9 (77.8%) inclisiran- and 1/4 (25.0%) placebo-treated participants experienced at least 1 treatment-emergent adverse events (AEs). Two (2/9; 22.2%) participants in the inclisiran and

none in the placebo group experienced a study drug related treatment-emergent AE; the difference was exclusively driven by mild injection site reactions (see below).

No treatment-emergent SAEs and no discontinuation of study drug due to treatment-emergent AEs were reported in either group.

There were no deaths in Part 1.

Table 29: Overall summary of adverse events – (Part 1 Primary analysis, Safety Set)

Category	Inclisiran N=9 n (%)	Placebo N=4 n (%)	Total N=13 n (%)
Participants with at least one TEAE	7 (77.8)	1 (25.0)	8 (61.5)
Participants with at least one study drug related TEAE	2 (22.2)	0	2 (15.4)
Participants with at least one TESAE	0	0	0
Participants with at least one study drug related TESAE	0	0	0
Participants who discontinued study drug due to TEAE	0	0	0
Participants who discontinued study drug due to TESAE	0	0	0
Participants who died	0	0	0

-MedDRA Version 26.1 has been used for the reporting of adverse events.
Source: [Study ORION-13 Table 14.3.1-1i]

In Part 2, 8/13 (61.5%) participants experienced at least 1 treatment-emergent AE, 5/9 (55.6%) in the inclisiran-inclisiran and 3/4 (75.0%) in the placebo-inclisiran group. One participant (1/13, 7.7%; inclisiran-inclisiran group) experienced a study drug related treatment-emergent AE, which was a mild injection site reaction.

No treatment-emergent SAEs and no discontinuation of study drug due to treatment-emergent AEs were reported.

No deaths occurred in Part 2.

Table 30: Overall summary of adverse events- Part 2 Analysis (Open-label phase analysis Set)

Category	Inclisiran- Inclisiran N=9 n (%)	Placebo- Inclisiran N=4 n (%)	Total N=13 n (%)
Participants with at least one TEAE	5 (55.6)	3 (75.0)	8 (61.5)
Participants with at least one study drug related TEAE	1 (11.1)	0	1 (7.7)
Participants with at least one TESAE	0	0	0
Participants with at least one study drug related TESAE	0	0	0
Participants who discontinued study drug due to TEAE	0	0	0
Participants who discontinued study drug due to TESAE	0	0	0
Participants who died	0	0	0

-MedDRA Version 27.1 has been used for the reporting of adverse events.
Source: [Study ORION-13 Table 14.3.1-1ii]

Common adverse events

Common AEs ($\geq 15\%$ total group) by PT are presented in the table below. In Part 1, the most common AE was COVID-19, reported in 4/9 (44.4%) participants in the inclisiran and 1/4 (25.0%) in the placebo group. The AEs of COVID-19 in the inclisiran group were mild in severity, considered not related to study drug, and resolved within 6 to 9 days. For 1 participant (007), the AE of COVID-19 resolved after Day 360 and was noted in the electronic data capture system after the data cut-off date. The AE of COVID-19 in the placebo group was mild in severity, considered not related to study drug, and resolved within 10 days. Other common AEs were abdominal pain upper, gastroenteritis, pyrexia, and injection site reaction, which were reported by ≤ 2 participants in either treatment group. Gastroenteritis was reported by 1/9 (11.1%) in the inclisiran and 1/4 (25.0%) in the placebo group. Abdominal pain upper and pyrexia were experienced by 2/9 (22.2%) participants in the inclisiran and no participants in placebo group. The AEs of abdominal pain upper, gastroenteritis, and pyrexia in the inclisiran group were all mild in severity, considered not related to study drug, and resolved within a few days. The AE of gastroenteritis in the placebo group was moderate in severity, considered not related to study drug, and resolved within 6 days. Injection site reactions (all mild) occurred in 2/9 (22.2%) participants in the inclisiran and no participants in the placebo group (see below).

Table 31: Most common treatment emergent adverse events (greater than or equal to 15%) by preferred term- Part 1 Primary Analysis (Safety Set)

	Inclisiran	Placebo	Total
	N=9	N=4	N=13
Preferred Term	n (%)	n (%)	n (%)
Number of participants with at least one TEAE	7 (77.8)	1 (25.0)	8 (61.5)
COVID-19	4 (44.4)	1 (25.0)	5 (38.5)
Abdominal pain upper	2 (22.2)	0	2 (15.4)
Gastroenteritis	1 (11.1)	1 (25.0)	2 (15.4)
Injection site reaction	2 (22.2)	0	2 (15.4)
Pyrexia	2 (22.2)	0	2 (15.4)

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-The PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.9i

Adverse events by SOC are presented in the table below. The most common AEs by SOC were infections and infestations, with 5/9 (55.6%) participants in the inclisiran and 1/4 (25.0%) in the placebo group, the difference being driven by the above-described AEs of COVID-19.

Table 32: Treatment emergent adverse events by primary system organ class, preferred term- Part 1 Primary Analysis (Safety Set)

	Inclisiran	Placebo	Total N=13
	N=9	N=4	n (%)
Primary system organ class Preferred term	n (%)	n (%)	
Number of participants with at least one TEAE	7 (77.8)	1 (25.0)	8 (61.5)
Gastrointestinal disorders	2 (22.2)	0	2 (15.4)
Abdominal pain upper	2 (22.2)	0	2 (15.4)
Toothache	1 (11.1)	0	1 (7.7)

Primary system organ class Preferred term	Inclisiran N=9 n (%)	Placebo N=4 n (%)	Total N=13 n (%)
Vomiting	1 (11.1)	0	1 (7.7)
General disorders and administration site conditions	4 (44.4)	0	4 (30.8)
Injection site reaction	2 (22.2)	0	2 (15.4)
Pyrexia	2 (22.2)	0	2 (15.4)
Influenza like illness	1 (11.1)	0	1 (7.7)
Injection site erythema	1 (11.1)	0	1 (7.7)
Infections and infestations	5 (55.6)	1 (25.0)	6 (46.2)
COVID-19	4 (44.4)	1 (25.0)	5 (38.5)
Gastroenteritis	1 (11.1)	1 (25.0)	2 (15.4)
Conjunctivitis	1 (11.1)	0	1 (7.7)
Gingivitis	0	1 (25.0)	1 (7.7)
Oral herpes	0	1 (25.0)	1 (7.7)
Viral infection	1 (11.1)	0	1 (7.7)
Injury, poisoning and procedural complications	1 (11.1)	0	1 (7.7)
Concussion	1 (11.1)	0	1 (7.7)
Head injury	1 (11.1)	0	1 (7.7)
Metabolism and nutrition disorders	1 (11.1)	0	1 (7.7)
Vitamin D deficiency	1 (11.1)	0	1 (7.7)
Reproductive system and breast disorders	0	1 (25.0)	1 (7.7)
Vaginal discharge	0	1 (25.0)	1 (7.7)
Skin and subcutaneous tissue disorders	1 (11.1)	1 (25.0)	2 (15.4)
Angioedema	0	1 (25.0)	1 (7.7)
Rash macular	1 (11.1)	0	1 (7.7)
Urticaria	0	1 (25.0)	1 (7.7)

-A participant with multiple TEAEs within a primary system organ class is counted only once in the total row.

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-System organ classes are presented in alphabetical order; the PTs are sorted in descending order of frequency in the total column.

-SOCs without any TEAEs are not shown.

-MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.1i

Common AEs ($\geq 15\%$ total group) by PT in Part 2 are presented in the table below. The only AEs experienced by >1 participant were headache and influenza, each reported by 2 participants (2/13; 15.4%). These AEs were considered not related to study drug.

Table 33: Most common treatment emergent adverse events (greater than or equal to 15%) by preferred term- Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran N=9 n (%)	Placebo- Inclisiran N=4 n (%)	Total N=13 n (%)
Preferred Term			
Headache	1 (11.1)	1 (25.0)	2 (15.4)
Influenza	1 (11.1)	1 (25.0)	2 (15.4)

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-The PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.9ii

Adverse events by SOC are presented in the table below. The most common AEs by SOC were infections and infestations (3/9 [33.3%] inclisiran-inclisiran, 1/4 [25.0%] placebo-inclisiran). This included the previously described AEs of influenza (2 participants; 15.4%) and additionally COVID-19, upper respiratory tract infection, and urinary tract infection reported in 1 participant each (7.7%). The only other SOC with AEs experienced by >1 participant was nervous system disorders (2/13, 15.4%), with 2 participants reporting an AE of headache.

Table 34: Treatment emergent adverse events by primary system organ class, preferred term- Part 2 Analysis (Open-label phase analysis Set)

Primary system organ class Preferred term	Inclisiran- Inclisiran N=9 n (%)	Placebo- Inclisiran N=4 n (%)	Total N=13 n (%)
Number of participants with at least one TEAE	5 (55.6)	3 (75.0)	8 (61.5)
Gastrointestinal disorders	1 (11.1)	0	1 (7.7)
Abdominal pain upper	1 (11.1)	0	1 (7.7)
General disorders and administration site conditions	1 (11.1)	0	1 (7.7)
Influenza like illness	1 (11.1)	0	1 (7.7)
Injection site erythema	1 (11.1)	0	1 (7.7)
Infections and infestations	3 (33.3)	1 (25.0)	4 (30.8)
Influenza	1 (11.1)	1 (25.0)	2 (15.4)
COVID-19	0	1 (25.0)	1 (7.7)
Upper respiratory tract infection	1 (11.1)	0	1 (7.7)
Urinary tract infection	1 (11.1)	0	1 (7.7)
Injury, poisoning and procedural complications	0	1 (25.0)	1 (7.7)
Ligament sprain	0	1 (25.0)	1 (7.7)
Investigations	0	1 (25.0)	1 (7.7)
Carotid intima-media thickness increased	0	1 (25.0)	1 (7.7)
Musculoskeletal and connective tissue disorders	1 (11.1)	0	1 (7.7)
Costochondritis	1 (11.1)	0	1 (7.7)
Nervous system disorders	1 (11.1)	1 (25.0)	2 (15.4)

Primary system organ class Preferred term	Inclisiran- Inclisiran N=9 n (%)	Placebo- Inclisiran N=4 n (%)	Total N=13 n (%)
Headache	1 (11.1)	1 (25.0)	2 (15.4)
Skin and subcutaneous tissue disorders	1 (11.1)	0	1 (7.7)
Xanthoma	1 (11.1)	0	1 (7.7)

-A participant with multiple TEAEs within a primary system organ class is counted only once in the total row.

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-System organ classes are presented in alphabetical order; the PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.1ii

Severity of adverse events

In Part 1, the majority of reported AEs were mild; 6/9 (66.7%) inclisiran-treated and 0/4 (0%) placebo-treated participants reported AEs with a maximum severity of mild. Moderate AEs were seen in 1/9 (11.1%) participants (PT of conjunctivitis) in the inclisiran and 1/4 (25.0%; PT of gastroenteritis) in the placebo group. No participant experienced severe events.

