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APPLICATION NUMBER:

214012Orig1s000

CLINICAL REVIEW(S)

Clinical Review
 E. Craig
 NDA 214012
 LEQVIO™ (inclisiran)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	214012
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Division/Office	DDLO/OCHEN/CDER
Reviewer Name(s)	Eileen Craig, MD
Review Completion Date	December 17, 2021
Established/Proper Name	Inclisiran
(Proposed) Trade Name	Leqvio
Applicant	Novartis Pharmaceuticals Co.
Dosage Form(s)	Subcutaneous (SC) injection
Applicant Proposed Dosing Regimen(s)	284 mg administered on Day 1, again at 3 months, then every 6 months.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

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Glossary

AC	advisory committee
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo-A1	apolipoprotein A1
ApoB	apolipoprotein B
aPTT	activated partial thromboplastin
AR	adverse reaction
ASCVD	atherosclerotic cardiovascular disease
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AUC	area under the curve
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHD	coronary heart disease
CK	creatinine kinase
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRL	complete response letter
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computed tomography
CTA	Computed tomographic angiography

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CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVD	cerebrovascular disease
CVOT	cardiovascular outcomes trial
DDLO	Division of Diabetes, Lipid Disorders and Obesity
dL	deciliter(s)
DLP	data lock point
DMC	data monitoring committee
EC	European Commission
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EOS	end of study
ETASU	elements to assure safe use
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FH	familial hypercholesterolemia
GalNAc	N-acetylgalactosamine
GCP	good clinical practice
GGT	gamma glutamyl transferase
GPV	Global Pharmacovigilance
GRMP	good review management practice
HbA1c	glycated hemoglobin A1C
HDL-C	high density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IFN- γ	interferon-gamma
IL6	interleukin 6
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISR	injection site reaction

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ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LDL-C	low-density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LNP	lipid nanoparticles
Lp(a)	lipoprotein(a)
Lp-PLA2	lipoprotein-associated phospholipase A2
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mITT	modified intent to treat
mL	milliliter(s)
mmHg	millimeters of mercury
mmol	millimole
MMRM	mixed-effect models for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NYHA	New York Heart Association
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAD	peripheral arterial disease
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	percutaneous coronary intervention
PCS	potentially clinical significant
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics
PEF	peak expiratory flow
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol

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PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	prothrombin time or preferred term
REMS	risk evaluation and mitigation strategy
RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SGE	special government employee
siRNA	short (small) interfering ribonucleic acid
SOC	system organ class
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TAVR	transcatheter aortic valve replacement
TBIL	total bilirubin
TC	total cholesterol
TEAE	treatment emergent adverse event
TNF- α	tumor necrosis factor-alpha
TTR	target transthyretin
ULN	upper limit of normal
US	United States
VLDL-C	very low-density lipoprotein cholesterol
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Inclisiran (proposed proprietary name of LEQVIO), a new molecular entity (NME), is a double-stranded small interfering ribonucleic acid (siRNA). In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of messenger RNA (mRNA) for proprotein convertase subtilisin/kexin type 9 (PCSK9). The reduction in intrahepatic PCSK9 levels leads to increased recycling and expression of the LDL-C receptor on the hepatocyte cell surface. This leads to increased low-density lipoprotein cholesterol (LDL-C) uptake and lowering of LDL-C levels in the circulation.

Inclisiran was developed as a single use prefilled syringe (300 mg inclisiran sodium in 1.5 mL aqueous solution containing 284 mg of inclisiran) for administration by a healthcare professional. Inclisiran is administered as a subcutaneous injection given at Day 1, again at 3 months, then every 6 months.

The Applicant proposes the following indication: INCLISIRAN is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

The initial application was submitted December 23, 2019. The Office of Pharmaceutical Quality (OPQ) recommended withholding approval because of deficiencies related to the (b) (4) drug product manufacturing site in (b) (4). Reviewers from all other review disciplines supported approval. The application received a Complete Response action on December 18, 2020 stating that FDA could not approve the application in its present form due to objectionable conditions noted at the drug product manufacturing site, (b) (4).

The Applicant now submits a Class 2 Complete Response Resubmission to address the deficiencies outlined in the Complete Response letter. During the End-of-Review meeting, the Applicant discussed the option of submitting Sandoz GmbH, Austria as a replacement or additional drug product manufacturing site in the Complete Response Resubmission. The Applicant has decided to replace the (b) (4) drug product manufacturing site in the Complete Response Resubmission with the Sandoz GmbH drug product manufacturing site in Austria. The Applicant is also submitting a safety update that follows feedback given by FDA on April 1, 2021 and June 9, 2021 on the submitted Content and Format Packages with an agreed Data Lock Point (DLP) date of May 10, 2021 for the safety update in the Resubmission. As agreed to with FDA, the safety update includes data from the ongoing open-label trials, ORION-3 and ORION-8, data from the recently completed double-blind phase (part 1) of the

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ORION-5 trial, and meeting minutes from the open session Data Monitoring Committee (DMC) meeting from the ongoing ORION-4 trial.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The initial submission of the application contained substantial evidence that the drug is effective for its intended use. LDL-C is a valid surrogate endpoint for evaluating risk reduction of atherosclerotic cardiovascular disease (ASCVD). Based on data showing robust LDL-C reductions and an acceptable safety profile, the Division of Diabetes, Lipid Disorders and Obesity (DDLO) recommended the following indication after review of the initial submission:

- INCLISIRAN is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

The effect of inclisiran on cardiovascular morbidity and mortality has not been determined in a dedicated cardiovascular outcomes trial.

1.3. Benefit-Risk Assessment

The following benefit-risk assessment table is based, in part, on information from the initial primary clinical review document (in DARRTS, dated November 6, 2020). Please refer to that review for details on the clinical efficacy and safety evaluation of inclisiran.

Benefit-Risk Integrated Assessment

Inclisiran (proposed proprietary name of LEQVIO) is a double-stranded siRNA that lowers LDL-C levels in the circulation. Based on data showing robust LDL-C reductions and an acceptable safety profile with inclisiran, this reviewer recommends approval of inclisiran as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C.

Hyperlipidemia, specifically an increase in LDL-C levels, is a major modifiable risk factor for the development of atherosclerosis and ASCVD. ASCVD continues to be the leading cause of death and disability worldwide. The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease.

Current treatment guidelines emphasize reducing the risk of ASCVD through lipid management, based on an individualized approach which considers a patient's overall risk for a cardiovascular (CV) event. Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on their risk category. Ezetimibe and/or PCSK9 inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk (secondary prevention and HeFH) who require additional LDL-C reduction.

The phase 3 trials ORION-9, ORION-10, and ORION-11 included a population of approximately 3500 subjects with HeFH or ASCVD with elevated LDL-C despite maximally tolerated statin therapy who were treated with inclisiran sodium 300 mg administered subcutaneously at Day 1, Day 90, and every 6 months afterward for a duration of 18 months. The trial population included relevant comorbidities such as increased age, renal impairment, hepatic impairment, hypertension, and diabetes. The data from these 3 trials demonstrated durable, clinically meaningful LDL-C reduction (48-52%) with supportive results in total cholesterol (TC), non-high density lipoprotein cholesterol (non-HDL-C), and apolipoprotein B (ApoB) endpoints. The majority of subjects in the inclisiran group experienced a sizable LDL-C reduction at Day 510 compared to the placebo group. Consistent, statistically significant placebo-adjusted LDL-C percent reductions from baseline to Day 510 were seen across various subpopulations defined by baseline demographic characteristics and disease comorbidities.

Inclisiran has a prolonged pharmacodynamic effect on LDL-C levels which allows for infrequent dosing, which may be preferable to some patients. It is possible, but not proven, that less frequent dosing with inclisiran may improve a patient's adherence. However, unlike alirocumab, evolocumab, and statins, we do not have CV outcome data with inclisiran that confirms a reduction in CV morbidity and mortality,

nor do we have the long-term safety data assessment that is possible from a CVOT that is several years in duration and enrolls thousands of patients. The lack of this data limits the scope of the indication to therapy that is add-on to statin therapy in individuals at high-risk for ASCVD.

Review of safety data in the original NDA submission identified few issues. More subjects assigned to inclisiran reported and discontinued study drug due to injection site reactions compared with subjects assigned to placebo, but no serious or severe reactions occurred. Other events with small imbalances greater in the inclisiran group included arthralgia and increases in blood glucose in patients with diabetes/impaired fasting glucose. The incidence of adverse events of concern, including hypersensitivity, neurocognitive events, renal events, increases in liver transaminase and ophthalmological events, were similar between the inclisiran and placebo groups. The incidence of persistent anti-drug antibodies was low and was not associated with attenuation of LDL-C lowering.

This Complete Response submission includes new and updated safety information on all reports of deaths, treatment-emergent adverse events (AEs), serious adverse events (SAEs), AEs leading to study drug discontinuation, AEs at the injection site, and clinical laboratory evaluation for inclisiran reported in the relevant ongoing open-label trials, ORION-3 and ORION-8, and from the recently completed double-blind phase (Part 1) of the ORION-5 trial, through May 10, 2021. The safety data set includes 3417 subjects given any dose of inclisiran. The overall safety profile for inclisiran in this update was similar to that previously seen in the phase 2 and 3 trials of the original NDA submission. No new safety concerns were identified.

The benefit-risk analysis for inclisiran is favorable for an indication as an adjunct to maximally tolerated statin therapy in high-risk patients with clinical ASCVD or HeFH, who require additional LDL-C lowering. The data support approval for these conditions of use. The applicant will be issued postmarketing requirements (PMRs) to conduct phase 3 efficacy and safety trials evaluating inclisiran in patients with HeFH ages 8 years (or ≥ 6 years of age and on apheresis) to less than 18 years. A PMR to collect prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant will also be issued.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Large burden of ASCVD worldwide and in the US: • ASCVD prevalence in United States excluding hypertension (coronary heart disease (CHD), heart failure (HF), and stroke only) is 9% overall (24.3 million in 2016).¹ • Leading cause of death in United States. • \$351 billion annual cost of ASCVD and stroke in US (2015).¹ LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes: • Meta-analysis of statin trials demonstrated that an absolute reduction of 38.7 mg/dL (1 mmol/L) with statins is associated with a 22% relative risk reduction in 5-year incidence of major vascular events (non-fatal myocardial infarction, coronary death, ischemic stroke, or coronary revascularization).² • CV outcomes trials (CVOTs) of the two approved PCSK9 inhibitors, alirocumab and evolocumab, demonstrated that reducing LDL-C levels led to a reduction in risk of CV events.^{3,4} LDL-C reduction with other agents is used in high-risk patients who require additional LDL-C lowering:	LDL-C reduction with therapies targeting upregulation of the LDL-C receptor is the cornerstone of preventive treatment (primary and secondary) for CV disease. Statins are considered first-line, standard-of-care for lowering LDL-C with the goal of reducing CV risk. CVOTs of statins and monoclonal antibody PCSK9 inhibitors demonstrated that reducing LDL-C levels with these agents led to a reduction in risk of CV events. Despite the availability of these drugs with proven CV benefit, the burden of ASCVD in the US remains large.

¹ Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–528.

² Baigent, et al. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.

³ Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; 379: 2097-107.

⁴ Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- CVOT with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering⁵; (b) (4) - Other agents, such as colesvelam and bempedoic acid, may be used as adjuncts to statins, PCSK9 inhibitors, and ezetimibe, but the incremental effects on CV outcomes are unknown. Patients with elevated LDL-C are treated for primary and secondary prevention of CV events: - Primary prevention: Reduce the risk for development of CV disease in patients at increased risk. - Secondary prevention: Reduce the risk for additional CV events.	
Current Treatment Options	<u>Treatment options</u> Monotherapy for LDL-C reduction - Statin: -22% (pravastatin 10 mg) to -63% (rosuvastatin 40 mg) - High-intensity statin, ≥50% reduction - Moderate-intensity statin, 30% to 49% reduction - Low-intensity statin, <30% reduction - Ezetimibe: -18% to -20% reduction Add-on therapy - Statin+ezetimibe: -12% to -19% additional lowering compared to statin - Statin+PCSK9 inhibitors: -46% to -71% additional lowering	Current treatment guidelines emphasize reducing risk of ASCVD through lipid management, based on an individualized approach which considers a patient’s overall risk for a CV event. In primary prevention, this is based on an ASCVD risk score and additional risk factors. Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on

⁵ Cannon, CP, Blazing, MA, Giugliano, RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	compared to statin • Statin+bempedoic acid: -17% to -18% additional lowering compared to statin • Ezetimibe+bempedoic acid: -13% additional lowering compared to ezetimibe <u>Treatment recommendations, 2018 ACC/AHA Guidelines⁶</u> • Primary prevention ○ Moderate-intensity statin to reduce LDL-C by 30% to ≥50% depending on calculated CV risk ○ High-intensity statin in severe hypercholesterolemia (LDL-C level ≥190 mg/dl) • Secondary prevention, high-risk for recurrence⁷ ○ High-intensity statin to reduce LDL-C by ≥50% +/- ezetimibe • Secondary prevention, very high-risk for recurrence⁸ ○ High-intensity statin to reduce LDL-C <70 mg/dL + ezetimibe +/- PCSK9 inhibitor	risk category. Low-intensity statins are not recommended for any population. Ezetimibe and/or PCSK9 inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk (secondary prevention and HeFH) who require additional LDL-C reduction. Statins reduce LDL-C by 25% to 60% depending on the statin intensity. PCSK9 inhibitors lower LDL-C by an additional 45% to 70%. Ezetimibe lowers LDL-C by an additional 15% to 20%. Other drug categories, such as fibrates or niacin, are not considered mainstays of LDL-C lowering therapy due to mild LDL-lowering ability and clinical trial data that shows no benefit in reducing CV morbidity or mortality among patients already treated with a

⁶ <https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000000625>

⁷ High-risk conditions are defined as age ≥65 years, heterozygous familial hypercholesterolemia (HeFH), prior coronary revascularization outside of the major ASCVD events, diabetes, hypertension, chronic kidney disease with estimated glomerular filtration rate 15-59 ml/min/1.72 cm², current smoker, and LDL-C ≥100 mg/dl despite maximally tolerated statin therapy and ezetimibe.