During Part 2 (Open-label period), all reported AEs were either mild or moderate, with 4/13 (30.8%) participants each reporting AEs with a maximum severity of mild and moderate, respectively. AEs with a maximum severity of mild were reported by 4/9 (44.4%) participants in the inclisiran-inclisiran and no participant in the placebo-inclisiran group. AEs with a maximum severity of moderate were reported in 1/9 (11.1%) participants in the inclisiran-inclisiran and 3/4 (75.0%) participants in the placebo-inclisiran group. No participants experienced severe events.

ORION-16 HeFH

During Part 1, 76.3% (71/93) of the participants in the inclisiran group experienced at least 1 treatment-emergent AE compared to 66.7% (32/48) in the placebo group (see table below). Also, more participants in the inclisiran (17.2%, 16/93) than in the placebo group (8.3%, 4/48) experienced a study drug related treatment-emergent AE, the difference being driven by a higher incidence of mild injection site reactions with inclisiran. No other clinically important differences in AEs between treatment groups were seen.

The incidence of treatment-emergent SAEs was low and comparable between the treatment groups, 3.2% (3/93) in the inclisiran and 2.1% (1/48) in the placebo group; none were considered related to study drug.

One (1) participant in the inclisiran group discontinued study drug due to mild treatment-emergent AEs of nausea and vertigo.

There were no deaths in Part 1.

Table 35: Overall summary of adverse events (Part 1 Primary Analysis, Safety Set)

	Inclisiran	Placebo	Total
	N=93	N=48	N=141
Category	n (%)	n (%)	n (%)
Participants with at least one TEAE	71 (76.3)	32 (66.7)	103 (73.0)
Participants with at least one study drug related TEAE	16 (17.2)	4 (8.3)	20 (14.2)
Participants with at least one TESAE	3 (3.2)	1 (2.1)	4 (2.8)
Participants with at least one study drug related TESAE	0	0	0
Participants who discontinued study drug due to TEAE	1 (1.1)	0	1 (0.7)
Participants who discontinued study drug due to TESAE	0	0	0
Participants who died	0	0	0

-TEAE=treatment-emergent adverse event, TESAE=treatment-emergent serious adverse event

-MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: [Study ORION-16 - Table 14.3.1-1i]

In Part 2, 62.6% (87/139) of participants overall experienced at least 1 treatment-emergent AE (65.9% [60/91] inclisiran-inclisiran, 56.3% [27/48] placebo-inclisiran) and 10.1% (14/139) a study drug related treatment-emergent AE (13.2% [12/91] inclisiran-inclisiran, 4.2% [2/48] placebo-inclisiran). Thirteen (13) of the 14 participants reporting study drug-related AEs had mild injection site reactions.

The incidence of treatment-emergent SAEs was low (4.3% [6/139] overall, 4.4% [4/91] inclisiran-inclisiran, 4.2% [2/48] placebo-inclisiran) and none were considered related to study drug.

There were no discontinuations of study drug due to treatment-emergent AEs and no deaths in the open-label Part 2.

Table 36: Overall summary of adverse events – Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran	Placebo- Inclisiran	Total
	N=91	N=48	N=139
Category	n (%)	n (%)	n (%)
Participants with at least one TEAE	60 (65.9)	27 (56.3)	87 (62.6)
Participants with at least one study drug related TEAE	12 (13.2)	2 (4.2)	14 (10.1)
Participants with at least one TESAE	4 (4.4)	2 (4.2)	6 (4.3)
Participants with at least one study drug related TESAE	0	0	0
Participants who discontinued study drug due to TEAE	0	0	0
Participants who discontinued study drug due to TESAE	0	0	0
Participants who died	0	0	0

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: [Study ORION-16 - Table 14.3.1-1iii]

Common adverse events

Common AEs ($\geq 3\%$ total group) by PT for Part 1 are presented in the table below. The most frequently observed AE was COVID-19 (16.1% [15/93] inclisiran vs. 25.0% [12/48] placebo). Other most common AEs were nasopharyngitis (14.0% [13/93] vs. 18.8% [9/48]), influenza (10.8% [10/93] vs. 12.5% [6/48]), and headache (12.9% [12/93] vs. 6.3% [3/48]). The majority (66.7%, 8/12) of participants reporting headaches in the inclisiran group had mild AEs, none were severe or serious; in

most participants (83.3%, 10/12) the headaches were considered not related to study drug and there was no time correlation to inclisiran administration. In addition, many participants (75%, 9/12) reporting a headache in the inclisiran group had a relevant medical history of headache (2), psychiatric disorders (attention deficit hyperactivity disorder, anxiety/depression) (3), or obesity (6); in 1 case the headache was judged to be a side effect of beta blocker use. All 5 events of syncope in the inclisiran group were considered not related to study drug, none was severe, serious, or had a recurrence and there was no time correlation to inclisiran administration. In 3 of the 5 cases clear triggers could be identified, as reported by the investigators, which were being in a hot and overcrowded [Circumstances] environment, emotional stress, and change from lying down to standing, respectively.

Table 37: Most common treatment-emergent adverse events (greater than or equal to 3%) by preferred term – Part 1 Primary Analysis (Safety Set)

	Inclisiran	Placebo	Total
	N=93	N=48	N=141
Preferred Term	n (%)	n (%)	n (%)
COVID-19	15 (16.1)	12 (25.0)	27 (19.1)
Nasopharyngitis	13 (14.0)	9 (18.8)	22 (15.6)
Influenza	10 (10.8)	6 (12.5)	16 (11.3)
Headache	12 (12.9)	3 (6.3)	15 (10.6)
Injection site reaction	8 (8.6)	1 (2.1)	9 (6.4)
Upper respiratory tract infection	6 (6.5)	2 (4.2)	8 (5.7)
Influenza like illness	3 (3.2)	3 (6.3)	6 (4.3)
Injection site pain	4 (4.3)	2 (4.2)	6 (4.3)
Pharyngitis	4 (4.3)	2 (4.2)	6 (4.3)
Vomiting	5 (5.4)	1 (2.1)	6 (4.3)
Fatigue	4 (4.3)	1 (2.1)	5 (3.5)
Gastroenteritis	4 (4.3)	1 (2.1)	5 (3.5)
Nausea	4 (4.3)	1 (2.1)	5 (3.5)
Oropharyngeal pain	3 (3.2)	2 (4.2)	5 (3.5)
Syncope	5 (5.4)	0	5 (3.5)

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-The PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.9i

AEs by SOC are presented in the table below. The most common AEs by SOC were Infections and infestations (51.6% [48/93] inclisiran, 56.3% [27/48] placebo) and General disorders and administrative site conditions (23.7% [22/93] inclisiran, 18.8% [9/48] placebo). The type and frequency of AEs were overall comparable, with no clinically relevant differences between treatment groups. The higher incidence of AEs in the Nervous system disorders SOC in the inclisiran group (22.6%) vs. the placebo group (8.3%) was mostly driven by AEs of headache and syncope (see above). The AEs in the Investigations SOC in the inclisiran group were "SARS-COVID-2 test positive" reported in 2 participants and different PTs of mild laboratory abnormalities, all considered not related to study drug.

**Table 38: Treatment-emergent adverse events by primary system organ class – Part 1
Primary Analysis (Safety Set)**

	Inclisiran N=93	Placebo N=48	Total N=141
Primary system organ class	n (%)	n (%)	n (%)
Number of participants with at least one TEAE	71 (76.3)	32 (66.7)	103 (73.0)
Blood and lymphatic system disorders	2 (2.2)	0	2 (1.4)
Cardiac disorders	1 (1.1)	2 (4.2)	3 (2.1)
Ear and labyrinth disorders	1 (1.1)	0	1 (0.7)
Endocrine disorders	1 (1.1)	0	1 (0.7)
Eye disorders	2 (2.2)	2 (4.2)	4 (2.8)
Gastrointestinal disorders	9 (9.7)	5 (10.4)	14 (9.9)
General disorders and administration site conditions	22 (23.7)	9 (18.8)	31 (22.0)
Hepatobiliary disorders	1 (1.1)	0	1 (0.7)
Immune system disorders	2 (2.2)	0	2 (1.4)
Infections and infestations	48 (51.6)	27 (56.3)	75 (53.2)
Injury, poisoning and procedural complications	12 (12.9)	6 (12.5)	18 (12.8)
Investigations	9 (9.7)	0	9 (6.4)
Metabolism and nutrition disorders	5 (5.4)	1 (2.1)	6 (4.3)
Musculoskeletal and connective tissue disorders	6 (6.5)	4 (8.3)	10 (7.1)
Nervous system disorders	21 (22.6)	4 (8.3)	25 (17.7)
Psychiatric disorders	2 (2.2)	0	2 (1.4)
Reproductive system and breast disorders	2 (2.2)	0	2 (1.4)
Respiratory, thoracic and mediastinal disorders	8 (8.6)	3 (6.3)	11 (7.8)
Skin and subcutaneous tissue disorders	6 (6.5)	1 (2.1)	7 (5.0)
Vascular disorders	0	2 (4.2)	2 (1.4)

-A participant with multiple TEAEs within a primary system organ class is counted only once in the total row.

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-System organ classes are presented in alphabetical order.

-SOCs without any TEAEs are not shown

-MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.1i

Common AEs ($\geq 3\%$ total group) by PT in Part 2 are presented in the table below. The most frequently observed AE was nasopharyngitis, which was reported in 10.1% (14/139) of participants overall, 9.9% (9/91) in the inclisiran-inclisiran and 10.4% (5/48) in the placebo-inclisiran group. Other most common AEs were influenza (7.9%, 11/139) and COVID-19 (5.0%, 7/139).

Table 39: Most common treatment emergent adverse events (greater than or equal to 3%) by preferred term – Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran	Placebo- Inclisiran	Total
	N=91	N=48	N=139
Preferred Term	n (%)	n (%)	n (%)
Nasopharyngitis	9 (9.9)	5 (10.4)	14 (10.1)
Influenza	6 (6.6)	5 (10.4)	11 (7.9)
COVID-19	6 (6.6)	1 (2.1)	7 (5.0)
Headache	3 (3.3)	3 (6.3)	6 (4.3)
Oropharyngeal pain	5 (5.5)	1 (2.1)	6 (4.3)
Injection site reaction	4 (4.4)	1 (2.1)	5 (3.6)

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-The PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.9ii

The most common AEs by SOC were Infections and infestations, with 30.9% (43/139) overall (28.6.% [26/91] inclisiran-inclisiran, 35.4% [17/48] placebo-inclisiran). This incidence in this SOC was driven by AEs of nasopharyngitis, influenza, and COVID-19 described above. Other AEs by SOC occurring at an incidence of >10.0% were Injury, poisoning, and procedural complications (14.4%, 20/139; with 9/20 participants experiencing fractures), General disorders and administration site conditions (10.8%, 15/139; mostly injection site reaction related AEs), and Nervous system disorders (10.8%, 15/139; with headache most commonly reported in this SOC).

Table 40: Treatment emergent adverse events by primary system organ class – Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran	Placebo- Inclisiran	Total
	N=91	N=48	N=139
Primary system organ class	n (%)	n (%)	n (%)
Number of participants with at least one TEAE	60 (65.9)	27 (56.3)	87 (62.6)
Blood and lymphatic system disorders	1 (1.1)	0	1 (0.7)
Cardiac disorders	1 (1.1)	0	1 (0.7)
Eye disorders	0	1 (2.1)	1 (0.7)
Gastrointestinal disorders	9 (9.9)	2 (4.2)	11 (7.9)
General disorders and administration site conditions	10 (11.0)	5 (10.4)	15 (10.8)
Immune system disorders	2 (2.2)	0	2 (1.4)
Infections and infestations	26 (28.6)	17 (35.4)	43 (30.9)
Injury, poisoning and procedural complications	10 (11.0)	10 (20.8)	20 (14.4)
Investigations	3 (3.3)	2 (4.2)	5 (3.6)
Metabolism and nutrition disorders	1 (1.1)	2 (4.2)	3 (2.2)
Musculoskeletal and connective tissue disorders	10 (11.0)	3 (6.3)	13 (9.4)
Nervous system disorders	9 (9.9)	6 (12.5)	15 (10.8)
Psychiatric disorders	3 (3.3)	1 (2.1)	4 (2.9)
Reproductive system and breast disorders	1 (1.1)	0	1 (0.7)
Respiratory, thoracic and mediastinal disorders	9 (9.9)	2 (4.2)	11 (7.9)
Skin and subcutaneous tissue disorders	8 (8.8)	1 (2.1)	9 (6.5)
Vascular disorders	3 (3.3)	0	3 (2.2)

-A participant with multiple TEAEs within a primary system organ class is counted only once in the total row.

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-System organ classes are presented in alphabetical order.

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.1ii

Severity of adverse events

In Part 1, the majority of participants had AEs, which were mild as maximum severity, 60.6% (43/71) in the inclisiran and 62.5% (20/32) in the placebo group. Severe AEs were only reported in 2 participants in the inclisiran group (SAEs of anaphylactic reaction to [Circumstances] and Status migrainosus, both not considered related to study drug).

In Part 2, all participants except 1 reported AEs that were mild or moderate, with 33.8% (47/139) of participants experiencing AEs with a maximum severity of mild and 28.1% (39/139) with a maximum severity of moderate. A maximum severity of mild was reported by 36.3% (33/91) in the inclisiran-inclisiran and 29.2% (14/48) in the placebo-inclisiran group and a maximum severity of moderate in 29.7% (27/91) and 25.0% (12/48), respectively. Only 1 participant (0.7%, 1/139) in the placebo-inclisiran group experienced a severe AE, which was post-traumatic stress disorder after the participant [Circumstances].; the participant was treated with lorazepam and zopiclone for 1 month and fully recovered.

Adverse events related to study drug

In Part 1, the incidence of AEs considered related to study drug was 17.2% (16/93) in the inclisiran and 8.3% (4/48) in the placebo group. The difference in study drug-related AEs was driven by AEs of mild injection site reactions. Fifteen (15/16) participants in the inclisiran group reported study drug-related AEs of injection site reaction. Only a few participants reported other study-drug related AEs, which were balanced between treatment groups.

Table 41: Treatment-emergent adverse events related to study drug, by primary system organ class and preferred term – Part 1 Primary Analysis (Safety Set)

	Inclisiran	Placebo	Total
Primary system organ class	N=93	N=48	N=141
Preferred term	n (%)	n (%)	n (%)
Number of participants with at least one TEAE	16 (17.2)	4 (8.3)	20 (14.2)
Ear and labyrinth disorders	1 (1.1)	0	1 (0.7)
Vertigo	1 (1.1)	0	1 (0.7)
Gastrointestinal disorders	2 (2.2)	1 (2.1)	3 (2.1)
Nausea	2 (2.2)	1 (2.1)	3 (2.1)
Abdominal pain	1 (1.1)	0	1 (0.7)
General disorders and administration site conditions	15 (16.1)	4 (8.3)	19 (13.5)
Injection site reaction	8 (8.6)	1 (2.1)	9 (6.4)
Injection site pain	4 (4.3)	2 (4.2)	6 (4.3)
Fatigue	2 (2.2)	1 (2.1)	3 (2.1)
Injection site pruritus	1 (1.1)	1 (2.1)	2 (1.4)
Injection site bruising	1 (1.1)	0	1 (0.7)
Injection site dryness	1 (1.1)	0	1 (0.7)
Injection site erythema	1 (1.1)	0	1 (0.7)
Injection site induration	1 (1.1)	0	1 (0.7)
Injection site rash	1 (1.1)	0	1 (0.7)
Injection site swelling	1 (1.1)	0	1 (0.7)
Injection site urticaria	1 (1.1)	0	1 (0.7)
Nervous system disorders	3 (3.2)	1 (2.1)	4 (2.8)
Headache	2 (2.2)	1 (2.1)	3 (2.1)
Taste disorder	1 (1.1)	0	1 (0.7)

-A participant with multiple TEAEs within a primary system organ class is counted only once in the total row.

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-System organ classes are presented in alphabetical order; the PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 26.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.4i

In Part 2, the incidence of AEs considered related to study drug was 10.1% (14/139), 13.2% (12/91) in the inclisiran-inclisiran and 4.2% (2/48) in the placebo-inclisiran group. Thirteen (13/14) participants reporting study drug-related AEs had mild injection site reactions (12 SOC "General

disorders and administration site conditions", 1 SOC "Nervous system disorders"). Only 1 participant reported another study-drug-related AE (mild abdominal pain).

Table 42: Treatment emergent adverse events related to study drug, by primary system organ class, preferred term – Part 2 Analysis (Open-label phase analysis Set)

	Inclisiran- Inclisiran	Placebo- Inclisiran	Total
Primary system organ class	N=91	N=48	N=139
Preferred term	n (%)	n (%)	n (%)
Number of participants with at least one TEAE	12 (13.2)	2 (4.2)	14 (10.1)
Gastrointestinal disorders	1 (1.1)	0	1 (0.7)
Abdominal pain	1 (1.1)	0	1 (0.7)
General disorders and administration site conditions	10 (11.0)	2 (4.2)	12 (8.6)
Injection site reaction	4 (4.4)	1 (2.1)	5 (3.6)
Injection site pain	2 (2.2)	2 (4.2)	4 (2.9)
Injection site erythema	2 (2.2)	0	2 (1.4)
Injection site bruising	0	1 (2.1)	1 (0.7)
Injection site induration	1 (1.1)	0	1 (0.7)
Injection site pruritus	1 (1.1)	0	1 (0.7)
Nervous system disorders	1 (1.1)	0	1 (0.7)
Taste disorder	1 (1.1)	0	1 (0.7)

-A participant with multiple TEAEs within a primary system organ class is counted only once in the total row.

-A participant with multiple occurrences of a TEAE under one treatment is counted only once in this TEAE category for that treatment.

-System organ classes are presented in alphabetical order; the PTs are sorted in descending order of frequency in the total column.

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: Table 14.3.1-1.4ii

Supportive safety data

ORION-5 (adult HoFH)

In the 6 months double-blind Part 1, the incidences of treatment-emergent AEs were 35.1% in the inclisiran and 31.6% in the placebo group; incidences of SAEs were 5.4% and 5.3%, respectively. No treatment-emergent SAEs were considered related to study drug and there were no discontinuations of study drug due to treatment-emergent AEs. No participants died during Part 1 of the study.

In the 18 months open-label, uncontrolled Part 2, 56.6% had at least 1 treatment-emergent AE, 55.9% in the inclisiran-inclisiran and 57.9% in the placebo-inclisiran group. The incidence of treatment-emergent SAEs was 20.8%, 23.5% in the inclisiran-inclisiran and 15.8% in the placebo-inclisiran group; these were not considered related to study drug. There were no discontinuations of study drug due to treatment-emergent AEs. Three (3) participants died during Part 2.

Table 43: Overall summary of adverse events (ORION-5 Part 1 and Part 2)

Category	Study Part 1			Study Part 2		
	Inclisiran	Placebo	Total	Inclisiran-Inclisiran	Placebo-Inclisiran	Total
	N=37 n (%)	N=19 n (%)	N=56 n (%)	N=34 n (%)	N=19 n (%)	N=53 n (%)
Participants with at least one TEAE	13 (35.1)	6 (31.6)	19 (33.9)	19 (55.9)	11 (57.9)	30 (56.6)
Participants with at least one TESAE	2 (5.4)	1 (5.3)	3 (5.4)	8 (23.5)	3 (15.8)	11 (20.8)
Participants with at least one study drug related TESAE	0	0	0	0	0	0
Participants who discontinued study drug due to TEAE	0	0	0	0	0	0
Participants who died	0	0	0	3 (8.8)	0	3 (5.7)

-MedDRA Version 21.1 has been used for the reporting of adverse events
Source: [Study A12302-Table 14.3.1-1.1] and [Study A12302-Table 14.3.1-1.2]

In Part 1, 2 participants in the inclisiran (5.4%) and no participants (0%) in the placebo group had AEs considered related to study drug (PTs diarrhoea and pyrexia, mild severity). In Part 2, 1 participant (2.9%) in the inclisiran-inclisiran group had an AE considered related to study drug (PT injection site erythema, mild severity).

Serious adverse event / deaths / other significant events

ORION-13 HoFH

Deaths and serious adverse events

No participants died and no SAEs were reported during either part of the study.

Injection site reactions

During Part 1, 2/9 (22.2%) participants on inclisiran and none (0/4) on placebo reported AEs of injection site reactions. The reported PTs were injection site reaction (2 participants) and injection site erythema (1 participant). All injection site reactions were mild and none were serious or led to study drug discontinuation; all were transient and resolved without sequelae.

In Part 2, 1/13 (7.7%) participant reported an injection site reaction. This was a single AE in a participant in the inclisiran-inclisiran group, with a reported PT of injection site erythema. This injection site reaction was mild, not serious, transient, resolved without sequelae, and did not lead to study drug discontinuation.

Other safety topics

In Part 1, no cardiac, hepatic, musculoskeletal, neurological, psychiatric, or renal events in either treatment group were reported and no participant experienced AEs of new onset or worsening of diabetes. There were also no ECG-related AEs. One (1/9, 11.1%) participant in the inclisiran and 1/4 (25.0%) in the placebo group reported non-serious events of hypersensitivity that were considered not related to study drug.

Also, no cardiac, hepatic, hypersensitivity, neurological, psychiatric, renal, or ECG-related AEs were reported for Part 2 and no participants experienced AEs of new onset or worsening of diabetes. Two

(2/13, 15.4%) participants, 1 in the inclisiran-inclisiran and 1 in the placebo-inclisiran group, reported a musculoskeletal event (costochondritis and ligament sprain, respectively) that were both considered not related to study drug.

ORION-16 HeFH

Deaths and serious adverse events

No participants died during either part of the study.

The incidence of SAEs during Part 1 was low (2.8% [4/141]) and comparable between treatment groups (3.2% [3/93] inclisiran, 2.1% [1/48] placebo). The 4 SAEs were in different SOC, all were considered not related to study treatment, and all were reported as resolved. The SAEs in the inclisiran group were anaphylactic reaction to lactose [Circumstances] in a participant with a medical history of [Medical History], Dengue fever, and hospitalisation to initiate dihydroergotamine for worsening headaches (status migrainosus) after failed outpatient therapy in a participant with a history of [Medical History] and [Medical History]. The SAE in the placebo group was an episode of supraventricular tachycardia in a participant with a medical history of intermittent [Medical History].