⁸ Very high risk for future ASCVD events includes a history of multiple major ASCVD events (ACS within 12 months, myocardial infarction, ischemic stroke, peripheral arterial disease defined as claudication with ankle-brachial index [ABI] <0.85, or previous revascularization or amputation, or one major event with multiple high-risk conditions).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Patient access to newer add-on therapies, such as PCSK9 inhibitors, has been challenging due to factors such as expense and payer coverage.⁹	statin.^{10,11} Additional agents may be used in patients who require additional LDL-C lowering despite optimum therapy.
Benefit	In patients with established ASCVD who took inclisiran for secondary prevention as add-on to background statin therapy, inclisiran lowered LDL compared to placebo: • At Day 510, -51% to -52% reduction In patients with HeFH who took inclisiran as add-on to background statin therapy, inclisiran lowered LDL compared to placebo: • At Day 510, -48% reduction A cardiovascular outcomes trial to evaluate the benefit of inclisiran as an adjunct to statin therapy is ongoing.	Inclisiran has a robust LDL-C lowering treatment effect. The LDL-C lowering treatment effect of inclisiran is similar to that achieved with alirocumab and evolocumab; however, alirocumab and evolocumab have both demonstrated CV risk reduction in outcomes trials. The LDL-C lowering treatment effect of inclisiran is greater than that of ezetimibe, bempedoic acid, and low-intensity statins; ezetimibe and low-intensity statins have been evaluated in CV outcomes trials. In the absence of outcomes data, the CV risk reduction is not definitively described. Nonetheless, inclisiran provides an additional

⁹ Navar AM, Tayler B, Mulder H, et al. Association of Prior Authorization and Out-of-pocket Costs With Patient Access to PCSK9 Inhibitor Therapy. JAMA Cardiol. 2017 Nov 1;2(11):1217-1225.

¹⁰ AIM-HIGH Investigators, W.E. Boden, J.L. Probstfield, T. Anderson, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 365 (2011), pp. 2255-2267

¹¹ The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005.366:1849-1861.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		option for patients who require LDL-C lowering despite optimized available therapies.
Risk and Risk Management	In phase 3 trials, inclisiran was associated with: • Injections site reactions (8.2% of patients) compared to placebo (1.8%) • Arthralgia (5.0% versus 4.0% in placebo) • Urinary tract infections (4.4% versus 3.6% in placebo) • Diarrhea (3.9% versus 3.5% in placebo) • Bronchitis (4.3% versus 2.7% in placebo) Review of updated safety data from the open-label extension phase 2 and 3 trials is consistent with that previously reported in the initial NDA submission.	Inclisiran is associated with injection site reactions (ISR) that were mild to moderate in severity and transient in nature. The risk for ISR is monitorable and can be adequately addressed through labeling. Other adverse events with imbalances were infrequent and included small increases in blood glucose in patients with diabetes/impaired glucose tolerance. However, new onset diabetes incidence was similar to placebo. Inclisiran continues to have an acceptable safety profile for its intended use in adults with ASCVD or HeFH.

2. The Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

Inclisiran is an NME, and it is not currently marketed in the U.S.

2.2. Summary of Presubmission/Submission Regulatory Activity

The original inclisiran NDA 214012 was submitted on December 23, 2019. The Complete Response Letter (CRL) was issued to the Applicant on December 18, 2020 stating that FDA could not approve the application in its present form due to the lack of an acceptable facility inspection at the (b) (4) drug product manufacturing facility located in (b) (4).

A Type A NDA End-of-Review Meeting was held on April 27, 2021 (refer to meeting minutes in DARRTS dated May 20, 2021). During the End-of-Review Meeting, the Applicant discussed the option of submitting Sandoz GmbH, Austria as a replacement or additional drug product manufacturing site in the Complete Response Resubmission. Subsequently, the Applicant informed the FDA that they would replace the (b) (4) drug product manufacturing site in the Complete Response Resubmission with the Sandoz GmbH drug product manufacturing site in Austria.

The Applicant submitted an initial Content and Format Package proposal on March 15, 2021, and FDA responded on April 1, 2021 that we agreed with the proposed content of the safety update and the overall proposed content and format to be included in the Complete Response Resubmission. The Applicant submitted an updated Content and Format Package proposal on June 2, 2021. The June submission contained the drug product manufacturing site change and a detailed outline of other sections of the proposed resubmission. FDA provided to the Applicant on June 9, 2021 the acknowledgement of the revised Content and Format for the resubmission and gave advice regarding what should be included in the chemistry, manufacturing, and controls (CMC) sections when it was submitted.

The Applicant now submits a Class 2 Complete Response Resubmission to address the deficiencies outlined in the CRL. This submission contains revised Module 3 drug product sections with information related to the Sandoz GmbH, Austria drug product manufacturing site as a replacement drug product manufacturing site for (b) (4). The revised module 3 includes the stability data and the drug product quality comparison between the phase 3 inclisiran trials and the to-be-marketed finished product manufactured at Sandoz GmbH site in Austria. The Applicant states that no changes have been made to the drug product composition, to the drug product release and end-of-shelf-life specifications, to the analytical procedure, to the drug product primary container closure system, to the drug substance, and to the excipients.

The Applicant submitted 3-month stability data on September 20, 2021.

The Applicant states that the last round of labeling negotiations with the FDA was submitted on December 16, 2020 (SN 0052) addressing comments on immunogenicity from the FDA as well as a request by the Applicant for FDA to review a counterproposal for the description of inclisiran in the product label. This submission is cross-referenced to the December 16, 2020 labeling submission, which included a response document with the tracked and clean versions of the label, in order to resume continued label negotiations from this timepoint.

2.3. Foreign Regulatory Actions and Marketing History

Inclisiran was approved in the European Union (EU) on December 9, 2020, and on December 11, 2020, the European Commission (EC) granted authorization for marketing inclisiran for the treatment of adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, alone or in combination with other lipid-lowering therapies.

Inclisiran was first launched in Germany and Austria in February 2021. Prior to May 10, 2021, inclisiran was also launched in 3 more EU countries and the United Arab Emirates (UAE).

3. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

3.1. Product Quality

In the initial review cycle, Office of Pharmaceutical Quality (OPQ) recommended a complete response (CR) action due to the Office of Pharmaceutical Manufacturing Assessment (OPMA)'s recommendation for 'withhold approval' because of deficiencies related to the (b) (4) drug product manufacturing site in (b) (4) (refer to review by Dr. Ramaswamy, in DARRTS dated October 1, 2020; Reference ID: 4679598 and Dr. Janoria' s facility review in Panorama dated September 30, 2020).

For this submission, the recommendation from OPQ for NDA 214012 is approval, which includes an acceptable recommendation for the facilities listed in the application (refer to review by Dr. Ramaswamy, in DARRTS dated November 30, 2021; Reference ID: 4896564 and Dr. Pai's manufacturing process review in Panorama, dated November 22, 2021). The microbiology review concluded that the proposed microbiological controls are adequate to support the NDA (refer to Dr. Pfeiler's microbiology review dated September 8, 2021 and November 30, 2021 in Panorama). In summary, there are currently no outstanding deficiencies related to the drug substance, drug product, process, microbiology, facility, environmental

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analysis, and container/ carton label sections of the NDA; the OPQ overall recommendation for NDA 214012 is approval.

4. Review of Safety

The DLP date used for the safety update in the Resubmission is May 10, 2021. The safety update includes new and updated safety information on all reports of deaths, treatment-emergent adverse events (TEAEs), SAEs, AEs leading to study drug discontinuation, AEs at the injection site, and clinical laboratory evaluation for inclisiran reported in the relevant ongoing open-label trials, ORION-3 and ORION-8, and from the recently completed double-blind phase (part 1) of the ORION-5 trial through May 10, 2021. The safety data set includes 3417 subjects given any dose of inclisiran (see table below for details).

ORION-4/KJX839B12301 is currently ongoing and blinded so no safety data from this trial was included in this update. However, per FDA's request, updates from the DMC's review of ORION-4 (open meeting minutes and the most recent recommendation letter) were submitted.

Table 1 Ongoing Trials Included in the Safety Update

Trial (countries)	Population	Control Group	# Subjects in Safety Data Set	Treatment Period	Data Included
Phase 2 ORION-3 (US, Canada, Netherlands, Germany, UK)	Extension of ORION-1 ASCVD, ASCVD-risk equivalents, and elevated LDL-C in adults	None	371	48 months	All data: from trial start (March 24, 2017) to current data cut-off (May 10, 2021) and New data: since original NDA (May 9, 2019) to current data cut-off (May 10, 2021)
Phase 3b ORION-8 (US, Ukraine, Canada, Czech Republic, Germany, Denmark, Spain, UK, Hungary, Netherlands, Poland, Sweden, South Africa)	Extension of ORION-9/10/11 ASCVD, ASCVD-risk equivalents, HeFH, or HoFH and elevated LDL-C in adults	None	2990	~36 months	All data: from trial start (April 16, 2019) to current data cut-off (May 10, 2021)
Phase 3 ORION-5 (Hong Kong, Israel, Russia, Serbia, South Africa, Taiwan, Turkey, Ukraine)	HoFH and elevated LDL-C in adults	Part 1: Double-blind (placebo or inclisiran) Part 2: Open-Label (inclisiran)	56	Part 1: 6 months Part 2: 18 months	All data: from trial start (February 6, 2019) to current data cut-off (May 10, 2021)

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Source: Table 1-3 from safety_update_response

ASCVD=atherosclerotic cardiovascular disease=ASCVD; FPFV= first patient first visit; HeFH= heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C= low-density lipoprotein cholesterol; UK=United Kingdom; US=United States

This safety update includes exposure data from 3 ongoing trials (ORION-3, ORION-8, and ORION-5) with a total of 3417 subjects. Across the 3 trials, the total doses given were 16,550, as shown in the following table. In the original submission, the Division had requested the pivotal phase 3 trials for inclisiran to be 18 months in duration, as opposed to the typical 12-month duration, in part to have sufficient exposure to 4 injection administrations. In contrast, the monoclonal antibody PCSK9 inhibitors are given every 2 or 4 weeks so there was ample opportunity in those phase 3 trials to assess for ISRs and hypersensitivity reactions related to the injections. These extension trials provide an additional opportunity to assess for any ISRs or other reactions, such as rash, hypotension, and recall ISRs,¹² that may occur in the setting of receiving the injection.

Table 2 Summary of Inclisiran Doses Administrated in Clinical Trials (Safety Population)

		ORION-3 Group 1 ^d N=284	ORION-3 Group 2 ^d N=87 ^b	ORION-8 N=2990	ORION-5 N=56
Number of inclisiran doses administered					
1	n (%)	6 (2.1)	1 (1.1)	39 (1.3)	2 ^a (3.6)
2	n (%)	7 (2.5)	2 (2.3)	105 (3.5)	2 ^a (3.6)
3	n (%)	8 (2.8)	1 (1.1)	112 (3.7)	9 ^a (16.1)
4	n (%)	8 (2.8)	2 (2.3)	630 (21.1)	19 ^a (33.9)
5	n (%)	2 (0.7)	1 (1.1)	2104 (70.4)	24 ^a (42.9)
6	n (%)	7 (2.5)	52 (59.8)	0 (0.0)	0 (0.0)
7	n (%)	12 (4.2)	28 (32.2)	0 (0.0)	0 (0.0)
8	n (%)	151 (53.2)	0 (0.0)	0 (0.0)	0 (0.0)

¹² "Recall ISRs" are reactions at sites where the drug was previously injected after the last injection. This phenomenon has been observed with mipomersen, etanercept, and others.