The incidence of SAEs was also low in Part 2 (4.3% [6/139] overall, 4.4% [4/91] inclisiran-inclisiran, 4.2% [2/48] placebo-inclisiran). The 6 SAEs were in different SOC, all were considered not related to study treatment, and all were reported as resolved. The SAEs in the inclisiran-inclisiran group were anaphylactic reaction to [Circumstances] in a participant with a medical history of [Medical History], [Medical History] in a participant with a medical history of [Medical History], blood CK increased, asymptomatic and considered by the investigator as caused by rosuvastatin, and varicose veins that led to hospitalisation for a scheduled stripping. The SAEs in the inclisiran-placebo group were concussion, due to an accident, and syncope secondary to a painful stimulus.

Injection site reactions

In Part 1, a higher incidence of AEs related to injection site reactions was observed in the inclisiran compared to the placebo group (16.1% [15/93] and 6.3% [3/48], respectively). All injection site reactions were mild, none were serious or led to study drug discontinuation, and all were transient and resolved without sequelae.

During Part 2, a total of 9.4% (13/139) of participants reported at least one injection site reaction (12.1% [(11/91) inclisiran-inclisiran, 4.2% [2/48] placebo inclisiran). All reactions were mild, none were serious or led to study drug discontinuation, and all were transient and resolved without sequelae. Most participants (10/13) reporting an injection site reaction in Part 2 had already experienced an injection site reaction in Part 1 (8/11 inclisiran-inclisiran, 2/2 placebo-inclisiran). The majority of participants (10/13; all inclisiran-inclisiran), had an isolated injection site reaction in this study part.

Other safety topics

During Part 1, there were no cardiac, neurological, renal events, or ECG-related AEs in either treatment group and no participants experienced AEs of new onset or worsening of diabetes. Musculoskeletal events (14.0% [13/93] inclisiran, 12.5% [6/48] placebo) and hypersensitivity events (4.3% [4/93] inclisiran, 6.3% [3/48] placebo) were balanced between groups. Hepatic and psychiatric events occurred at a low frequency in the inclisiran group (3.2% [3/93] and 4.3% [4/93], respectively), while no such events (0% [0/48]) occurred in the placebo group; these events were not

considered related to study drug. The hepatic AEs were mild, transient elevations in liver function tests, including 1 case of mild hepatic steatosis in a participant with medical history of [Medical History] and [Medical History]. The psychiatric events were anxiety, insomnia, obstructive sleep apnoea syndrome, and tension headache (none were serious or severe) in participants with corresponding relevant medical histories.

In Part 2, there were also no cardiac, neurological, or renal events. Hepatic, hypersensitivity, musculoskeletal, and psychiatric events occurred at a similar frequency as during Part 1 and none of these events were considered related to study drug. The 2 hepatic AEs (1.4%) were mild, transient elevations in LFTs. The hypersensitivity events included an anaphylactic reaction to [Circumstances]. One (1) participant with a family history of [Medical History] was diagnosed with type 1 diabetes, considered not related to study drug; no participants experienced AEs of new onset or worsening of type 2 diabetes.

Supportive safety data

ORION-5 (adult HoFH)

Deaths and serious adverse events

In Part 1, no participants died. In Part 2, 3 (8.8%) deaths occurred in the inclisiran-inclisiran group; these were not considered related to the study drug by the investigators. The causes of death by PT were multiple organ dysfunction syndrome, sudden cardiac death, and pneumonia viral in participants with coronary heart disease.

The overall incidence of SAEs in Part 1 was low and comparable between treatment groups (5.4% inclisiran [non-cardiac chest pain, endocarditis, adenocarcinoma of the colon]; 5.3% placebo [family stress]). None of the SAEs were considered related to study treatment. In Part 2, SAEs were reported in 20.8% (23.5% inclisiran-inclisiran, 15.8% placebo-inclisiran). The SOC categories with the highest proportion of participants were Infections and infestations (9.4%) and Cardiac disorders (5.7%). The most common SAEs by PT were aortic valve stenosis and pneumonia viral (each 3.8%, 2/53). None of the SAEs were considered related to study treatment.

Other safety topics

In Part 1, there was no incidence of MACE, neurological events / neurocognitive disorders, renal events, or AEs related to new onset or worsening of diabetes. No participant in the inclisiran and 1 (5.3%) in the placebo group experienced a hepatic-related event (PTs of ALT and AST increased). The incidence of hypersensitivity events was 2.7% in the inclisiran (PT mouth ulceration) and 5.3% in the placebo group (PT of rhinitis allergic). There were no potentially clinically significant changes in biomarkers for diabetes, myopathy, or renal function.

In Part 2, 2 (5.9%) participants in the inclisiran-inclisiran-group experienced a MACE (PTs sudden death and angina unstable). Two (2; 5.9%) participants had a hepatic AE of INR increased and 1 participant (2.9%) had an AE of LFT abnormal in the inclisiran-inclisiran group and in the placebo-inclisiran group, 1 (5.3%) participant had hepatic events of INR increased, ALT increased, and AST increased and 1 (5.3%) had an AE of ALT abnormal; all of the hepatic events were mild to moderate in severity and were not considered related to study drug. Two (2; 5.9%) participants in the inclisiran-inclisiran group had renal-related events (acute kidney injury and mild renal impairment); both were not considered related to study treatment and had the outcome recovered / resolved. Four (4; 11.8%) participants in the inclisiran-inclisiran and 1 (5.3%) in the placebo-inclisiran group had TEAEs related to a new onset or worsening of diabetes; these events were either mild or moderate in severity and

were not considered related to study drug. One (1; 2.9%) participant each in the inclisiran-inclisiran group had AEs related to hypersensitivity (PT rhinitis allergic) and neurological events / neurocognitive disorders (PTs neuralgia and neuropathy peripheral), all not considered related to study drug.

VICTORION-PEDS-OLE

Deaths and serious adverse events

No participants died.

The incidence of treatment-emergent SAEs was 3.2% (4/125); all 4 participants derived from study ORION-16 in HeFH. These SAEs were in different SOC and all were not considered related to study drug. The SAEs were gastroenteritis of unknown cause in a participant with a medical history of [Medical History], the AE resolved within 3 days following treatment with an antibiotic and a proton pump inhibitor; mastoid disorder, i.e. leakage from a previous [Medical History] in a participant with a medical history of [Medical History], which was described by the investigator as a common complication of the procedure, hospitalisation for worsening of phimosis and surgical procedure to resolve the condition in a participant with medical history of [Medical History]; [Medical History], i.e. two episodes of worsening cervicolumbar pain in a participant with a medical history of intermittent [Medical History]. The SAEs were reported as resolved or resolved with sequelae (spinal pain) at the time of the data cut-off date. See also tables below.

Table 44: Overall summary of adverse events (Safety set)

Category	Feeder Study	Feeder Study	Total
	ORION-16 (HeFH)	ORION-13 (HoFH)	
	N=116	N=9	N=125
	n (%)	n (%)	n (%)
Participants with at least one TEAE	45 (38.8)	4 (44.4)	49 (39.2)
Participants with at least one study drug related TEAE	0	0	0
Participants with at least one TESAE	4 (3.4)	0	4 (3.2)
Participants with at least one study drug related TESAE	0	0	0
Participants who discontinued study drug due to TEAE	0	0	0
Participants who discontinued study drug due to TESAE	0	0	0
Participants who died	0	0	0

-MedDRA Version 27.1 has been used for the reporting of adverse events.
Source: [Study C12001B-Table 14.3.1-1]

Table 45: Treatment emergent serious adverse events by primary system organ class and preferred term (Safety set)

Category	Feeder Study	Feeder Study	Total
	ORION-16 (HeFH)	ORION-13 (HoFH)	
	N=116	N=9	N=125
	n (%)	n (%)	n (%)
Number of subjects with at least one TESA	4 (3.4)	0	4 (3.2)
Congenital, familial and genetic disorders	1 (0.9)	0	1 (0.8)
Phimosis	1 (0.9)	0	1 (0.8)
Ear and labyrinth disorders	1 (0.9)	0	1 (0.8)
Mastoid disorder	1 (0.9)	0	1 (0.8)
Infections and infestations	1 (0.9)	0	1 (0.8)
Gastroenteritis	1 (0.9)	0	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (0.9)	0	1 (0.8)
Spinal pain	1 (0.9)	0	1 (0.8)

-A participant with multiple TESAEs within a primary system organ class is counted only once in the total row.

- A participant with multiple occurrences of a TESA under one treatment is counted only once in this TESA category for that treatment.

- System organ classes are presented in alphabetical order; the PTs are sorted in descending order of frequency in the total column

-MedDRA Version 27.1 has been used for the reporting of adverse events.

Source: [Study C12001B-Table 14.3.1-1.5]

Laboratory findings

ORION-13 HoFH

Clinical laboratory evaluations, physical findings, and other observations

During Part 1, there were no clinically meaningful changes or between-group differences in safety laboratory parameters of haematology or biochemistry. No adverse effects regarding growth (height, weight, BMI), pubertal development (Tanner staging), or hormonal status (oestradiol in females, testosterone in males, LH, FSH, DHEA-S, cortisol) were seen with inclisiran treatment. There were no clinically meaningful differences in sex hormones between the inclisiran and placebo groups and the results for sex hormones and Tanner stage in males and females were consistent with the expected progression through puberty in the age groups that were studied. Height and body weight increased over time in both groups. The mean ($\pm$ SD) height increases from baseline to Day 330 in the inclisiran and placebo groups were 2.2 cm ($\pm$ 3.02) and 2.3 cm ($\pm$ 1.25), respectively; the mean baseline height was lower in the inclisiran (156.6 cm) than the placebo group (169.9 cm). Consistent increases were also seen for body weight and mean changes in BMI were minimal in both treatment groups.

In Part 2, there were also no clinically meaningful changes in safety laboratory parameters of haematology or biochemistry and no adverse effects regarding growth (height, weight, BMI), pubertal development (Tanner staging), or hormonal status (oestradiol females, testosterone males, LH, FSH, DHEA-S, cortisol) were seen with inclisiran treatment. No notable changes from baseline in sex hormones were seen and the results for sex hormones and Tanner stages were consistent with the expected progression through puberty in the age groups studied. Regarding the Tanner assessment at EoS (Day 720), in males, for genitalia and pubic hair stage, the number of participants who either had a change in Tanner stage or were already at the maximum Tanner stage at baseline was 2/2 (100%) in the inclisiran-inclisiran and 1/2 (50%) in the placebo-inclisiran group. In females, for breast

development stage, the number of participants who either had a change in Tanner stage or were already at the maximum Tanner stage at baseline was 6/7 (85.7%) in the inclisiran-inclisiran and 2/2 (100%) in the placebo-inclisiran group; for pubic hair stage, this were 5/7 (71.4%) and 1/2 (50.0%), respectively. Height and body weight increased over time during the 2-year study duration. The mean ($\pm$ SD) height increase at EoS (Day 720) was 4.9 cm ($\pm$ 5.93) in the inclisiran-inclisiran (mean baseline 156.6 cm) and 3.8 cm ($\pm$ 3.59) in the placebo-inclisiran group (mean baseline 169.9 cm). Consistent increases were also seen for body weight; mean changes in BMI were minimal.

Immunogenicity (ADA measurements)

For the analysis of formation of ADA to inclisiran, whole blood study samples were collected in part 1 on Day 1 prior to study drug (inclisiran or placebo) injection (referred to as Day 1 0h) and 4 hours after injection (referred to as Day 1 +4h), as well as on Day 150 and Day 330.

In Part 2 (Year 2), samples for the ADA analysis collected on Day 510 and Day 720. In both parts, if necessary, unscheduled or Early Termination (ET) study samples were also to be collected and analysed.

Whole blood study samples from the ORION-13 Clinical Study No. CKJX839C12302 were processed into serum and recovered serum study samples were shipped to the Test Site on dry ice for analysis.

Part 1 (Double-blind period)

The frequency of participants experiencing treatment-induced persistent and transient ADA is presented in the table below. Persistent and transient ADA were assessed using the definitions proposed by Shankar et al (2014). There were no persistent or transient treatment-induced ADA responses reported in either the inclisiran or the placebo treatment group. One participant in the inclisiran group had a positive ADA result at the pre-dose timepoint on Day 1, and the result remained positive at subsequent assessments in Study Part 1.

Table 46: Frequency (percentage) of subjects with treatment induced persistent and transient ADA- Part 1 Primary Analysis - Safety Set

	Inclisiran	Placebo
	(N=9)	(N=4)
Category	n/m (%) (*)	n/m (%) (*)
Treatment Induced ADA response (**)		
Persistent	0/9 (0%)	0/4 (0%)
Transient	0/9 (0%)	0/4 (0%)
No Treatment-Induced ADA response	9/9 (100%)	4/4 (100%)

(*) n: Subjects with ADA response; m: Subjects tested for ADA.

(**) Treatment Induced ADA: a negative ADA sample at baseline and at least one positive ADA sample post-baseline.

Persistent: negative ADA at baseline and confirmed positive ADA on 2 or more timepoints where the first and last were separated by a period of at least 16 weeks or positive ADA at the last timepoint or at a timepoint less than 16 weeks before an ADA negative last sample.

Transient: Treatment-induced ADA detected at only 1 time point post-baseline, or 2 or more sampling time points where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

[Source: ORION-13 CSR Table 14.3-7.1i]

Part 2 (Open-label period)

The frequency of participants experiencing treatment-induced persistent and transient ADA is presented in the table below. As for Study Part 1 (double-blind period), ADA was assessed using the

definitions proposed by Shankar et al (2014). There were no persistent or transient treatment-induced ADA responses reported during Study Part 2.

The single participant in the inclisiran-inclisiran group, who had a positive ADA result at the pre-dose timepoint on Day 1 and at the subsequent assessments during Study Part 1, continued to have a positive ADA result and low titers at the assessments in Study Part 2, using the modified ADA method which cross-validated according to the Applicant (for details see Section Methods, subsection Bioanalytics (anti-drug antibodies (ADA) measurement; immunogenicity assessment)).

Table 47: Frequency (percentage) of subjects with treatment induced persistent and transient ADA- Part 2 Analysis - Open-label phase analysis Set

	Inclisiran-Inclisiran (N=9)	Placebo-Inclisiran (N=4)	Total (N=13)
Category	n/m (%) (*)	n/m (%) (*)	n/m (%) (*)
Treatment Induced ADA response (**)			
Persistent	0/9 (0%)	0/4 (0%)	0/13 (0%)
Transient	0/9 (0%)	0/4 (0%)	0/13 (0%)
No Treatment-Induced ADA response	9/9 (100%)	4/4 (100%)	13/13 (100%)

(*) n: Subjects with ADA response; m: Subjects tested for ADA.

(**) Treatment Induced ADA: a negative ADA sample at baseline and at least one positive ADA sample post-baseline.

Persistent: negative ADA at baseline and confirmed positive ADA on 2 or more timepoints where the first and last were separated by a period of at least 16 weeks or positive ADA at the last timepoint or at a timepoint less than 16 weeks before an ADA negative last sample.

Transient: Treatment-induced ADA detected at only 1 time point post-baseline, or 2 or more sampling time points where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

(Source: ORION-13 CSR Table 14.3-7.1ii]

There were no persistent or transient treatment-induced ADA responses reported in either the inclisiran or the placebo treatment group in both Part 1 and Part 2 of study ORION-13. One (1) participant in the inclisiran group had a positive ADA result at the pre-dose timepoint on Day 1 and the result remained positive at subsequent assessments in study Part 1 as well as Part 2.

ORION-16 HeFH

Clinical laboratory evaluations, physical findings, and other observations

During Part 1, there were no clinically meaningful changes or between-group differences in safety laboratory parameters of haematology or biochemistry (including liver enzymes, CK, FPG, HbA1c). Also, no adverse effects regarding growth (height, weight, BMI), pubertal development (Tanner staging), or hormonal status (oestradiol in females, testosterone in males, LH, FSH, DHEA-S, cortisol) were seen with inclisiran treatment. There were no clinically meaningful differences in sex hormones between inclisiran and placebo groups over the course of Part 1 and the results for sex hormones and Tanner stage in males and females were consistent with the expected progression through puberty in the age groups studied. Height and body weight increased similarly over time in the inclisiran and placebo treatment groups; mean ($\pm$ SD) height increases from baseline to Day 330 in the inclisiran and placebo groups were 2.7 cm ($\pm$ 2.88) and 2.7 cm ($\pm$ 2.90), respectively, and these changes occurred from similar mean baseline heights of 163.0 cm and 165.4 cm. Consistent increases were also seen for body weight, while mean changes in BMI were minimal in both treatment groups.

In Part 2, there were also no clinically meaningful changes in safety laboratory parameters of haematology or biochemistry, and no adverse effects regarding growth, pubertal development, or hormonal status were seen with inclisiran treatment. There were no notable changes from baseline in sex hormones over the course of Part 2 and the results for sex hormones and Tanner stage in males

and females were consistent with the expected progression. Regarding Tanner assessment at EoS (Day 720), in males, for genitalia stage, the percentage of participants who either had a change in Tanner stage or were already at the maximum Tanner stage at baseline was 90.2% in the inclisiran-inclisiran and 91.7% in the placebo-inclisiran group; for pubic hair stage, this was 85.4% and 91.7%, respectively. In females, for breast development stage, the percentage of participants who either had a change in Tanner stage or were already at the maximum Tanner stage at baseline was 94.0% in the inclisiran-inclisiran and 95.8% in the placebo-inclisiran group; for pubic hair stage, this was 96.0% and 91.7%, respectively. Height and body weight increased over time during the 2-year study duration. The mean ($\pm$ SD) height increase at EoS (Day 720) was 4.5 cm ($\pm$ 4.92) in the inclisiran-inclisiran (mean baseline 163.0 cm) and 5.3 cm ($\pm$ 5.99) in the placebo-inclisiran group (mean baseline 165.4 cm). Consistent increases were also seen for body weight, while mean changes in BMI were small.

Immunogenicity (ADA measurements)

For the analysis of formation of ADA to inclisiran, whole blood study samples were collected in part 1 on Day 1 prior to study drug (inclisiran or placebo) injection (referred to as Day 1 0h) and 4 hours after injection (referred to as Day 1 +4h), as well as on Day 150 and Day 330. Unscheduled samples and Early Termination (ET) samples collected prior to Day 360 (due to unscheduled visits or early termination/premature discontinuation) were also collected and analysed.

In Part 2 (Year 2), samples for the ADA analysis collected on Day 510 and Day 720.

Whole blood study samples from the ORION-16 Clinical Study No. CKJX839C12301 were processed into serum and recovered serum study samples were shipped to the Test Site on dry ice for analysis.

Part 1 (Double-blind period)

The frequency of participants experiencing treatment-induced persistent and transient ADA is presented in the table below. Persistent and transient ADA were assessed using the definitions proposed by Shankar et al (2014). There were no persistent or transient treatment-induced ADA responses reported in either the inclisiran or the placebo treatment group. In addition, no participant had a positive ADA result at any of the measured timepoints (Day 1 pre-dose, Day 1 4h post-dose, Day 150 and Day 330).

Table 48: Frequency (percentage) of subjects with treatment induced persistent and transient ADA- Part 1 Primary Analysis - Safety Set

	Inclisiran	Placebo
	(N=93)	(N=48)
Category	n/m (%) (*)	n/m (%) (*)
Treatment Induced ADA response (**)		
Persistent	0/93 (0%)	0/48 (0%)
Transient	0/93 (0%)	0/48 (0%)
No Treatment-Induced ADA response	93/93 (100%)	48/48 (100%)

(*) n: Subjects with ADA response; m: Subjects tested for ADA.

(**) Treatment Induced ADA: a negative ADA sample at baseline and at least one positive ADA sample post-baseline.

Persistent: negative ADA at baseline and confirmed positive ADA on 2 or more timepoints where the first and last were separated by a period of at least 16 weeks or positive ADA at the last timepoint or at a timepoint less than 16 weeks before an ADA negative last sample.

Transient: Treatment-induced ADA detected at only 1 time point post-baseline, or 2 or more sampling time points where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

[Source: ORION-16 CSR Table 14.3-7.1i]

Part 2 (Open-label period)

The frequency of participants experiencing treatment-induced persistent and transient ADA is presented in the table below. As for Study Part 1 (double-blind period), ADA was assessed using the definitions proposed by Shankar et al (2014). In the vast majority of participants (94.2%, 131/139), no treatment-induced ADA responses were reported, (i.e., the participants remained ADA negative). Out of the 139 participants analysed, 8 participants (5.8%) showed a positive ADA response, 5/91 (5.5%) in the inclisiran-inclisiran group and 3/48 (6.3%) in the placebo-inclisiran group. All positive samples were of low titre.

Table 49: Frequency (percentage) of subjects with treatment induced persistent and transient ADA- Part 2 Analysis - Open-label phase analysis Set

	Inclisiran-Inclisiran (N=91)	Placebo-Inclisiran (N=48)	Total (N=139)
Category	n/m (%) (*)	n/m (%) (*)	n/m (%) (*)
Treatment Induced ADA response (**)			
Persistent	5/91 (5.5%)	1/48 (2.1%)	6/139 (4.3%)
Transient	0/91 (0%)	2/48 (4.2%)	2/139 (1.4%)
No Treatment-Induced ADA response	86/91 (94.5%)	45/48 (93.8%)	131/139 (94.2%)

(*) n: Subjects with ADA response; m: Subjects tested for ADA.

(**) Treatment Induced ADA: a negative ADA sample at baseline and at least one positive ADA sample post-baseline.

Persistent: negative ADA at baseline and confirmed positive ADA on 2 or more timepoints where the first and last were separated by a period of at least 16 weeks or positive ADA at the last timepoint or at a timepoint less than 16 weeks before an ADA negative last sample.

Transient: Treatment-induced ADA detected at only 1 time point post-baseline, or 2 or more sampling time points where the first and last ADA-positive samples are separated by a period less than 16 weeks, and the subject's last sampling time point is ADA-negative.