- van Meer L, Moerland M, Gallagher J, van Doorn MB, Prens EP, Cohen AF, Rissmann R, Burggraaf J. Injection site reactions after subcutaneous oligonucleotide therapy. *Br J Clin Pharmacol*. 2016 Aug;82(2):340-51.
- González-López MA, Martínez-Taboada VM, González-Vela MC, Blanco R, Fernández-Llaca H, Rodríguez-Valverde V, Val-Bernal JF. Recall injection-site reactions associated with etanercept therapy: report of two new cases with immunohistochemical analysis. *Clin Exp Dermatol*. 2007 Nov;32(6):672-4.
- De Aramburu Mera T, Reguero Capilla M, Ochando Diez-Canseco M, Prados Castaño M. Recall Injection-Site Reactions After Treatment With Anakinra. *J Investig Allergol Clin Immunol* 2021; Vol. 31(3): 275-276

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9	n (%)	83 (29.2)	0 (0.0)	0 (0.0)	0 (0.0)
Total number of doses	N	2167	529	13625	229
Exposure					
Patient years exposure in current study		941.5	216.4	4729.6	82.5
Patient years exposure from feeder study through current study ^c		1323.9	N/A	7362.8	N/A

Source: Table 2-1 from Clinical Complete Response: safety_update_response_inclisiran

n: number of subjects who received doses (1 to 9).

^a Number of subjects receiving x doses was calculated as the number of subjects from Placebo-Inclisiran group receiving x inclisiran doses in Part 2 plus the number of subjects from inclisiran-inclisiran group receiving x inclisiran doses overall.

^b Out of 90 subjects, 87 received inclisiran.

^c Patient years exposure to inclisiran is defined as the number of days from the first date of inclisiran treatment to the date of last recorded contact/participation date in the database divided by 365.25 Percentage was calculated as: $n/N \times 100$.

^d Group 1 (inclisiran only arm) received inclisiran only and Group 2 (switching arm) received evolocumab for 1 year followed by inclisiran for the remainder of the trial.

As of September 2021, which is 4 months after the DLP date used for the safety update, the total number of subjects exposed to inclisiran as well as the duration of exposure to inclisiran is summarized in the table below. While the majority of the data originates from open-label trials, limiting the interpretability of the safety findings, it does provide over 2 years of exposure to inclisiran for approximately 3,000 subjects. This database can support and potentially confirm the safety findings found in the placebo-controlled trials from the original NDA submission.

Table 3 Duration of Exposure to Inclisiran in Clinical Trials (Safety Population)

	ORION-3 Group 1 ^c	ORION-3 Group 2 ^c	ORION-8	ORION-5 Inclisiran- Inclisiran ^a	ORION-5 Placebo- Inclisiran ^b	TOTAL
	N=284 n (%)	N=87 n (%)	N=2990 n (%)	N=37 n (%)	N=19 n (%)	N=3417 n (%)
Number of subjects exposed to inclisiran:						
<6 months	1 (0.4)	0	51 (1.7)	3 (8.1)	0	55 (1.6)
≥6 months	283 (99.6)	87 (100.0)	2939 (98.3)	34 (91.9)	19 (100.0)	3362 (98.4)
≥12 months	272 (95.8)	84 (96.6)	2837 (94.9)	33 (89.2)	18 (94.7)	3244 (94.9)
≥18 months	265 (93.3)	83 (95.4)	2758 (92.2)	32 (86.5)	14 (73.7)	3152 (92.2)
≥24 months	259 (91.2)	81 (93.1)	2669 (89.3)	28 (75.7)	0	3037 (88.9)
≥36 months	246 (86.6)	36 (41.4)	0	0	0	282 (8.3)

≥48 months	131 (46.1)	0	0	0	0	131 (3.8)
Duration of exposure to inclisiran (months):						
n	284	87	2990	37	19	3417
Mean ± SD	44.07±10.51	34.57±6.166	25.22±4.830	22.42±6.094	18.13±2.306	26.95±7.751
Median	47.90	35.93	26.57	24.53	18.40	26.63
Q1, Q3	47.35, 48.32	35.70, 36.40	25.73, 27.17	24.03, 25.53	17.97, 19.40	25.77, 27.53
Min, Max	2.33, 51.33	6.00, 41.17	0.03, 29.70	3.83, 26.57	9.50, 20.30	0.03, 51.33

^a This group received inclisiran in the 6-month double-blind period and in the 18-month open-label follow-up period.

^b This group received placebo in the 6-month double-blind period (before Day 180) and, starting at Day 180, received inclisiran in the 18-month open-label follow-up period.

^c Group 1 (inclisiran only arm) received inclisiran only and Group 2 (switching arm) received evolocumab for 1 year followed by inclisiran for the remainder of the trial.

Duration of exposure was defined as minimum of (Date of last dose of treatment – Date of first dose of Inclisiran treatment + 180.

Date of last known visit – Date of first dose of Inclisiran treatment)/30.

Subjects continuing in on-going trial ORION-3 and ORION-8, exposure was truncated at data cut-off date 23-Sep-2021.

Subjects continuing in on-going trial ORION-5, exposure was truncated at data cut-off date 14-Sep-2021.

Source: Applicant’s Response to FDA Information Request_Submitted October 22, 2021_Table 2-1

4.1. Specific Safety Studies/Clinical Trials

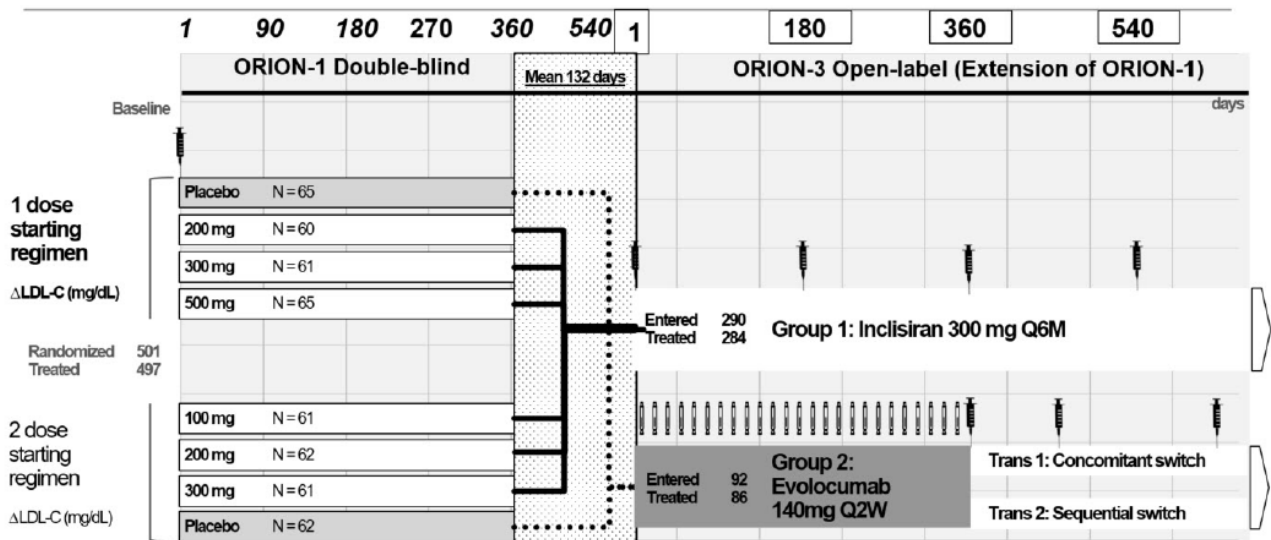
4.1.1. Phase 2 Trial: ORION-3

ORION-3 is an ongoing, open-label, multicenter, long-term (4 year) extension trial in subjects who completed the phase 2 trial ORION-1. Subjects have ASCVD or ASCVD-risk equivalents (e.g., diabetes or familial hypercholesterolemia) and elevated LDL-C despite maximum tolerated dose (as determined by the investigator) of LDL-C lowering therapies. Subjects from ORION-1 were eligible to enroll into ORION-3 if they completed ORION-1 to at least Day 210 and if their LDL-C had returned to within 20% of the baseline value or if they completed the Day 360 visit (ORION-1) with no contraindication to receiving inclisiran or evolocumab. In addition, subjects had to fulfill all inclusion and exclusion criteria of ORION-3 and sign an informed consent form.

The trial consists of 2 treatment groups: Group 1 (inclisiran only arm) received inclisiran only and Group 2 (switching arm) received evolocumab for 1 year followed by inclisiran for the remainder of the trial. Subjects in Group 2 were allocated by the site number to two transition patterns:

- Transition 1 (staged): Day 336 was the final dose of evolocumab therapy and the first dose of inclisiran was administered at the Day 360 visit.
- Transition 2 (concurrent): Day 336 was the final dose of evolocumab therapy at home. At the Day 360 visit, subjects received an additional dose of evolocumab and their first dose of inclisiran, both administered by the investigator.

Figure 1 ORION-3: Trial Design



Source: Figure 1-1 from Clinical Complete Response: safety_update_response_inclisiran

In the original submission, the Applicant included all available data up to Day 630 of the trial. In this Safety Update, the Applicant provides all safety data up to May 10, 2021 as well as new safety data since the original NDA submission (from May 9, 2019 to May 10, 2021) for 284 subjects in Group 1 receiving inclisiran and 87 out of 90 subjects in Group 2 who switched from evolocumab to inclisiran and received inclisiran. Group 2 was broken down by transition pattern (Transition 1 [staged] and Transition 2 [concurrent]). Out of the 87 subjects in Group 2 (evolocumab→inclisiran arm) who completed the Day 360 Visit and were continuing in the trial, 60 subjects were treated in Transition 1 and 27 subjects were treated in Transition 2.

Safety Assessments:

Refer to the Appendix for tables of study assessments for ORION-3.

- Physical examination: Days 1, 360, 720, 1080, and at the end of study (EOS) visit.
- Vital signs (heart rate and blood pressure): Days 1, 30, 90, 180, 210, 270, 360, 390, 450, 540, 570, 630, 720, 810, 770, 990, 1080, 1170, 1260, 1350, and at the EOS visit.
- Electrocardiograms (ECGs): Days 1, 360, 720, 1080, and at the EOS visit.

Laboratory assessments include:

- Hematology – Day 1, Day 360, Day 720, Day 1080, and EOS: hemoglobin, hematocrit, erythrocytes, reticulocytes, platelet counts, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), white blood cell count, differential blood count.
- Coagulation – Day 1, Day 360, Day 720, Day 1080, and EOS: prothrombin time (PT),

- international normalized ratio (INR), activated partial thromboplastin (aPTT).
- Full serum chemistry – Day 1, Day 360, Day 720, Day 1080, and EOS: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), uric acid, creatine phosphokinase (CK), albumin, total protein, urea (BUN), creatinine, sodium, potassium, chloride, inorganic phosphate, direct and indirect bilirubin, estimated glomerular filtration rate (eGFR), calcium, and bicarbonate.
 - Fasting serum glucose and glycated hemoglobin A1C (HbA1C): Days 1, 1080, and EOS only,
 - High sensitivity C-reactive protein (hsCRP) (fasting): Days 1, 360, 720, and EOS only.
 - Limited serum chemistry all subjects – Days 30, 90, 180, 270, 390, 450, (510 Group 2 only), 540, (570 Group 1 only), 630, 810, (870 Group 1 only), (900 Group 2 only), 990, 1170, 1260, and 1350: AST, ALT, ALP, GGT, TBIL, CK, creatinine, and eGFR.
 - Fasting serum glucose and HbA1C: Days 270, 540, 810, and 1350 only.
 - Tryptase and inflammatory markers such as interleukin 6 (IL6), interferon-gamma (IFN- γ) and tumor necrosis factor-alpha (TNF- α) may be performed from stored samples centrally at a later date, as required. Should a subject develop anaphylaxis on days when inclisiran is injected, the investigator is to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logistically possible).
 - Anti-inclisiran antibodies: Group 1 (Inclisiran only arm): Days 1, 90, 180, and 270. Group 1 and 2: Days 360, 450, 540, 630, 720, 810, 770, 990, 1080, 1170, 1260, 1350, and at the EOS visit.

Safety Population: all subjects who received at least one dose of study drug. Treatment classification was based on the actual treatment received. This was the primary population for the safety analyses.

Adverse Event Assessment:

- Pre-existing conditions: Planned hospital admissions and/or surgical operations for an illness or disease that existed at baseline and did not aggravate during the study are not to be reported as AEs.
- AE Severity
 - 1 = Mild: Discomfort noticed, but no disruption to daily activity. Requires minimal or no treatment.
 - 2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity. Requires therapeutic measures.
 - 3 = Severe: Inability to work or perform normal daily activity. May require systemic drug therapy or other treatment.
- New onset of diabetes in subjects with no medical history of diabetes was reported

when:

- HbA1C becomes $\geq 6.5\%$ and/or
- Two consecutive values of fasting plasma glucose that are ≥ 126 mg/dL
- 'Worsening of the glycemic control' or 'diabetic complications' in subjects with a medical history of disease (HbA1C $\geq 6.5\%$ at baseline) was reported when:
 - HbA1C increases from Baseline (Day 1 of ORION-3) $> 0.5\%$ and/or
 - New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level.