(Source: ORION-16 CSR Table 14.3-7.1ii]

The incidence of treatment-induced transient ADA was 1.4% (2/139; 0% in the inclisiran-inclisiran group and 4.2% (2/48) in the placebo-inclisiran group), and the incidence of treatment-induced persistent ADA was 4.3% (6/139; 5.5% (5/91) in the inclisiran-inclisiran group and 2.1% (1/48) in the placebo-inclisiran group). Two of the 6 responses classified as persistent were observed at a single timepoint (EoS), while for the remaining 4 cases, positive responses were seen at 2 timepoints.

The difference in ADA detected between Study Part 2 (very low incidence of treatment-induced ADA) and Study Part 1 (no treatment-induced ADA) could be attributed to analytical variability of the different cross-validated method used in Study Part 2 (see section on methods above for details).

In study ORION-16, no participants developed ADAs during study Part 1. During Part 2, 8/139 participants (5.8%) showed a positive ADA response (5.5% inclisiran-inclisiran, 6.3% placebo-inclisiran). The difference in ADA detected between study Part 2 (low incidence of treatment-induced ADA) and Part 1 (no treatment-induced ADA) could be attributed to analytical variability of the different cross-validated method used in Part 2 (see section 8.2.1 Methods – Immunogenicity above).

Importantly, for ADA positive participants in study Part 2, although detection of ADA may have been slightly more sensitive, titres were low. No clinically meaningful differences in the efficacy and safety of inclisiran were observed in participants who tested ADA positive or negative.

Supportive safety data

ORION-5 HoFH

In both parts, there were no cases of clinically significant haematology parameters.

In Part 1, there were no cases of clinically significant serum creatinine ($\geq 50\%$ increase from baseline and/or > 2 mg/dL) or CK levels ($> 5 \times$ ULN) in either group. There were also no cases of potentially clinically significant changes in HbA1c ($\geq 6.5\%$ and $\geq 0.5\%$ change from baseline). In Part 2, there were no cases of serum creatinine > 2 mg/dL; elevated serum creatinine $\geq 50\%$ increase from baseline was observed in 2 participants (3.8%; inclisiran-inclisiran group). There were no cases of clinically significant CK levels ($> 5 \times$ ULN). The incidence of potentially clinically significant changes in HbA1c ($\geq 6.5\%$ and $\geq 0.5\%$ change from baseline) was 7.5% (5.9% inclisiran-inclisiran, 10.5% placebo-inclisiran).

In Part 1, no participant in the inclisiran and one (5.3%; 1/19) in the placebo group had a clinically significant biomarker for hepatic function, increases in ALT and AST $> 3 \times$ and $\leq 5 \times$ ULN; there were no notable elevations in ALP or total bilirubin and also no cases meeting the definition of Hy's law in either group. In Part 2, 2 participants (3.8%) showed clinically significant biomarkers for hepatic function (1 inclisiran-inclisiran increase in ALT $> 3 \times$ and $\leq 5 \times$ ULN, 1 placebo-inclisiran increases in ALT and AST $> 3 \times$ and $\leq 5 \times$ ULN). There were no notable elevations in ALP and total bilirubin and no cases meeting the definition of Hy's law.

In Part 1, there were no urinary tract infections. In Part 2, 1 participant (inclisiran-inclisiran) experienced an SAE of urinary tract infection, which was not considered related to study drug and fully recovered.

Anti-inclisiran antibodies were not detected in any of the samples [Study A12302 Section 11.6].

Vital signs (SBP, DBP, heart rate) were comparable between the two treatment groups.

Since study ORION-5 was conducted in adult patients, assessments of growth, Tanner stage, and menarche status were not evaluated.

Safety in special populations

Due to the small sample size, no subgroup analyses based on intrinsic or extrinsic factors were performed in study ORION-13. In addition, no specific extrinsic factors were considered important for inclisiran.

In study ORION-16, subgroup analyses by gender, age group (≥ 12 to < 15 and ≥ 15 to < 18 years of age), race, and BMI were performed for all treatment-emergent AEs, AEs leading to study drug discontinuation, AEs related to study drug and separately for injection site reactions. There were generally no clinically relevant differences in the AE profile between subgroups. In the inclisiran group, injection site reactions AEs were reported more frequently in the younger (24.4%; 11/45) compared to the older age group (8.3%; 4/48), but in the placebo group, injection site reaction AEs were reported more frequently in the older (12.0%; 3/25) compared to the younger age group (0%; 0/23). Additionally, in the older age group, injection site reaction AEs (known ADR) were reported more frequently in the placebo (12.0%; 3/25) compared to the inclisiran group (8.3%; 4/48). In Part 2, no clinically relevant differences were seen in the AE profile between subgroups. Interpretation of these data is limited by the small sample size and the 2:1 randomisation ratio in Part 1. No specific extrinsic factors were considered important for inclisiran.

Safety related to drug-drug interactions and other interactions

No new drug-drug interaction studies with inclisiran have been performed in support of this application.

Discontinuation due to adverse events

ORION-13 HoFH

No AEs leading to study drug discontinuation were reported in either Part of the study.

ORION-16 HeFH

During Part 1, AEs that led to study drug discontinuation were reported for 1 participant (1.1%) in the inclisiran group; in addition to a transient (1.5 hours) mild injection site reaction, this participant experienced AEs of mild vertigo and nausea, starting on the day of the second study drug injection (Day 90), which were reported to have led to study drug discontinuation. These symptoms were accompanied by mild fatigue and headache and, starting two days later, moderate abdominal pain. The participant fully recovered 4 days after onset of the first AE. No AEs that led to study drug discontinuation were reported for Part 2.

Supportive safety data

In both studies, ORION-5 and VICTORION-PEDS-OLE, no AEs that led to study drug discontinuation were reported.

Post marketing experience

Inclisiran is currently approved for use in adults and the post-marketing data is limited to the adult population.

The most recent PSUR for inclisiran covered the period from 01 January 2024 to 31 December 2024. Up to this cut-off date, worldwide cumulative patient exposure since the IBD of 09 December 2020 is estimated to be approximately 368,582 patient treatment years. For the PSUR reporting interval, the exposure to inclisiran from post-marketing experience was 233,286 patient treatment years. The assessment of post-marketing usage for inclisiran remained consistent with the known safety profile.

2.5.1. Discussion on clinical safety

HoFH

Inclisiran is currently only licensed in adults, including those with HeFH, but not with HoFH, since in the phase III, two-part (double-blind placebo-controlled / open-label), multicentre study ORION-5 (MDCO-PCS-17-02) in adult patients with HoFH, inclisiran treatment failed to reduce LDL-C levels despite substantial lowering of PCSK9 levels¹⁰.

Assessment of paediatric data on clinical safety

No new or unexpected safety signals have been reported from study ORION-13 in adolescents from ≥12 to <18 years of age with HoFH; the sparse safety data (13 participants overall, 9 inclisiran, 4 placebo) in this population gathered from both parts of the study are considered to be in line with the known general safety profile in adult patients, but it has to be kept in mind that inclisiran has not been

¹⁰ Raal F, Durst R, Bi R, Talloczy Z, Maheux P, Lesogor A, Kastelein JJP; ORION-5 Study Investigators. Efficacy, Safety, and Tolerability of Inclisiran in Patients With Homozygous Familial Hypercholesterolemia: Results From the ORION-5 Randomised Clinical Trial. *Circulation*. 2024 Jan 30;149(5):354-362. doi: 10.1161/CIRCULATIONAHA.122.063460. Epub 2023 Oct 18. PMID: 37850379; PMCID: PMC10815002

licensed in adults with HoFH (see above). No adverse effects regarding growth, pubertal development, or hormonal status were seen with inclisiran treatment in either period of the study.

However, interpretation of the provided data is limited by the very low number of participants included in study ORION-13 (see above) as well as by the open-label uncontrolled design of Part 2. No definite conclusions on the safety of inclisiran in adolescents with HoFH can be drawn from these sparse data. As regards the supportive safety information from study ORION-5 in adult patients with HoFH, the study also included only 56 adult participants, placebo-controlled data are limited to 6 months and Leqvio is not authorised in adults with HoFH.

HeFH

As regards adolescents from ≥ 12 to < 18 years of age with HeFH, study ORION-16 (CKJX839C12301) included 141 participants (93 inclisiran, 48 placebo). The safety data in this population gathered from both parts of the study are considered to be in line with the known safety profile of inclisiran in adult patients and no new or unexpected safety signals have been observed. There were 5 events of syncope in the inclisiran group, which were considered not related to study drug. The applicant has provided clarification on the possible reasons for 5 events of syncope in the inclisiran group and it was agreed that there is currently no indication of a causal relationship to inclisiran treatment.

No adverse effects regarding growth, pubertal development, or hormonal status were seen with inclisiran treatment in either period of the study. Differences in the number of ADA between Part 1 (no treatment-induced ADA) and Part 2 (positive ADA response in 5/91 (5.5%) in the inclisiran-inclisiran group and 3/48 (6.3%) in the placebo-inclisiran group) of Study ORION-16 were further discussed. The Applicant clarified that the observed difference in the number of ADA between Part 1 and Part 2 could be related to analytical variability of the different cross-validated method used in Study Part 2. The changes and modification of the ADA assay resulted in a more sensitive assay potentially resulting in a slight increase in positive ADA readout, reducing the probability of false negative readout. Importantly, for participants ADA-positive in study Part 2 / Year 2, although the detection of ADA may have been slightly more sensitive, titers were low. To note, there were no clinically meaningful differences in the efficacy and safety of inclisiran in participants who tested ADA positive or negative. The Applicant discussed, based on the available data from adults, if there is a risk of developing ADA increases with the duration of inclisiran treatment. The applicant argued that the available data do not indicate that the risk of developing anti-drug antibodies (ADA) to inclisiran increases with the duration of inclisiran treatment and that there is no substantiative immune response with GalNAc-conjugated siRNA's such as inclisiran. This was agreed by CHMP.

Overall, interpretation of the provided safety data was limited by the low number of participants (n=141) included in study ORION-16.

In addition, supportive safety data from the ongoing extension study VICTORION-PEDS-OLE available so far, do not indicate new or unexpected safety signals.

Additional expert consultations

N/A

2.5.2. Conclusions on clinical safety

In conclusion, safety data from study ORION-13 in adolescents from ≥ 12 to < 18 years of age with HoFH are limited.

The provided safety data from study ORION-16 in adolescents from ≥ 12 to < 18 years of age with HeFH do not indicate any new or unexpected safety issues and, although very limited, together with the established safety profile of inclisiran in the adult population are considered adequate for the risk evaluation in this patient population. The overall safety of inclisiran in in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH) can be considered satisfactorily addressed.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Direct Healthcare Professional Communication

N/A

2.7. Significance / Non-Conformity of paediatric studies

N/A

2.8. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Table 2-14 **Part II SVIII.1: Summary of safety concerns**

Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy and breast-feeding Use in patients with severe hepatic impairment

Pharmacovigilance plan

Table 3-1 Part III.1: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Inclisiran PRenancy outcomes Intensive Monitoring (PRIM) Status: Ongoing	The overall objective of the inclisiran PRIM programme is to collect data on pregnancy outcomes in patients treated with inclisiran during pregnancy or prior to pregnancy (including congenital malformations, spontaneous abortions, stillbirths and other adverse birth outcomes) as well as infant outcomes at 3 and 12 months post-delivery, including breast-feeding status and exposures, neonatal and infant deaths and developmental delays. The findings from this programme will be used to evaluate the missing information 'Use in pregnancy and	Use in pregnancy and breast-feeding	Interim progress reports: Final report submission	Annual interim progress reports will be provided with PSURs. 31-Jul-2031 The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	breast-feeding', according to the RMP.			

Risk minimisation measures

Table 5-2 **Summary of pharmacovigilance activities and risk minimisation activities by safety concerns**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and breast-feeding	Routine risk minimisation measures: SmPC section 4.6 PL section: 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: PRIM study (Date of final CSR (planned): 31-Jul-2031) The PRIM NIS will apply until a maximum of 10 years from the first launch or 500 prospectively reported live births with known status of malformations, whichever occurs first.
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC section 4.2, 5.2 PL section: 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

2.9. Changes to the Product Information

As a result of this variation, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are being updated to include information from studies ORION-13 and ORION-16. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes agreed changes to the Product Information (PI).

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

Consultation with the target patient population regarding the readability of the PL for Leqvio was conducted as part of the initial MAA. The results of this user consultation demonstrated that the PL meets the criteria for readability as set out in the EU Guideline on the readability of the labelling and package leaflet of medicinal products for human use (v1, 12 January 2009).

Given that the proposed changes to the Leqvio PL are not considered significant and that the new information proposed to be included in the PL with this type II variation application maintains the currently approved layout / structure and format, a new user consultation has not been provided by the MAH. This is considered acceptable.

2.9.2. Additional monitoring

N/A

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Familial hypercholesterolaemia (FH) is a genetic disorder of lipoprotein metabolism manifested by lifelong and marked elevation in LDL-C levels from birth. If left untreated, it is characterised by premature cardiovascular disease (CVD). FH is caused by variants in genes encoding proteins which regulate LDL Receptor (LDLR)-mediated clearance of LDL-Cholesterol (LDL-C); there are two clinical manifestations, Heterozygous FH (HeFH) and the more severe Homozygous (HoFH), depending on the presence of one or two affected alleles in these genes.

3.1.2. Available therapies and unmet medical need

The underlying atherosclerotic vascular lesions that cause CVD, and peripheral vascular occlusive disease are caused by an elevated LDL-C level. An outstanding role to reduce the risk of major CV events is lowering of LDL-C, which has been established for a long time. Data to support the relationship between LDL-C and cardiovascular (CV) events and specifically the relationship with inhibition of Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) has been shown in genetic studies of variations in the genes that influence LDL-C and from studies in patients with FH. In Mendelian randomisation studies evaluating multiple genetic targets that impact LDL-C levels, the variants in genes that regulate LDL-C levels (e.g., LDL-R, PCSK9) have demonstrated that lowering of LDL-C is associated with a lower risk for CV events. To minimise this risk factor, lipid-lowering therapies are recommended. To reach this goal, specific targets have been suggested. It has been shown that the higher the CV risks, the more aggressive the lipid-lowering therapy should be.

Early initiation of treatment in patients with FH is considered crucial for Atherosclerotic Cardiovascular Disease (ASCVD) risk reduction (Reijman et al 2021). Despite the availability of multiple options of lipid-lowering therapies, including statins, ezetimibe, and newer treatments like anti-PCSK9 or anti-ANGPTL3 (HoFH only) monoclonal antibodies, many patients with HeFH or HoFH, including adolescents, do not reach recommended LDL-C goals and a relevant unmet medical need is considered to remain, in particular for the young patient population, who is at high risk of future CV events and thus requires intensive management of hypercholesterolaemia. In addition, as adherence to lipid-lowering therapies is known to be a particular challenge in adolescents (Joyce et al 2016, Langslet et al 2021, Weinstock et al 2023), effective treatments to reduce LDL-C, which do not require frequent self-administration, might be especially beneficial in this age group.

3.1.3. Main clinical studies

Inclisiran was first approved in the EU on 09 December 2020 under the proprietary name of Leqvio and is currently only licensed in adults, including patients with heterozygous, but not with homozygous FH, from 18 years of age onwards.

Paediatric data

The completed paediatric studies ORION-16 (CKJX839C12301) and ORION-13 (CKJX839C12302) are part of agreed Paediatric Investigation Plan (PIP) for inclisiran and were intended to investigate the use

of inclisiran in adolescents from ≥ 12 to < 18 years of age with HoFH (ORION-13) or HeFH (ORION-16) and elevated LDL-cholesterol.

Both were conducted as two-part, multicentre, randomised studies; Part 1 (year 1) investigated inclisiran versus placebo in a double-blind setting, while in Part 2 (year 2) all participants received open-label inclisiran. Inclisiran was applied at the licensed standard dose and posology for adults.

HeFH / ORION-16

The study population consisted of adolescents ≥ 12 to < 18 years with a genetic or clinical diagnosis of HeFH, an LDL-C > 130 mg/dL (3.4 mmol/L), and being on a maximally tolerated dose of statin at the investigator's discretion with or without other lipid lowering therapy (excluding PCSK9 inhibitors). Patients with HoFH or secondary hypercholesterolaemia were excluded.

The initial planned sample size was approximately 150 adolescents which was significantly reduced to at least 102 participants in a protocol amendment in October 2022. A sample size of ≥ 102 participants allowed only for detecting a $\geq 30\%$ reduction in LDL-C in the chosen setting.

During the double-blind Part 1 (year 1) of the study, the primary efficacy and safety data comparing inclisiran to placebo were collected. The open-label single arm Part 2 (year 2) of the study allowed the collection of longer-term data on inclisiran, with a focus on longer-term safety. Study ORION-16 also included PK and pharmacogenetic assessments; PK assessment was based on sparse PK sampling (pre-dose, 4-, 24-hours after first dose).

The primary endpoint was the percentage change in LDL-C from baseline to the end of the double-blind treatment period at day 330 (year 1). Secondary endpoints included absolute change in LDL-C and other lipid parameters during Part 1 as well as assessments from baseline to the end of the open-label Part 2, i.e. day 720. Exploratory endpoints included individual responsiveness of participants, changes in LDL-C by type of underlying causal mutation, change in carotid intima-media thickness (cIMT), and evaluation of inclisiran pharmacokinetics (PK) based on sparse data. The endpoints are considered to be in line with previous adult inclisiran studies.

HoFH / ORION-13

No formal hypothesis testing was planned and none was performed for study ORION-13. There was also no formal sample size calculation; the sample size was selected based on feasibility.

The study included 13 male and female adolescents, 9 in the inclisiran and 4 in the placebo group, with a genetic confirmation of HoFH, excluding LDLR null/null genotypes, and an LDL-C > 130 mg/dL who were on a maximally tolerated dose of a statin, with or without other lipid lowering therapy (except PCSK9 inhibitors, mipomersen, lomitapide). Patients with HeFH or secondary hypercholesterolemia were excluded. One (1) participant in the placebo group was on LDL-apheresis. All participants completed both parts of the study and were analysed.

During the double-blind Part 1 (year 1) of the study, the primary efficacy and safety data comparing inclisiran to placebo were collected. The open-label single arm Part 2 (year 2) of the study collected longer-term data on inclisiran with a focus on longer-term safety. To explore PK of inclisiran in adolescents with HoFH, the study also included PK and pharmacogenetic assessments.

The primary endpoint was the percentage change in LDL-C from baseline to the end of the double-blind treatment period at day 330 (year 1). Secondary endpoints included time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330, absolute changes in LDL-C and other lipid parameters during Part 1, as well as assessments from baseline to the end of the open-label Part

2, i.e. day 720. Exploratory endpoints included individual responsiveness of participants, changes in LDL-C by type of underlying causal mutation, change in cIMT, reduced frequency of LDL-apheresis treatment at Day 720 (Year 2) compared to baseline, and evaluation of inclisiran pharmacokinetics (PK) based on sparse data. The endpoints are considered to be in line with previous inclisiran studies in adults.

3.2. Favourable effects

ORION-16 HeFH

In the primary analysis, study ORION-16 met the primary objective of demonstrating superiority of inclisiran compared to placebo in reducing LDL-C in adolescents with HeFH on maximally tolerated statin treatment. The effect of a between-group difference (95% CI) of -28.54% (-35.81, -21.27; $p < 0.0001$) between inclisiran and placebo is considered clinically relevant.

Results of sensitivity and subgroup analyses were consistent with the primary analysis.

As regards key secondary efficacy endpoints, in Part 1 of the study, relevant reductions were seen for time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330; the between-group difference in mean percent change was -29.30% (-36.24, -22.36; $p < 0.0001$).

Relevant reductions were also seen for absolute change in LDL-C, and percent change in Apo B, non-HDL-C, and total cholesterol (all p -values < 0.0001), while results for Lp(a) were not statistically significant (p -value 0.1419) and, given the hierarchical testing of the key secondary endpoints, further results are to be considered exploratory.

Results of pre-specified sensitivity and subgroup analyses for the key secondary endpoints were consistent with the primary analysis.

During the open-label Part 2, consistent reductions were seen in LDL-C, sustained over 2 years of treatment. The mean percent change in LDL-C ($\pm$ SD) from baseline to Day 720 was -33.7% ($\pm$ 24.0).

As regards exploratory results, 56.7% (51/90) in the inclisiran versus 12.5% (6/48) in placebo group reached an LDL-C < 130 mg/dL and 27.8% (25/90) versus none, respectively, an LDL-C < 100 mg/dL. A $\geq 50\%$ reduction in LDL-C was reached by 16/90 (17.8%) in the inclisiran and none in the placebo group.

During the open-label Part 2, 90/139 (64.7%) participants reached an LDL-C < 130 mg/dL and 53/139 (38.1%) an LDL-C < 100 mg/dL. A $\geq 20\%$ reduction in LDL-C was reached by 105/139 (75.5%), $\geq 30\%$ by 85/139 (61.2%), and $\geq 50\%$ by 33/139 (23.7%) participants.

Consistent LDL-C lowering was seen with inclisiran across the included genetic variant groups in Part 1. For the open-label Part 2, such an analysis was not specified in the protocol but added for completeness in the SAP; as for Part 1, consistent LDL-C lowering was seen across the included genetic variant groups.

No clinically relevant effect of inclisiran on cIMT was seen during Part 1 or 2.

ORION-13 HoFH

For study ORION-13 no formal hypothesis testing was planned. As regards primary analysis, the mean percent change in LDL-C from baseline to Day 330 was -21.6% in the inclisiran and +11.7% in the

placebo group (mean between-group difference [95% CI] -33.25% [-59.17, -7.34]). A supplementary analysis excluding the participant (n=1) on LDL-apheresis showed consistent results.

A waterfall plot of individual percentage changes in LDL-C from baseline to Day 330 by participant showed a variable magnitude; all participants in the inclisiran group showed a reduction in LDL-C albeit with significant differences in magnitude, while response in the placebo group was less consistent with an increase in LDL-C of 54.9%, as well as a decrease of -15.4%.

Two thirds (66.7%) of the participants in the inclisiran group achieved a >15% and more than half (55.6%) a ≥20% reduction in LDL-C from baseline to Day 330.

In the secondary analyses, in line with the primary endpoint, the mean time-adjusted percent change in LDL-C (after Day 90 up to Day 330) was -21.0% in the inclisiran and 13.0% in the placebo group (between-group difference [95% CI] -33.97% [-67.54, -0.39]). A supplementary analysis excluding the participant on apheresis showed consistent results.