Exposure and Disposition:

Group 1

The median duration on the trial was 1262 days (~3.5 years) and the exposure was 941.5 patient-years in ORION-3. A total of 42 subjects (15%) in Group 1 (inclisiran only arm) discontinued the trial (see Table 4). Withdrew consent was the most common reason for discontinuation from the trial. Eight subjects discontinued due to TEAEs and 5 deaths were reported from the initiation of the trial until the cut-off (May 10, 2021). A total of 242 subjects (85%) were ongoing at the cut-off date.

Group 2

The median duration on the trial was 1266 days (~3.5 years) and the exposure was 216.4 patient-years in ORION-3. A total of 10 subjects (11%) in Group 2 (evolocumab→inclisiran arm) discontinued the trial. Withdrew consent and physician decision were the most common reasons for discontinuation from the trial. No subjects discontinued due to TEAEs and 1 death (from COVID-19) was reported from the initiation of the trial until the cut-off (May 10, 2021). A total of 76 subjects (84%) were ongoing at the cut-off date and 4 subjects (4%) completed the trial.

Table 4 ORION-3: Treatment Exposure and Subject Disposition in Group 1 and Group 2 - Safety Population

	GROUP 1 Inclisiran-Inclisiran n (%) ^a	GROUP 2 Evolocumab-Inclisiran n (%) ^a
	N=284	N=90
Discontinued before Day 360	9 (3.2)	3 (3.3)
Discontinued at or past Day 360	33 (11.6)	7 (7.8)
Ongoing	242 (85.2)	76 (84.4)
Completers	0 (0.0)	4 (4.4)
Discontinued	42 (14.8)	10 (11.1)
Withdrew (W/d) Consent	15 (5.3)	4 (4.4)
W/d to further study procedures	2 (0.7)	2 (2.2)

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W/d to all further follow-up	13 (4.6)	2 (2.2)
Physician Decision	4 (1.4)	3 (3.3)
Lost to Follow-up	2 (0.7)	0 (0.0)
Death	5 (1.8) ^b	1 (1.1) ^b
Adverse Event	8 (2.8)	0 (0.0)
Inclusion/Exclusion	0 (0.0)	0 (0.0)
Other	8 (2.8)	2 (2.2)
Duration on Trial (Days) – N	284	90
Mean ± SD	1210.9±243.3	1237.6±224.2
Median	1262.0	1266.0
Q1, Q3	1256,1348	1256,1346
Min, Max	71,1395	215,1464
Patient years exposure to inclisiran in ORION-3	941.5	216.4
^a Subject disposition for the entire treatment period up to the cut-off date (May 10, 2021). ^b Deaths reported since the Day 120 safety update cut-off date (February 1, 2020) ^c Group 1 (inclisiran only arm) received inclisiran only and Group 2 (switching arm) received evolocumab for 1 year followed by inclisiran for the remainder of the trial. Source: Reviewer created from JMP Clinical 8.1, Tables 3-1 and 3-2 from Clinical Complete Response: safety_update_response and Supplement to Safety Update Table 1.1.2.4.1		

Additional information was requested from and provided by the Applicant for the subjects who discontinued for 'other' reasons. The 'other' reasons for discontinuation included: (1) there were 2 consecutive dosing visits missed in the trial; as a result, the subject had been without open-label inclisiran treatment for more than a year and was discontinued from the study at the sponsor's request, (2) it was the investigator's and/or subject's decision to not continue in the trial, (3) a new prescription of ezetimibe was started, and the sponsor requested discontinuation according to protocol since the subject had initiated a prohibited medication, and (4) subject relocated and was no longer able to participate in the study.

Reviewer Comment: The mean and median duration of exposure to inclisiran were similar in both groups. The percentage of subjects discontinuing was generally similar between Group 1 and Group 2, although there was a higher incidence of adverse events in Group 1. The median duration of exposure to inclisiran of ~3.5 years is helpful in assessing events that are rare or easily attributed to study drug, like ISRs. However, as it is open-label and uncontrolled (i.e., all subjects are on inclisiran) it is a limited data source to determine if a finding is associated or caused by the drug versus merely reflects the events typically seen in that study population.

Demographics:

- The population in Group 1 consisted of 184 (65%) male subjects, the mean age was 63

years, 94% of subjects were White, 4% were Black or African American, 1% were Asian, 1% were American Indian or Alaska Native, and <1% were Native Hawaiian or Other Pacific Islander. Subjects came from the Netherlands (37%), United States (US) (19%), United Kingdom (UK) (18%), Canada (14%), and Germany (12%).

- The population in Group 2 consisted of 54 (60%) male subjects, the mean age was 62 years, 93% of subjects were White, and 6% were Black or African American. Subjects came from the Netherlands (32%), US (18%), UK (18%), Canada (17%), and Germany (16%).
- Combining Groups 1 and 2, there were 238 (64%) male subjects and 136 (36%) female subjects; the mean age was 63 years, median age was 64 years, and 48% were age 65 years and older. Overall, 93% of subjects were White, 4% were Black or African American, 1% were Asian, 1% were American Indian or Alaska Native, and <1% were Native Hawaiian or Other Pacific Islander; 6% were of Hispanic or Latino ethnicity. Subjects came from the Netherlands (35%), US (19%), UK (18%), Canada (15%), and Germany (13%).

Treatment Compliance:

- Group 1: Group 1 subjects were to receive subcutaneous (SC) doses on Days 720, 810, 990, 1170, and 1350 since the last safety update (January 31, 2020). As of the cut-off of May 10, 2021, 255 subjects, 242 subjects, 234 subjects, 243 subjects, and 100 subjects received SC doses, administered by clinical study site staff, on Days 720, 810, 990, 1170, and 1350 respectively. The majority (~99%) of the injections were in the abdomen. The dose administered was 300 mg in all subjects except one subject receiving an unspecified dose other than 300 mg on Day 720.
- Group 2 subjects were to receive SC doses on Days 810, 990, 1170, and 1350 since the last safety update. As of the cut-off of May 10, 2021, 82 subjects, 81 subjects, 78 subjects, and 31 subjects received planned SC doses on Days 810, 990, 1170, and 1350. The majority (~99%) of the injections were in the abdomen. The dose administered was 300 mg in all the subjects except one subject receiving 200 mg on Day 990.

Safety Data:

The translation of investigator-reported terms for the adverse event to preferred terms was examined by this reviewer. Overall, few errors in translation were identified, and no adverse events were reclassified. Based on comparing the reported term to the dictionary-derived preferred term, this reviewer believes that AEs were generally categorized appropriately. Overall, this safety data submission, in particular the patient narratives, was high-quality, complete, and well-organized.

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A summary of the safety data in Group 1 (inclisiran only arm) and Group 2 (evolocumab→inclisiran arm) is shown in the table below. For Group 2, all 90 subjects who were dosed at any time during the trial were included in the “Safety population” as detailed in Table 4. However, for the purposes of some of the following safety analyses, only the 87 subjects who received inclisiran on or after Day 360 (two subjects discontinued before Day 360 and one subject discontinued at Day 360) are included in the Group 2 Evolocumab-Inclisiran population.

Table 5 ORION-3: Summary of Adverse Events in Group 1 and Group 2 - Safety Population

Category	GROUP 1 Inclisiran-Inclisiran n (%) N=284	GROUP 2 Evolocumab-Inclisiran n (%) N=87
Subjects Died	5 (1.8)	1 (1.1)
Subjects with at Least One TEAE	273 (96.1)	78 (89.7)
Subjects with at Least One Serious TEAE	95 (33.5)	28 (32.2)
Subjects Discontinued Study Drug Due to TEAE	14 (4.9)	4 (4.6)
Subjects Discontinued Study Drug Due to TESAE	5 (1.8)	2 (2.3)
Subjects with at Least One Severe TEAE	50 (17.6)	22 (25.3)

Reporting period: Trial start on Day 1 to May 10, 2021; Group 2 only includes data when subjects were on inclisiran, which is on or after Day 360 (prior to that time they were on evolocumab)

TEAE=treatment emergent adverse event; TESAE= treatment emergent serious adverse event

Source: Reviewer created from JMP Clinical 8.1, Tables 6-1 and 6-2 from Clinical Complete Response: safety_update_response and Supplement to Safety Update Tables 1.6.1.4.1a and 2.6.1.4.2a.

Deaths:

Since the trial initiation up to the cut-off of May 10, 2021 (all data), a total of six deaths were reported. One death (Group 1) was reported in the original NDA and five deaths (4 in Group 1 and 1 in Group 2) were reported since the initial NDA DLP of the original NDA (May 8, 2019). Five deaths were reported in Group 1 (inclisiran arm only) from the preferred terms (PTs) of Corona virus infection (1), respiratory failure (1), ischemic stroke (1)¹³, aortic aneurysm rupture

¹³ This case had been previously reported in the initial NDA in Group 1: Patient ID# (b) (6) a 78-year-old, White male died due to ischemic cardiovascular accident. The patient’s ischemic cardiovascular accident occurred

(1) and coronary artery occlusion (1). One death was reported in Group 2 from the PT of Corona virus infection. None of the deaths were likely related to study drug based on my review of the narratives. Further, deaths secondary to CV events are not unexpected in a trial population of subjects with baseline ASCVD or ASCVD risk equivalents.

Reported since initial NDA DLP:

Group 1: Inclisiran only arm

- Patient ID# [REDACTED] (b) (6), an 83-year-old Black male died from coronavirus infection.
- Patient ID# [REDACTED] (b) (6), a 72-year-old White male died from respiratory failure due to pneumonia and underlying congestive heart failure and severe emphysema.
- Patient ID# [REDACTED] (b) (6), a 60-year-old White male with coronary artery occlusion. PMH included hyperlipidemia, hypertension, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), current smoker.
- Patient ID3 [REDACTED] (b) (6), a 74-year-old White male with history of aortic aneurysm and transcatheter aortic valve replacement (TAVR) died from an aortic aneurysm rupture.

Group 2: Evolocumab/inclisiran arm

- Patient ID# [REDACTED] (b) (6), an 80-year-old White female died from coronavirus infection.

TESAEs:

- Group 1: Inclisiran only arm

Since the initiation of the trial until the cut-off date, 95 (34%) subjects had at least one TESAE in Group 1. The most frequent SAEs reported were in the system organ class (SOC) cardiac disorders (11%; 31/284); CV events would be expected in patients with established ASCVD/ASCVD risk equivalents and dyslipidemia. The most common TESAEs were angina pectoris and osteoarthritis (each 2%, 6/284), followed by angina unstable (2%, 5/284), atrial fibrillation, coronary artery disease, corona virus infection, pneumonia, prostate cancer, and transient ischemic attack (each 1%, 4/284) (as shown in Table 6 below).

- Group 2: Evolocumab/inclisiran arm

As shown in Table 6, from Day 360 to May 10, 2021, 28 out of 87 (32%) subjects treated with inclisiran reported a TESAE. The most common TESAE by PT were coronary artery disease (3, 3%), transient ischaemic attack (2, 2%), and hypertensive crisis (2, 2%).

Table 6 ORION-3: Treatment Emergent Serious Adverse Events (≥ 2 events in total) in Group 1 and Group 2 by Preferred Terms - Safety Population

	Group 1	Group 2	

in the setting of a traffic accident. This patient had a medical history that included hyperlipidemia, hypertension, peripheral artery disease, prior transient ischemic attack, and right internal carotid artery stenosis.

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Preferred Term	Inclisiran-Inclisiran (N=284)		Evolocumab- Inclisiran (N=87)		Total
	Count	%	Count	%	
Coronary artery disease	4	1.4%	3	3.4%	7
Angina pectoris	6	2.1%	1	1.1%	7
Osteoarthritis	6	2.1%	.	.	6
Transient ischaemic attack	4	1.4%	2	2.3%	6
Angina unstable	5	1.8%	.	.	5
Atrial fibrillation	4	1.4%	1	1.1%	5
Corona virus infection	4	1.4%	1	1.1%	5
Pneumonia	4	1.4%	1	1.1%	5
Acute myocardial infarction	3	1.1%	1	1.1%	4
Prostate cancer	4	1.4%	.	.	4
Non-cardiac chest pain	2	0.7%	1	1.1%	3
Syncope	3	1.1%	.	.	3
Abdominal pain upper	3	1.1%	.	.	3
Anaemia	3	1.1%	.	.	3
Humerus fracture	2	0.7%	1	1.1%	3
NOT CODED	2	0.7%	1	1.1%	3
Peripheral arterial occlusive disease	3	1.1%	.	.	3
Myocardial infarction	2	0.7%	.	.	2
Acute kidney injury	2	0.7%	.	.	2
Aortic aneurysm	2	0.7%	.	.	2
Benign prostatic hyperplasia	2	0.7%	.	.	2
Cardiac failure	2	0.7%	.	.	2
Cholecystitis acute	2	0.7%	.	.	2
Coronary artery occlusion	1	0.4%	1	1.1%	2
Coronary artery stenosis	1	0.4%	1	1.1%	2
Epistaxis	2	0.7%	.	.	2
Hypertensive crisis	.	.	2	2.3%	2
Ischaemic stroke	2	0.7%	.	.	2
Malignant melanoma	2	0.7%	.	.	2
Plasma cell myeloma	1	0.4%	1	1.1%	2
Rotator cuff syndrome	2	0.7%	.	.	2
Squamous cell carcinoma of skin	1	0.4%	1	1.1%	2
Urosepsis	2	0.7%	.	.	2
Ventricular tachycardia	1	0.4%	1	1.1%	2

Reporting period: Trial start to May 10, 2021; Group 2 only includes data when subjects were on inclisiran, which is on or after Day 360 (prior to that time they were on evolocumab)

Data is sorted by the number of events in Total column

Source: Reviewer created from JMP Clinical 8.1, Tables 6-3 and 6-4 from Clinical Complete Response: safety_update_response and Supplement to Safety Update Table 2.6.3.4.3a

In the placebo-controlled database submitted with the original NDA, the most commonly reported SAEs were in the Cardiac disorders SOC (9.4% in placebo and 8.0% in inclisiran), followed by Infections (3.6% in placebo and 3.9% in inclisiran), and Nervous System disorders (2.7% in placebo and 2.4% in inclisiran). The preferred terms atrial fibrillation (n=20, 1.1%),

pneumonia (n=21, 1.1%), and myocardial infarction (n=12, 0.7%) were reported at slightly higher incidence rates for inclisiran than placebo (0.8%, 0.9%, and 0.5%), respectively.