The percentage changes from baseline in LDL-C in Part 1 were largely consistent across visits, with isolated outliers; the participant in the placebo group treated with LDL-apheresis showed some visit-to-visit fluctuation. Reductions were seen for absolute change in LDL-C and percent change in ApoB, non-HDL-C, VLDL-C, and total cholesterol.

No reduction was seen in Lp(a) and only small variable effects for triglycerides, HDL-C, and Apo A1.

As regards Part 2, there was a lower extent of the overall mean change in LDL-C compared to Part 1; the difference between treatments groups was driven by 2 participants in the inclisiran-inclisiran group who had increases in LDL-C of +27.3% and +47.4%, respectively. A waterfall plot of percentage change in LDL-C from baseline to Day 720 showed a variable magnitude; 10/13 participants had a decrease in LDL-C at Day 720, while in 3/13 participants, LDL-C increased at Day 720.

3.2.1. Uncertainties and limitations about favourable effects

ORION-16 HeFH

As regards the use of inclisiran in adolescents with HeFH, study ORION-16 included only 141 participants (93 inclisiran, 48 placebo) and placebo-controlled data are limited to 1 year of treatment.

ORION-13 HoFH

As regards the use of inclisiran in adolescents with HoFH, the Applicant has provided only data from a very small study in 13 paediatric patients (9 inclisiran, 4 placebo) with an exploratory design. The provided results indicate heterogeneous effects, including LDL-C increases in patients treated with inclisiran, in this patient population and no criteria are available to distinguish between patients who might or might not profit from treatment with inclisiran. Due to very limited number of HoFH subjects included it is not possible to conclude on efficacy in this population of patients.

Furthermore, inclisiran is not licensed in adults with HoFH since study ORION-5 (MDCO-PCS-17-02) failed to show an effect in this patient population (Raal et al., 2024).

3.3. Unfavourable effects

The safety of inclisiran in adults has been characterised and assessed from the Phase III development program, including data from 1833 adults with ASCVD, ASCVD risk equivalents, or HeFH exposed to inclisiran on top of maximally tolerated statin therapy. Data from these studies and from relevant extension studies indicate a favourable safety profile in adults. A higher incidence of injection site reactions is an identified common adverse drug reactions (ADR) of inclisiran (8.2% inclisiran, 1.8% placebo); these were mild or moderate in severity, transient, and resolved without sequelae. There were more frequent elevations of serum hepatic transaminases $>1x$ and $\leq 3x$ ULN in patients on inclisiran (ALT: 19.7%, AST: 17.2%) than on placebo (ALT: 13.6%, AST: 11.1%); these elevations did not progress to $>3x$ ULN, were asymptomatic, and not associated with adverse reactions or other evidence of liver dysfunction. Confirmed Anti-Drug Antibodies (ADA) positivity was detected in 1.8% prior to dosing and 4.9% during 18 months of treatment with inclisiran; no clinically significant differences in the clinical efficacy, safety, or pharmacodynamic profiles of inclisiran were observed in the patients who tested positive for anti-inclisiran ADAs. No overall differences in safety were observed between these elderly and younger patients. Inclisiran is not associated with an increased risk for renal dysfunction, hypersensitivity, or neurologic events / neurocognitive disorders, and there was no difference from placebo in new onset or worsening of diabetes.

For the current application, the existing safety data in adults have been complemented by safety data from the use of inclisiran in the treatment of adolescents with HoFH or HeFH (ORION-16 or ORION-13, respectively). Furthermore, supportive safety data have been provided from study ORION-5 in adults with HoFH, an indication that has not been licensed, and from the ongoing extension study VICTORION-PEDS-OLE in adolescents.

As regards adolescents with HeFH, study ORION-16, the safety data gathered in this population are considered to be in line with the known safety profile of inclisiran in adult patients and no new or unexpected safety signals have been observed. No adverse effects regarding growth, pubertal development, or hormonal status were seen with inclisiran treatment in either period of the study.

No new or unexpected safety signals have been reported from study ORION-13 in adolescents with HoFH; the sparse safety data (13 participants overall, 9 inclisiran, 4 placebo) in this population gathered from both parts of the study are considered to be in line with the known general safety profile in adult patients. No adverse effects regarding growth, pubertal development, or hormonal status were seen with inclisiran treatment in either period of the study.

In addition, supportive safety data in adolescents with either HoFH or HeFH from the ongoing extension study VICTORION-PEDS-OLE available so far, do not indicate new or unexpected safety signals.

3.4. Uncertainties and limitations about unfavourable effects

Interpretation of the provided safety data from study ORION-16 in adolescents with HeFH, these are also based on a limited sample size of 141 participants (93 inclisiran, 48 placebo). While inclisiran safety profile in adolescents with HeFH can be considered overall addressed, the observed difference in the number of ADA between Part 1 and Part 2 in ORION-16 study were initially of concern. could be related to analytical variability of the different cross-validated method used in Study Part 2. The changes and modification of the ADA assay resulted in a more sensitive assay potentially resulting in a slight increase in positive ADA readout, reducing the probability of false negative readout. Importantly, for participants ADA-positive in study Part 2 / Year 2, although the detection of ADA may have been

slightly more sensitive, titers were low. To note, there were no clinically meaningful differences in the efficacy and safety of inclisiran in participants who tested ADA positive or negative.

Interpretation of the provided safety data in adolescents with HoFH (ORION-13) is limited by the very low number of participants (N=13; 9 inclisiran, 4 placebo) included in the study. Furthermore, inclisiran has not been licensed in adults with HoFH and the supportive safety information from the failed study ORION-5 in adults with HoFH also encompass only 56 adult participants and the placebo-controlled data from this study are limited to 6 months of treatment.

The provided supportive safety data from the ongoing open-label, single arm, multicentre extension study VICTORION-PEDS-OLE in participants with HoFH or HeFH who have completed studies ORION-13 or ORION-16, are limited by the age of participants included. Since this is an extension study, a considerable part of the population is already in the adult age range (mean age at time of entry 17.1 years; 40.8% ≥ 18 years of age). Furthermore, the trial includes only participants who derived a benefit in the investigator's judgement.

3.5. Benefit-risk assessment and discussion

3.5.1. Importance of favourable and unfavourable effects

Significant and consistent reduction of LDL-C is considered to be of outstanding importance for the prevention of CHD, CVD, and peripheral vascular occlusive disease and lipid-lowering therapies are recommended in patients with HeFH or HoFH. Furthermore, early initiation of treatment in patients with these conditions is considered crucial for ASCVD risk reduction. Despite the availability of multiple options of lipid-lowering therapies, many patients with HeFH or HoFH, including adolescents, do not reach recommended LDL-C goals and a relevant unmet medical need is considered to remain.

Inclisiran shows a higher incidence of injection site reactions compared to placebo; however, after initiation of treatment, injections are limited to twice a year and the events were mild or moderate in severity, transient, and resolved without sequelae. Elevations of serum hepatic transaminases could be indicators of potential liver disease; however, elevations seen with inclisiran treatment did not progress to $>3\times$ ULN, were asymptomatic, and not associated with adverse reactions or other evidence of liver dysfunction. Development of ADAs could potentially influence efficacy or safety of treatment, but so far, no clinically significant differences in the clinical efficacy, safety, or pharmacodynamic profiles of inclisiran were observed in the patients who tested positive for anti-inclisiran ADAs. Furthermore, inclisiran is not associated with an increased risk for renal dysfunction, hypersensitivity, or neurologic events / neurocognitive disorders, and there was no difference from placebo in new onset or worsening of diabetes. The safety data provided within this application do not indicate new or unexpected safety issues in adolescents with HoFH or HeFH. No adverse effects regarding growth, pubertal development, or hormonal status were seen with inclisiran treatment in either period of the study. The sparse safety data gathered from both studies are considered to be in line with the known general safety profile in adult patients.

3.5.2. Balance of benefits and risks

As regards the use of inclisiran in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH), the efficacy data of the pivotal Study ORION-16 together with the available efficacy data from the use of inclisiran in the adult population with HeFH, are, in general, considered to support the proposed relevant change to the indication:

in paediatric patients aged 12 years and older with heterozygous familial hypercholesterolaemia (HeFH): in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The safety data provided do not indicate any new or unexpected safety issues and, although very limited, together with the established safety profile of inclisiran in the adult population are considered to support the preliminary risk evaluation in this patient population. In summary, the benefit-risk balance for the use of inclisiran in adolescents with HeFH was considered positive.

As regards the use of inclisiran in adolescents with HoFH (study ORION-13), the available efficacy data are considered insufficient to support the proposed indication. The very limited sample size, exploratory design, heterogeneity of response, and lack of supportive efficacy findings from the adult HoFH study ORION-5 result in substantial remaining uncertainty regarding efficacy in this population. During the procedure, the MAH confirmed that they no longer wish to pursue the proposed indication in paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia (HoFH). Nevertheless, a concise summary of study results was included in sections 4.8, 5.1 and 5.2 of the SmPC.

3.5.3. Additional considerations on the benefit-risk balance

N/A

3.6. Conclusions

The overall B/R of Leqvio is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		Type
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	Variation type II
C.4	Change(s) in the summary of product characteristics, labelling or package leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Variation type II

Grouping of two Type II variations to support the extension of the indication to paediatric patients aged 12 to less than 18 years with heterozygous familial hypercholesterolaemia, and to include update to sections 4.8, 5.1 and 5.2 of the SmPC concerning treatment of paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia:

C.I.6: Extension of indication to include the treatment of paediatric patients aged 12 to less than 18

years with heterozygous familial hypercholesterolaemia (HeFH) for based on the final results from study CKJX839C12301 (ORION-16). ORION-16 is a two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicentre study to evaluate safety, tolerability, and efficacy of inclisiran in paediatric patients (12 to less than 18 years) with heterozygous familial hypercholesterolemia and elevated LDL-cholesterol. As a consequence of this variation, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance.

C.4: Update to sections 4.8, 5.1 and 5.2 of the SmPC to include the treatment of paediatric patients aged 12 to less than 18 years with homozygous familial hypercholesterolaemia (HoFH) based on the final results from study CKJX839C12302 (ORION-13). ORION-13 is a two part (double-blind inclisiran versus placebo [Year 1] followed by open-label inclisiran [Year 2]) randomised multicentre study to evaluate safety, tolerability, and efficacy of inclisiran in paediatric patients (12 to less than 18 years) with homozygous familial hypercholesterolemia and elevated LDL-cholesterol. The Package Leaflet is updated in accordance.

Version 4.1 of the RMP has also been submitted.

The group of variations leads to amendments to the annex(es) I, and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric data

The requirements for the submitted dossier in relation to paediatrics are described in section 1 of this report.

In this procedure, the CHMP reviewed the available paediatric data from studies conducted in accordance with the agreed Paediatric Investigation Plan P/0321/2018 (and its subsequent modifications, on 2 December 2022 (EMA decision P/0495/2022) and on 11 August 2023 (EMA decision

P/0322/2023)). The results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

5. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Leqvio EMA/VR/0000293324'

For more information, please refer to the Summary of Product Characteristics.