Overall, TESAEs in this safety update were similar to those seen in the original NDA and included CV events such as angina pectoris, coronary artery disease, atrial fibrillation, and transient ischemic attack that are expected in a population of subjects with ASCVD or ASCVD risk equivalents, as well as other SAEs commonly seen in this older population, including osteoarthritis, prostate cancer, and infections (pneumonia, coronavirus).

TEAEs leading to study drug discontinuation:

- Group 1: Inclisiran only arm

In all data up to May 10, 2021, 14 (5%) subjects in Group 1 discontinued the study drug due to a TEAE, including 5 subjects who discontinued since the original NDA DLP. These TEAEs leading to study drug discontinuation included multi-organ failure, corona virus infection, eye contusion, muscle strain, hepatic enzyme increased, liver function test abnormal, failure to thrive, muscular weakness, myalgia, Hodgkin's disease stage IV, plasma cell myeloma, prostate cancer, skin depigmentation, epistaxis, and abortion induced.

My review of the subject narratives revealed some events in which a relationship to inclisiran cannot be ruled out:

- Patient: (b) (6), a 71-year-old White male with a medical history which included hyperlipidemia, hypertension, prior MI, prior percutaneous coronary intervention, duodenal ulcer, gout, and vagotomy; and concomitant medications including aspirin, clopidogrel, valsartan, bisoprolol, carbasalate calcium, and colchicine, who experienced muscle strain on Day 635. The patient received the last dose of study drug on Day 726. The patient did not have CK elevations. At the time of this report, the event of muscle strain did not resolve. The investigator considered the event of muscle strain to be moderate and reasonably attributable to the study drug.
- Patient: (b) (6), a 23-year-old Black male, who was administered inclisiran on Day 1 and Day 176. PMH: hyperlipidemia on ezetimibe. No other medications listed. On Day 176, the patient experienced a non-serious adverse event of worsening of myalgia to lower limbs. Lab results for this visit indicated the patient had a creatine kinase level (reference range 25-210) of 256 U/L. Muscle pain was not associated with a clinically significant elevation of creatine kinase (only 1.2 x ULN). Mildly elevated creatine kinase levels were observed from Day 1 throughout the study. The patient was discontinued from the study drug due to the worsening of myalgia to lower limbs. The patient had received the last dose of the study drug on Day 176. At the time of this report, the patient did not recover from the event of myalgia. The investigator considered the event of myalgia to be severe and reasonably possibly attributable to the study drug.
- Group 2: Evolocumab/Inclisiran arm

In all data up to May 10, 2021, four subjects in Group 2 discontinued the study drug due to a TEAE, including three subjects since the original NDA DLP. These TEAEs leading to study drug discontinuation included hepatic enzyme increased, coronary artery disease, intraocular pressure increased, low density lipoprotein increased, and restless legs syndrome.

The patient with hepatic enzyme increased was described in the original review. Patient (Pt ID# [REDACTED] (b) (6)) treated with inclisiran from Day 360 to the data cut-off date had an SAE (hepatic enzyme increased) leading to withdrawal from treatment. The patient had hepatitis C and reported recent excessive alcohol consumption. My review of the subject narratives did not reveal events that were likely attributable to inclisiran.

TEAEs:

- Group 1: Inclisiran only arm

TEAEs from trial initiation to the current safety update cut-off are shown in the table below. The most common TEAEs include nasopharyngitis, hypertension, urinary tract infection, influenza, and arthralgia. Although the table summarizes all data, the TEAEs across the 3 study periods (submitted in original NDA, Day 1 to May 9, 2019; May 9, 2019 to May 10, 2021; and Day 1 to May 10, 2021 [all data]), were similar.

- Group 2: Evolocumab/inclisiran arm

In Group 2, the most common TEAEs in subjects treated with inclisiran from trial start to May 10, 2021 were hypertension, nasopharyngitis, influenza, and back pain.

In the phase 3 placebo-controlled trials submitted with the original NDA, TEAEs that occurred more frequently in inclisiran-treated subjects included ISRs (includes IS pain, rash, and erythema) (8%); arthralgia (5%); urinary tract infection, diarrhea, bronchitis (4% each); and pain in extremity and dyspnea (3% each). The most common AEs observed in placebo-controlled trials are similar to ORION-3, with the exception of ISRs, which occurred more frequently in the phase 3 trials.

Although several TEAEs were reported with high frequency in the open-label ORION-3 (e.g., nasopharyngitis, hypertension, influenza, diabetes mellitus, back pain, upper respiratory tract infection, fall, dizziness, myalgia, fatigue), an imbalance in these TEAEs was not observed in placebo-controlled Phase 3 data submitted with the original NDA. Further, some reported AEs are common even outside of clinical trials (e.g., back pain), some AEs may be associated with concomitant LLT (e.g., myalgia), and some AEs are common for the enrolled trial population (e.g., diabetes mellitus). Note also that analysis of AEs and blood pressure data during the original NDA review did not indicate a signal for worsening blood pressure with inclisiran.

Table 7 ORION-3: Treatment Emergent Adverse Events (in ≥ 5% of subjects in all data in either group) in Group 1 and Group 2 by Preferred Terms - Safety Population

Preferred Term	All data Group 1 N=284 n (%)	All data Group 2 N=87 n (%)
Subject with at least one TEAE	273 (96.1)	78 (89.7)
Nasopharyngitis	55 (19.4)	13 (14.9)
Hypertension	40 (14.1)	16 (18.4)
Urinary tract infection	37 (13.0)	7 (8.0)
Influenza	36 (12.7)	10 (11.5)
Arthralgia	31 (10.9)	5 (5.7)
Diabetes mellitus	27 (9.5)	2 (2.3)
Back pain	27 (9.5)	13 (14.9)
Upper respiratory tract infection	24 (8.5)	5 (5.7)
Fall	24 (8.5)	3 (3.4)
Pain in extremity	24 (8.5)	5 (5.7)
Dizziness	24 (8.5)	5 (5.7)
Myalgia	23 (8.1)	4 (4.6)
Fatigue	21 (7.4)	10 (11.5)
Dyspnoea	21 (7.4)	5 (5.7)
Angina pectoris	20 (7.0)	7 (8.0)
Headache	20 (7.0)	6 (6.9)
Cough	19 (6.7)	5 (5.7)
Osteoarthritis	18 (6.3)	7 (8.0)
Nausea	17 (6.0)	5 (5.7)
Cataract	15 (5.3)	2 (2.3)
Injection site reaction	15 (5.3)	4 (4.6)
Influenza like illness	15 (5.3)	3 (3.4)
Non-cardiac chest pain	15 (5.3)	5 (5.7)
Contusion	15 (5.3)	3 (3.4)
Muscle spasms	15 (5.3)	2 (2.3)
Diarrhoea	14 (4.9)	7 (8.0)
Cystitis	5 (1.8)	6 (6.9)
Gastrooesophageal reflux disease	6 (2.1)	5 (5.7)
Gout	12 (4.2)	5 (5.7)
Musculoskeletal pain	13 (4.6)	5 (5.7)
Tendonitis	3 (1.1)	5 (5.7)

Reporting period: Trial start to May 10, 2021; Group 2 only includes data when subjects were on inclisiran, which is on or after Day 360 (prior to that time they were on evolocumab)

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Data is sorted by the number of subjects with TEAE in 'all data' for Group 1
Source: Reviewer created from JMP Clinical 8.1, Tables 6-5 and 6-6 from Clinical Complete Response:
safety_update_response and Supplement to Safety Update Tables 1.6.2.4.2a and 2.6.2.4.2a

AEs of Special Interest:

Injection Site Reactions (ISRs)

- Group 1: Inclisiran only arm

In 'all data' up to the May 10, 2021 data cut-off, TEAEs at the injection site (MedDRA high-level term of 'injection site reactions') in Group 1 were similar to what was reported in ORION-3 in the original NDA submission: 38/284 (13.4%) subjects reported any TEAE at the injection site, compared to 34/284 (12.0%) in the original NDA. Injection site reaction, injection site erythema, and injection site pain were the most common AEs at the injection site in both 'all data' (5%, 4%, and 4%) and the original NDA (4%, 4%, and 4% respectively). My review of the data shows that most cases were transient, mild, and with Grade I or II of erythema.

- Group 2: Evolocumab/inclisiran arm

In all data up to May 10, 2021, TEAEs at the injection site in Group 2 were similar to what was reported in the original NDA: 11/87 (12.6%) subjects reported any TEAE at the injection site, compared to 9/87 (10.3%) in the original NDA. Injection site bruising, injection site pain, and injection site reaction were the most common AEs at the injection site in all data (4%, 5%, and 5% respective) and in the original NDA (2%, 5%, and 2% respectively).

From trial start to May 10, 2021, ISRs occurred in 13.2% (49/371) of ORION-3 subjects in Groups 1 and 2 combined (Group 2 only includes data when subjects were on inclisiran, which is on or after Day 360 as prior to that time they were on evolocumab).

Chemistry (ALT/AST/Creatinine/CK Elevations) and Hematology Abnormalities:
Refer to the Appendix for a listing of potentially clinically significant laboratory tests.

Table 8 ORION-3: Clinically Significant Chemistry Parameters - Safety Population – Group 1 and Group 2

Parameter	Group 1 Inclisiran-Inclisiran n (%) N=284	Group 2 Evolocumab-Inclisiran n (%) N=87
Subjects with at Least One Clinically Significant Chemistry Parameter	22 (7.7)	9 (10.3)
Alanine Aminotransferase (U/L)	4 (1.4)	1 (1.1)
>3 and ≤5 × ULN	1 (0.4)	0

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>5 and ≤10 x ULN	3 (1.1)	1 (1.1)
>10 x ULN	0	0
Aspartate Aminotransferase (U/L)	7 (2.5)	1 (1.1)
>3 and ≤5 × ULN	5 (1.8)	0
>5 and ≤10 x ULN	2 (0.7)	0
>10 and ≤20 x ULN	0	1 (1.1)
>20 x ULN	0	0
Alkaline Phosphatase (U/L)		
>2 × ULN	0	0
Total Bilirubin (mg/dL)		
>2 × ULN	1 (0.4)	2 (2.3)
Hy's Law: ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN	0	0
Serum Creatinine (mg/dL)		
≥50% increase from Baseline or >2 mg/dL	7 (2.5)	6 (6.9)
Creatine Kinase (U/L)	8 (2.8)	0
>5 and ≤10 x ULN	5 (1.8)	0
>10 and ≤20 x ULN	1 (0.4)	0
>20 x ULN	2 (0.7)	0

Data cut: May 10, 2021; Group 2 only includes data when subjects were on inclisiran, which is on or after Day 360 (prior to that time they were on evolocumab)

For each test, the most severe result is used for each subject.

Clinically significant criteria are met when both of the following occur: post-baseline values meet the thresholds, and baseline values or any prior post-baseline values do not meet the thresholds.

Source: Reviewer created from supplement to safety update Tables 1.7.13.4.1 and 2.7.13.4.2 and confirmed with JMP Clinical 8.1

- Group 1: Inclisiran only arm

As of the cut-off of May 10, 2021, 22 subjects (8%) subjects had at least one clinically significant increase in chemistry lab value. Most subjects' ALT or AST levels decreased at their next assessment. One subject had a temporary increase in bilirubin > 2x ULN. There were no Hy's law cases. Additional information on subjects with abnormal hepatic-related chemistry parameters are described below:

1. Subject (b) (6): (ULN of ALT=41 U/L) 48-year-old White male with a PMH of asthma, depression, diabetes mellitus, GERD, hyperlipidemia, HTN, insomnia, chronic peripheral venous insufficiency, restless leg syndrome, and seasonal

- allergies. Concomitant medications include atorvastatin 20 mg, beclomethasone, Breo Ellipta, famotidine, dulera, fexofenadine, lisinopril, methotrexate, tramadol, and sertraline. Baseline ALT was 0.5 x ULN, ALT 5.3 x ULN at Days 1170 and 1177; at Day 1260 had returned to 0.8 x ULN. No other adverse events were recorded around the time of this event.
2. Subject (b) (6): 66-year-old White female with a PMH of hyperlipidemia and HTN on aspirin and atorvastatin 80 mg. Her baseline ALT was 0.5 x ULN; ALT was 5.4 x ULN at Day 1170 and had decreased to 1.2 x ULN at Day 1184. Baseline AST was 0.4 x ULN; AST was 6.5 x ULN at Day 1170 and had decreased to 1.5 x ULN at Day 1184. On Day 729 an AE of liver function test abnormal (mild) was recorded and on Day 1170 the subject experienced elevated liver enzymes due to alcohol intake (mild) which was considered a significant AE. The participant was on study drug treatment when the event occurred.
 3. Subject (b) (6): 78-year-old White male, baseline ALT 0.5 x ULN; ALT was 4.4 x ULN at Day 180, 5.4 x ULN at Day 189 and had decreased to 0.9 x ULN at Day 270. Baseline AST 0.6 x ULN; AST was 3.9 x ULN at Day 180, 4.7 x ULN at Day 189 and had decreased to 0.9 x ULN at Day 270. This subject with a PMH of hyperlipidemia, diabetes mellitus, chronic kidney disease, hypertension, angina pectoris, and former smoker was diagnosed with Gleason 3+4 prostate cancer on Day 16 and opted for conservative treatment and regular blood monitoring rather than external beam radiotherapy. Due to the non-serious AE of abnormal liver function tests at Day 182, the investigator decided to discontinue the study drug permanently. On Day 209, the patient had a non-serious AE of cholelithiasis. On Day 270, the event of liver function test abnormal resolved. The patient was receiving multiple concomitant therapies at baseline and throughout the study (including atorvastatin 40 mg, aspirin, lisinopril, senna, nicorandil, atorvastatin 40 mg, omeprazole, metformin, diclofenac, and ingenol mebutate (topical for actinic keratosis). The elevated serum aminotransferases accompanied by elevated alkaline phosphatase and gamma-glutamyl transpeptidase suggested a cholestatic pattern of abnormal liver function tests. The events of cholelithiasis and prostate cancer did not resolve at the time of this narrative report. The patient was withdrawn from the study at Day 364 (~ 6 months after stopping study drug). I agree with the investigator that the events of cholelithiasis and prostate cancer are not likely to be attributable to the study drug.
 4. Subject (b) (6): 63-year-old White female with PMH of coronary artery disease, hyperlipidemia, arthritis, drug hypersensitivity, hypothyroidism, tendon disorder, and vertigo; concomitant medications include fish oil, metoprolol, thyroid medication, diphenhydramine, and ibuprofen. Her baseline ALT was 0.8 x ULN; ALT was 4.9 x ULN at Day 1260 but decreased to 0.7 x ULN at Day 1350. Baseline AST was 1.1 x ULN, AST was 5.7 x ULN at Day 1260 but decreased to 0.9 x ULN at Day 1350. The patient also experienced corona virus infection on Day 1226 and viral diarrhea on Day 1264, around the time she was experiencing elevations in ALT and AST.

5. Subject (b) (6): AST ULN=34 U/L; 36-year-old White female (concomitant medications include atorvastatin 80 mg, ezetimibe, and Excedrin prn headaches), baseline AST was 0.6 x ULN; AST was 4.5 x ULN at Day 630 but decreased to 1.8 x ULN at Day 636. This subject, described in more detail in the CK labs section, also had a CK 53 x ULN at study day 630 that had decreased to 5 x ULN 6 days later and subsequent values were in the normal range. The AST elevation was likely related to the CK elevation/myopathy event. She had no AEs recorded around the time of the AST elevation.
6. Subject (b) (6): 60-year-old White male with a PMH of hyperlipidemia, hypertension, atrial fibrillation, asthma, GERD, insomnia, osteoarthritis, scoliosis and seasonal allergy. His concomitant medications included fluvastatin 80 mg, ezetimibe, aspirin, metoprolol, meloxicam, lisinopril/hydrochlorothiazide, Symbicort, albuterol, acetaminophen, ondansetron, pantoprazole, and escitalopram. His baseline AST was 0.6 x ULN and the AST was 3.7 x ULN at last study visit, Day 1350. On Day 1244, the patient reported symptoms of nausea, vomiting, fatigue, and hypotension (blood pressure was 98/55 mmHg). The patient was hospitalized due to the SAEs of alcohol withdrawal syndrome and hyponatremia. The patient was treated with lisinopril, lorazepam, and thiamine. On Day 1247, the patient recovered from the events of alcohol withdrawal syndrome and hyponatremia and was discharged. The AST elevation was likely due to recent alcohol-induced liver injury.
7. Subject (b) (6): 49-year-old White female with PMH of DM, hyperlipidemia, anxiety, dysmenorrhea, polycystic ovarian syndrome, hypothyroidism, and sleep apnea. Her concomitant medications included metformin, sitagliptin, perindopril, candesartan, levothyroxine, spironolactone, Marvelon 28, and escitalopram. Her baseline AST was 0.4 x ULN. AST was 3.3 x ULN at Day 390, 2.7 x ULN at Day 450 and 1 x ULN at Day 540. She had recurrent events of mild ISRs during the trial and an upper respiratory tract infection recorded at Day 459, but no AEs recorded around the time of the AST elevation (recorded as an AE of hepatic enzyme increase on Day 386). Drug treatment was continued.
8. Subject (b) (6): 40-year-old White male, with a PMH of DM, diabetic retinopathy, hyperlipidemia, depression, and back pain (concomitant medications include insulin glargine and citalopram), had a baseline AST 0.6 x ULN. AST was 3.3 x ULN at Day 180 but decreased to 0.7 x ULN by Day 270. This subject, described in more detail in the CK labs section, also had a CK 42 x ULN at Day 180 that remained elevated ranging from 1.1 to 3.4x ULN through Day 1350. The AST elevation was likely related to the CK elevation/myopathy event. An AE of CPK increased was recorded on Day 190; there were no other AEs recorded around that time.
9. Subject (b) (6): 72-year-old White male (concomitant medications include simvastatin 10 mg, Lovaza 2000 mg, spironolactone, furosemide, bisoprolol, aspirin, clopidogrel, inhaled fluticasone, tamsulosin, and pantoprazole) with baseline bilirubin of 1.1 x ULN, increased to 2 x ULN at Days 990 and 1080 and was 1.9 x ULN

at Day 1170, last study visit. This subject with a PMH of congestive heart failure, hyperlipidemia, peripheral artery disease, aortic valve disease, COPD, ischemic cardiomyopathy, former smoker and prior PCI, on Day 1201 was admitted to the hospital with severe apical centrilobular emphysema by CT, pneumonia, and respiratory failure. On Day 1214, pneumonia worsened, and the patient was intubated. The patient went into cardiopulmonary arrest and died due to the event of respiratory failure. An autopsy was not performed.

Although some subjects reported elevations in AST or ALT, an imbalance in hepatic enzymes was not observed in the placebo-controlled Phase 3 data submitted with the original NDA. In these Phase 3 trials, the incidence of elevations in ALT or AST was low and balanced between the two treatment groups (for example, ALT > 3x ULN occurred in 0.5% of inclisiran-treated subjects and 0.4% of placebo-treated subjects). There were no Hy's Law cases. The incidence of hepatic disorders SMQ was 3.8% on inclisiran and 4.2% on placebo. There was no signal for drug-induced hepatic injury in the 18-month duration, placebo-controlled trials. Additionally, most subjects who experienced an AST/ALT elevation in ORION-3 had a plausible alternative etiology (e.g., statin use, cholelithiasis, hospitalization).

Abnormal increases in serum creatinine ($\geq 50\%$ increase from baseline or > 2 mg/dL) were reported in 7 subjects (2.5%). Most subjects' abnormal increase in serum creatinine levels were transient and decreased at their next assessment. The following subjects had increases that persisted. The creatine elevations are not unexpected given the patients' underlying medical condition and are unlikely drug-associated.

1. Subject (b) (6): 74-year-old white male with PMH of hyperlipidemia, hypertension, peripheral artery disease (PAD), prior cardiovascular arterial bypass graft (CABG), MI, TIA, TAVR, former smoker who received the last dose of study drug on Day 805. On Day 918, the patient had an aortic aneurysm rupture and died. Baseline creatinine was 1.12 mg/dL and ranged from 1.68 to 1.85 from Day 390 to Day 870.
2. Subject (b) (6): 69-year-old white female with PMH of hyperlipidemia, hypertension, prior CABG, MI, prior PCI, former smoker who experienced the following AEs during the trial: anemia (Day 256), hospitalized for pulmonary embolism and cardiac failure (Day 256), DM (Day 264), renal impairment (Day 275), muscle spasms (Day 533), and urinary tract infection (UTI) (Days 1172 and 1261), who experienced elevated creatinine levels from Day 270 through Day 1080.
3. Subject (b) (6): 57-year-old white male with PMH of hyperlipidemia, hypertension, prior MI, left bundle branch block, and current smoker who experienced the following AEs during the trial: MI (Day 640), ventricular tachycardia (Days 955 and 1024) treated with amiodarone and electrophysiological examination with cooled radiofrequency ablation, reported elevated creatinine levels on Days 570 and 990. Creatinine level had decreased and was close to baseline value by Day 1080.

Abnormal increases in creatine kinase (CK) were reported in 8 subjects (2.8%) (>5x to 10x ULN: 5; >10x to 20x ULN: 1; >20x ULN: 2). In subjects who had CK data at a subsequent visit, most of these elevations normalized or improved.

- Subject (b) (6), a 64-year-old white female with a PMH of hyperlipidemia, xanthoma, arcus lipoides, coronary artery stenosis, GERD, arthralgia, and osteopenia. Her background medications included rosuvastatin 40 mg, ezetimibe, metoprolol, aspirin, clopidogrel, omeprazole and ibuprofen. She had a CK 19 x ULN which had normalized within 5 days. The rapid decrease in CK within the setting of continued exposure to inclisiran makes this unlikely to be drug induced.
- Subject (b) (6), 36-year-old White female with HeFH, background medications included atorvastatin 80 mg and ezetimibe 10 mg daily. Baseline CK levels were normal. On Day 630, the CK was unexpectedly increased to 11,155 U/L (normal range: 25-210; central laboratory, 53 x ULN). The last subcutaneous injection of inclisiran prior to this abnormal laboratory value was administered on Day 540 (90 days before the CK elevation). This triggered an unscheduled visit 6 days later and the CK values remained elevated but at a much lower value of 1054 U/L (5 x ULN). By Day 720, the CK had returned to normal and remained so for the remainder of the trial on active treatment (2 years). Liver enzymes were normal. The inclisiran treatment was not interrupted by the investigator, and this CK abnormality was not reported as an adverse event. The investigator concluded that the increase in CK was most probably induced by exercise and there was no evidence of any other contributing factors or changes in the background medications. Based on narrative review, I agree that this event is not likely attributable to study drug and was most probably induced by exercise.
- Subject (b) (6), a 40-year-old White male, with medical history of type 2 diabetes, diabetic retinopathy, depression, recurrent back pain and gonarthrosis. Background medication included 4 daily injections of basal and prandial insulins, citalopram 20 mg daily and codeine/paracetamol used on an as-needed basis. Beside the study medication, there were no other lipid-lowering therapies in the background therapies. The subject's baseline CK was elevated at 1.8 x ULN. On Day 180, a CK at 8752 U/L (41.7 x ULN) was documented. The event was entered as an adverse event. The inclisiran treatment was not interrupted by the investigator. The investigator obtained 2 local CK measurements, 3 and 9 days later, which showed values of 969 U/L and 390 U/L, respectively (no normal local reference range available). CKs remained elevated ranging from 1.1 to 3.4x ULN throughout the study (EOS Day 1440). There are no documented concurrent causes for the peak increase in CK levels and there are no documented reasons for the overall small chronic increase of CK over the course of the entire study. The investigator concluded that the peak increase of CK levels on Day 180 was "due to exercising". I am not sure what the cause of the peak elevation and smaller chronic elevations of CK are, but it is unlikely to be caused by active study drug based on the rapid improvement in the peak CK level despite continued drug treatment and the lack of a signal for CK elevation in placebo-controlled phase 3 data.

Although a few subjects reported transient elevations in CK, an imbalance in CK was not seen in the placebo-controlled Phase 3 trials submitted with the original NDA. In these Phase 3 trials, there were 4 (0.2%) inclisiran-treated subjects and 2 (0.1%) placebo-treated subjects who had creatinine kinase >10X ULN and ≤20X ULN. Four (0.2%) placebo-treated subjects had creatinine kinase >20 XULN as compared to none on inclisiran. No inclisiran treated subject with a clinically significant creatinine kinase increase had an associated treatment emergent adverse event related to musculoskeletal complaints. Thus, the transient CK elevations seen in ORION-3 are unlikely to represent a drug-related safety signal in the setting of continued drug exposure and the CK elevations are not corroborated by placebo-controlled data.

- Group 2: Evolocumab/inclisiran arm

As of the cut-off of May 10, 2021, 9 subjects (10%) in Group 2 had at least one clinically significant increase in chemistry lab value. One subject (1.1%) had a temporary clinically significant increase in ALT (>5 and ≤10 x ULN) and one subject (1.1%) had a temporary clinically significant increase in AST (>10 and ≤20 x ULN). Two subjects (2.3%) had an increase in bilirubin > 2x ULN; both subjects had elevations at baseline and throughout the trial. There were no Hy's law cases. Abnormal increases in serum creatinine (≥50% increase from baseline or >2 mg/dL) were reported in 6 subjects (6.9%). Review of the narratives did not reveal any cases that were likely related to study drug (e.g., one subject had chronic kidney disease, one subject had elevations in the setting of being recently hospitalized for pneumonia and coronary artery stenosis). There were no abnormal increases in creatine kinase. Additional information on notable subjects with abnormal chemistry parameters are described below:

1. Subject (b) (6): 47-year-old white female with PMH of hyperlipidemia, hypertension, CABG, current smoker with AEs of respiratory distress (Days 97, 162, 188, and 206), hemorrhoidal hemorrhage (Day 238), hyponatremia (Day 240), non-cardiac chest pain (Day 240), chronic obstructive pulmonary disease (COPD) (Days 381 and 440), laceration with report of consuming 4-8 beers per day (Day 401), SAE of hepatic enzyme increased and patient was discontinued from the study drug (Day 409) and hepatitis C (Day 438) with ALT 5.8 x ULN at Day 390, 9.1 x ULN at Day 406, and 1.8 x ULN at EOS/Day 586. AST was 9.4 x ULN at Day 390, 14.5 x ULN at Day 406, and 2.8 x ULN at EOS/Day 586. On Day 421, the patient had a gastroenterology consultation. A diagnostic work-up was initiated which included a hepatitis C panel which came back positive. The patient was diagnosed with chronic viral hepatitis C, a FibroScan image showed stage II fibrosis and stage III steatosis, and elevated liver function test. The hepatic enzyme increase is likely due to the patient's underlying liver disease and alcohol use rather than study drug.

There were no clinically significant changes in hematology parameters (i.e., platelet counts ≤ 150,00 or ≥ 700,00) in Group 1 or in Group 2.

Anti-Inclisiran Antibodies:

In ORION-3, the planned last patient last visit (LPLV) date is at the end of December 2021. To date, anti-drug antibody (ADA) datasets are available for ORION-3 through the cut-off date of February 14, 2020. As ADA samples for this trial are analyzed at specific milestones, additional long-term data will be available at the completion of this ongoing trial. Using the definitions by Shankar et al.,¹⁴ the percentage of subjects with treatment-induced ADA, as well as persistent and transient ADA responses, is summarized in the table below. None of the 22 subjects with treatment-induced ADAs had an associated hypersensitivity event.

Table 9 Frequency (Percentage) Of Subjects with Treatment Induced ADA: Persistent and Transient ADA Responses (ORION-3 Safety Population)

	Inclisiran (N=371) n/m* (%)
Treatment Induced ADA response **	22/355 (6.2%)
Persistent	4/355 (1.1%)
Transient	18/355 (5.1%)
Not Treatment-Induced ADA response	333/355 (93.8%)

* n: # of subjects with anti-drug antibody (ADA) response; m: # of subjects tested for ADA.

** Treatment Induced ADA: 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 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: Tables 2-1 and 2-2 from Novartis Responses to FDA Questions, dated November 2, 2021.

In the phase 3 placebo-controlled trials (ORION-9, -10, and -11), 1830 out of a total of 1833 inclisiran-treated subjects had samples tested for anti-drug antibodies. A treatment-induced ADA response was detected in 90 (4.9%) subjects during the 18 months of treatment with inclisiran. Thirty-one (1.7%) inclisiran-treated subjects had a persistent ADA response and 41 (2.2%) had a transient ADA response. The observed frequencies, particularly for the persistent ADA response with 1.1% in ORION-3 and 1.7% in the pooled phase 3 trials, are low and similar

¹⁴ Shankar G, Arkin S, Cocea L, et al., American Association of Pharmaceutical Scientists. Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations. AAPS J. 2014 Jul;16(4):658-73. doi: 10.1208/s12248-014-9599-2. Epub 2014 Apr 24. PMID: 24764037; PMCID: PMC4070270.

between the two groups.

Reviewer's Conclusion: The overall safety profile for inclisiran in the phase 2 OLE trial ORION-3 was similar to that seen in the original NDA submission and the Day 120 safety update for ORION-3. The most common TESAEs were angina pectoris and osteoarthritis, and the most common TEAEs were nasopharyngitis, hypertension, urinary tract infection, influenza, and arthralgia. Urinary tract infection and arthralgia were identified as inclisiran-associated safety signals during the original NDA review. A drug association with angina, osteoarthritis, nasopharyngitis, hypertension, and influenza are not supported given a lack of corroboration in placebo-controlled data and the common nature of these AEs in the enrolled population, even outside of a clinical trial context. Injection site reactions that occurred throughout ORION-3 are similar in frequency and severity to what has been reported previously. No new safety concerns were identified.

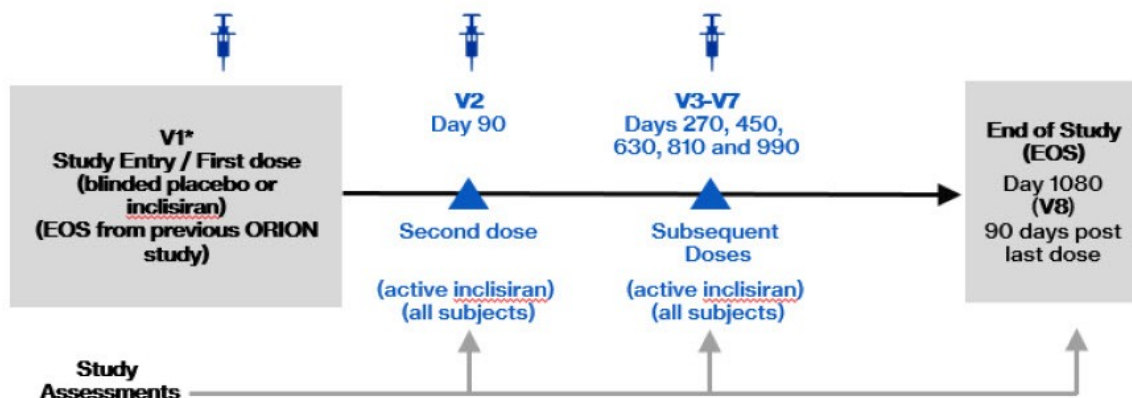
4.1.2. Phase 3b Trial: ORION-8

ORION-8 is an ongoing long-term extension trial in 2990 subjects with ASCVD, ASCVD-risk equivalents (e.g., diabetes and familial hypercholesterolemia), HeFH, or HoFH, and elevated LDL-C despite maximum tolerated doses of statin therapy who have completed one of the phase 3 lipid-lowering trials (ORION-9, ORION-10, or ORION-11). Subjects who received placebo in one of these phase 3 trials initiated inclisiran treatment with the proposed dosage regimen (Day 1, Day 90, and then every 6 months). Subjects who received inclisiran in the previous trial continued their inclisiran treatment every 6 months (see figure below).

A summary of safety data from 2967 subjects from ORION-8 were included in the Day 120 safety update in the original NDA submission (cut-off date was January 31, 2020). This current safety update includes the safety data from the trial initiation (first person first visit [FPFV] was April 16, 2019) until the cut-off date of May 10, 2021 on a total of 2990 subjects who consented to participate in this long-term extension trial and received inclisiran.

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Figure 2 ORION-8: Trial Design



Source: Figure 1-2 from Clinical Complete Response: safety_update_response_inclisiran
FUP=follow-up; V=visit

Safety Assessments:

Refer to the Appendix for tables of study assessments for ORION-8.

- Physical examination: Day 1080 (≥ 90 days post final dose)
- Vital signs (heart rate and blood pressure): Day 90, then every 180 days, Day 1080 (≥ 90 days post final dose)
- Hematology and coagulation: Day 1080 (≥ 90 days post final dose)
 - Hemoglobin, hematocrit, erythrocytes, reticulocytes, MCH, MCV, MCHC, platelet count, white blood cell count with differential, PT, INR, and aPTT
- Full serum chemistry: Day 1080 (≥ 90 days post final dose)
 - AST, ALT, ALP, GGT, TBIL, direct and indirect bilirubin, CK, lactate, bicarbonate, uric acid, creatinine, BUN, eGFR, sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), HbA1C, and hsCRP
- Limited serum chemistry: Days 90, 270, 450, 630, 810, and 990
 - AST, ALT, ALP, GGT, TBIL, CK, creatinine, eGFR, and HbA1C
- Urinalysis: Day 1080 (≥ 90 days post final dose)
 - Dipstick analyses at the investigational site to include nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells/erythrocytes, white blood cells/leukocytes, pH, urine sediment (microscopic examination will be only performed in the event of abnormalities)
- Anti-inclisiran antibodies: collected on Day 90, then every 180 days, Day 1080 (≥ 90 days post final dose)

Safety Population: all subjects who received at least one dose of study drug. Treatment

classification was based on the actual treatment received. This was the primary population for the safety analyses.

Adverse Event Assessment:

- AE Severity
 - 1 = Mild: Discomfort noticed, but no disruption to daily activity.
 - 2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.
 - 3 = Severe: Inability to work or perform normal daily activity.
- New onset of diabetes in subjects with no medical history of diabetes was reported when:
 - HbA1C becomes $\geq 6.5\%$ and/or
 - If a new concomitant medication for control of plasma glucose is added, further information to assess for a diagnosis of new onset diabetes will be collected
- 'Worsening of the glycemic control' or 'diabetic complications' in subjects with a medical history of disease (HbA1C $\geq 6.5\%$ at baseline) was reported when:
 - HbA1C increases from baseline $>0.5\%$ and/or
 - New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level.

Exposure and Disposition:

The median duration on the trial was 624 days (~1.9 years) and the exposure was 4729.6 patient-years in ORION-8.

Among these 2990 subjects, a total of 216 (7%) subjects discontinued the study, including 169 subjects who discontinued after the cut-off date of the Day 120 safety update (January 31, 2020), as shown in the following table.

Table 10 ORION-8: Subject Disposition - Safety Population

Category	Inclisiran n (%) Cut-off May 10, 2021 N=2990
Subjects Who Completed the Trial *	5 (0.2)
Subjects Ongoing in the Trial	2769 (92.6)
Discontinued	216 (7.2)
Withdrew Consent	64 (2.1)
Physician Decision	6 (0.2)
Lost To Follow-Up	15 (0.5)
Death**	71 (2.4)

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Adverse Event	31 (1.0)
Initiation of Protocol Prohibited Approved PCSK9 inhibitor	1 (0)
Other	28 (0.9)
Duration on Trial (Days)***	
N	2990
Mean ± SD	577.8 ± 106.50
Median	624.0
Q1, Q3	600,632
Min, Max	1,852
Patient years exposure in ORION-8	4729.6
* A completer is defined as completing the Day 1080 visit. ** Deaths reported by trial discontinuation. *** Duration on trial is defined as the number of days from the first date of treatment to the date of last recorded contact/participation date in the database. Source: JMP Clinical 8.1, Table 3-3 from Clinical Complete Response: safety_update_response_inclisiran and Table 14.1.2.4 from CKJX839A12306B Supplement to the safety update	

Additional information was requested from and provided by the Applicant for the subjects who discontinued for 'other' reasons. The reasons included that (1) there were 2 consecutive dosing visits missed in the trial, often because of COVID-19 issues; as a result, the subject had been without open-label inclisiran treatment for more than a year and was discontinued from the study at the sponsor's request, (2) subject's decision to not continue in the trial, some subjects were concerned that there would be too much risk of contracting COVID-19 when attending study visits at the research site, (3) study site closure, and (4) subject relocated and was no longer able to participate in the study.

Demographics:

The population in ORION-8 included 2032 (68%) male subjects, the mean age was 64 years, the median age was 65 years (min, max: 20, 90 years; 51% were age 65 and older), 93% of subjects were White, 6% were Black or African American, 0.8% were Asian, 0.2% were American Indian or Alaska Native, and 0.3% were Native Hawaiian or Other Pacific Islander. Subjects came from the US (43%), Poland (20%), UK (11%), South Africa (9%), Ukraine (3%), Hungary (3%), Spain (3%), Germany (2%), Denmark (2%), Netherlands (1%), Sweden (1%), Czech Republic (1%), and Canada (1%).

Treatment Compliance:

Subjects received SC doses of 300 mg from Day 1 through Day 810 as of the cut-off of May 10, 2021. The majority (> 89%) of the injections were in the abdomen. Doses received were as follows:

- Day 1 (100%; 2990/2990)
- Day 90 (98%; 2940/2990)

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- Day 270 (91%, 2731/2990)
- Day 450 (92%, 2747/2990)
- Day 630 (74%, 2216/2990) and
- Day 810 (0%, 1/2990)

Safety Data:

The translation of investigator-reported terms for the adverse event to preferred terms was examined by this reviewer. Overall, few errors in translation were identified, and no adverse events were reclassified. Based on comparing the reported term to the dictionary-derived preferred term, this reviewer believes that AEs were generally categorized appropriately. Overall, this safety data submission, in particular the patient narratives, was high-quality, complete, and well-organized.

Table 11 ORION-8: Overall Summary of Treatment Emergent Adverse Events -Safety Population

Category	Inclisiran n (%) N=2990
Subjects Died*	78 (2.6)
Subjects with at Least One TEAE	1919 (64.2)
Subjects with at Least One Serious TEAE	658 (22.0)
Subjects with any TEAE leading to permanent treatment discontinuation	55 (1.8)
Subjects with severe TEAE	424 (14.2)

Treatment Emergent Adverse Event, TESA = Treatment Emergent Serious Adverse Event

* The total number of deaths (78) is greater than the number of deaths (71) reported in subject's disposition (Table 10), as additional deaths were reported post the subjects' trial discontinuation.

Source: Reviewer created from JMP Clinical 8.1, Table 6-9 from Clinical Complete Response: safety_update_response and Table 14.3.1.1 from CKJX839A12306B Supplement to the safety update

Deaths:

In ORION-8, seventy-eight subjects (3%) died during the trial, including 15 deaths at the Day 120 safety update and 63 deaths since the Day 120 safety update in the previous NDA review cycle (data cut-off of January 31, 2020). As shown in the following table, the cause of death was not predominated by a particular SOC or PT category, with the notable exception of deaths related

to corona virus infection. There were in total 12 deaths due to COVID-19 (7 in PT COVID-19, 1 in COVID pneumonia, 3 in Pneumonia viral, 1 uncoded), confirmed by the narratives.

For comparison with the placebo-controlled Phase 3 parent trials, a total of 54 deaths occurred during the 18 months of the 3 Phase 3 trials in the original NDA submission. The incidence of deaths on inclisiran and placebo was the same at 27 deaths or 1.5% on each treatment arm. The most common cause of death was in cardiac disorders and occurred at 0.7% on inclisiran as compared to 0.5% on placebo. Inclisiran did not appear to increase the risk of death from any particular cause.

From the integrated summary of safety (ISS) pool of the original NDA submission, the incidence of deaths related to infections was similar in the two treatment arms, 4/1822 (0.2%) on placebo and 1/1833 (0.1%) on inclisiran. The incidence in ORION-8 (14/2990, 0.5%) was greater, likely from the higher number of deaths from infections (14 in ORION-8 vs. 1 in inclisiran-treated subjects in ISS safety pool). Twelve out of 14 deaths due to infections in ORION-8 was attributed to COVID-19.

From the ISS of the original NDA, the incidence of deaths related to neoplasms was similar in the two treatment arms, 6/1822 (0.3%) on placebo and 4/1833 (0.2%) on inclisiran. The neoplasms in the placebo group, by PT, were adenocarcinoma, bladder cancer, gastroesophageal cancer, hepatocellular cancer, lung adenocarcinoma, metastases to liver, and metastatic carcinoma of the bladder. The neoplasms in the inclisiran group, by PT, were gastrointestinal lymphoma, lung neoplasm malignant, esophageal carcinoma, and metastases to liver. There was no pattern of carcinomas in the ISS that would point to a specific organ class vulnerable to inclisiran. A review of the neoplasms in Table 12, shows similar categories of malignancy, except for a small increase in pancreatic cancer.

Table 12 ORION-8: Summary of Deaths by System Organ Class and Preferred Term - Safety Population

	Inclisiran (N=2990)
System Organ Class Preferred Term	n (%)
Number of TEAEs with a Fatal Outcome	78 (2.6)
Cardiac disorders	19 (0.6)
Acute myocardial infarction	1 (0.0)
Angina pectoris	1 (0.0)
Arrhythmia	1 (0.0)
Cardiac arrest	4 (0.1)
Cardiac disorder	1 (0.0)

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Cardiac failure	2 (0.1)
Cardiac failure chronic	1 (0.0)
Cardiac failure congestive	2 (0.1)
Cardio-respiratory arrest	1 (0.0)
Myocardial infarction	3 (0.1)
Myocardial ischaemia	1 (0.0)
Ventricular fibrillation	1 (0.0)
Gastrointestinal disorders	2 (0.1)
Intestinal obstruction	1 (0.0)
Pancreatitis acute	1 (0.0)
General disorders and administration site conditions	10 (0.3)
Death	9 (0.3)
Sudden cardiac death	1 (0.0)
Infections and infestations	14 (0.5)
COVID-19	7 (0.2)
COVID-19 pneumonia	1 (0.0)
Pneumonia	2 (0.1)
Pneumonia viral	3 (0.1)
Septic shock	1 (0.0)
Injury, poisoning and procedural complications	2 (0.1)
Road traffic accident	2 (0.1)
Musculoskeletal and connective tissue disorders	1 (0.0)
Rhabdomyolysis ¹⁵	1 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (0.4)
Colon cancer	1 (0.0)
Diffuse large B-cell lymphoma	1 (0.0)
Lung cancer metastatic	1 (0.0)

¹⁵ Subject (b) (6): 63-year-old white male with PMH of ASCVD, DM, hyperlipidemia, hypertension, CABG, PCI. The patient received study drug on Days 1, 69 and 281. On Day 321, the patient was discharged to home following C3-C6 cervical laminectomy and fusion with the instruction of not to live alone initially. On an unspecified date, the patient had a fall in his house and was found by his brother and police twelve hours later with no movement unilaterally. On Day 325, the patient was hospitalized for treatment of SAE of rhabdomyolysis (total creatine kinase was 1286 U/L [6.4 x ULN; reference range: 30-200 U/L]). This reviewer believes the CK value is low for a diagnosis of drug-related rhabdomyolysis and that the unknown period of time on the floor after a fall, rather than study drug, contributed to the rhabdomyolysis. On Day 331, patient was obtunded, and overdose was suspected as narcotics and benzodiazepines were found at bedside. He was treated with naloxone intravenous drip. An imaging to the cervical spine showed hematoma of posterior neck so patient underwent revision laminectomy of C3-7 and hematoma evacuation. The patient then developed quadriplegia and mental status did not improve. On Day 336, the patient expired in the hospital. Although reported as a death due to rhabdomyolysis, it is unlikely that this death is drug-related.

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Lung neoplasm malignant	2 (0.1)
Lymphoma	1 (0.0)
Malignant neoplasm of unknown primary site	1 (0.0)
Non-small cell lung cancer	1 (0.0)
Oesophageal carcinoma	1 (0.0)
Oesophageal neoplasm	1 (0.0)
Pancreatic carcinoma	3 (0.1)
Pancreatic carcinoma metastatic	1 (0.0)
Nervous system disorders	6 (0.2)
Cerebrovascular accident	3 (0.1)
Ischaemic stroke	2 (0.1)
Syncope	1 (0.0)
Psychiatric disorders	2 (0.1)
Completed suicide	2 (0.1)
Renal and urinary disorders	1 (0.0)
Renal failure	1 (0.0)
Respiratory, thoracic and mediastinal disorders	4 (0.1)
Acute respiratory failure	3 (0.1)
Dyspnoea	1 (0.0)
Vascular disorders	1 (0.0)
Arteriosclerosis	1 (0.0)
NOT CODED	9 (0.3)
Not Coded*	9 (0.3)

TEAE = Treatment Emergent Adverse Event

* Death not coded by the cut-off of May 10, 2021. Uncoded nine deaths include pneumonia viral (1), gastric bleeding (1), carcinoma due to lung and bronchus (1), intracerebral hemorrhage (1), coronary artery disease (1) and unknown cause (4)

Source: JMP Clinical 8.1 and Table 6-10 from Clinical Complete Response: safety_update_response_inclisiran and Table 14.3.1.15 from CKJX839A12306B Supplement to the safety update

TESAEs:

A total of 22% (658/2990) of subjects treated with inclisiran reported a TESAE, which is similar to the 20% (374/1833) of inclisiran-treated subjects in the ISS Safety Population pool of ORION-9, -10, and -11 who reported a TESAE (23% of subjects in the placebo group reported at least one SAE and the SAEs were largely balanced between the inclisiran and placebo groups).

In ORION-8, the most frequent SAEs reported were in the SOC cardiac disorders (6.7%; 199/2990). The 5 most common TESAEs were in the PTs coronary artery disease (1.4%), angina pectoris (1.0%), acute myocardial infarction (0.9%), COVID-19 (0.9%), and ischemic stroke (0.7%). These events are not unexpected in an older trial population that includes patients with ASCVD, ASCVD risk equivalents, HeFH, or HoFH.

Table 13 ORION-8: Treatment Emergent Serious Adverse Events (> 0.2% of subjects) by Preferred Term - Safety Population

Preferred Term	Inclisiran (N=2990)	
	n (%)	Event Count
Subject with at least one TESAE	658 (22.0)	1109
Coronary artery disease	42 (1.4)	45
Angina pectoris	29 (1.0)	31
Acute myocardial infarction	28 (0.9)	32
COVID-19	28 (0.9)	28
Ischaemic stroke	20 (0.7)	21
Acute kidney injury	19 (0.6)	21
Angina unstable	19 (0.6)	21
Atrial fibrillation	18 (0.6)	21
Pneumonia	18 (0.6)	21
Myocardial infarction	15 (0.5)	15
Non-cardiac chest pain	15 (0.5)	16
Cardiac failure	14 (0.5)	21
Osteoarthritis	14 (0.5)	16
Peripheral arterial occlusive disease	13 (0.4)	17
Syncope	13 (0.4)	13
Acute respiratory failure	12 (0.4)	12
Cardiac failure congestive	10 (0.3)	14
Prostate cancer	10 (0.3)	10
Aortic aneurysm	9 (0.3)	9
Chronic obstructive pulmonary disease	9 (0.3)	10
Death	9 (0.3)	9
Pneumonia viral	9 (0.3)	10
Cellulitis	8 (0.3)	8
Cerebrovascular accident	8 (0.3)	8

TEAE = Treatment Emergent Serious Adverse Event

Source: Reviewer created from JMP Clinical 8.1 and Table 6-11 from Clinical Complete Response: safety_update_response, Table 14.3.1.5 from CKJX839A12306B Supplement to the safety update

In the Day 120 safety update for ORION-8, where all subjects were on inclisiran, the most common TESAEs were coronary artery disease (0.6%; 17/2967), acute myocardial infarction and angina pectoris (0.3%; 9/2967), and ischemic stroke, peripheral arterial occlusive disease (0.2%; 6/2967). With the noted exception of COVID-19 SAEs, the most common TESAEs by the cut-off of May 10, 2021 were similar to those in the Day 120 safety update (data cut-off of January 31,

2020).

TEAEs leading to study drug discontinuation:

Fifty-five (1.8%) subjects withdrew from treatment due to TEAEs (including 45 subjects post the Day 120 safety update), compared to 2.5% of inclisiran-treated subjects in the ISS Safety Population of ORION-9, -10 and -11. Events that led to withdrawal in at least 2 subjects are summarized in the following table.

Table 14 ORION-8: Treatment Emergent Adverse Events Leading to Withdrawal of Study Treatment (≥ 2 Subjects) by Preferred Term - Safety Population

Preferred Term	Inclisiran (N=2990)	
	n (%)	Event Count
Subject with at least one TEAE leading to withdrawal	55 (1.8)	70
Ischaemic stroke	3 (0.1)	3
Injection site rash	2 (0.1)	2
Injection site reaction	2 (0.1)	2
COVID-19	2 (0.1)	2
Myalgia	2 (0.1)	2
Lung neoplasm malignant	2 (0.1)	2
Dyspnoea	2 (0.1)	2
NOT CODED ^a	5 (0.2)	5

^a Study is ongoing, so some terms are yet to be coded

TEAE = Treatment Emergent Adverse Event

Source: Reviewer created from Table 14.3.1.14 from CKJX839A12306B Supplement to the safety update

A review of the subject narratives revealed some events that are likely or possibly attributable to inclisiran:

- Subject (b) (6): 79-year-old White male with PMH of hyperlipidemia, hypertension, MI, and multiple other chronic medical issues received study drug on Days 1 and 107. He was diagnosed with prostate cancer on Day 78 and study drug was interrupted because of this. He experienced an ISR on Day 109, moderate in severity, with the symptoms of erythema, induration, warmth, and pruritus, which resolved. Study drug was withdrawn due to this AE. I agree with the investigator that this AE of ISR is likely due to study drug.
- Subject (b) (6): 52-year-old White female with PMH of hyperlipidemia, MI, CABG, and carotid artery stenosis. The subject received injections on Days 1, 91, and 276. On Day 276, on the same day of the patient received study drug, the patient experienced injection site reaction. The patient permanently discontinued from the

study treatment and study due to the event of injection site reaction. The investigator considered the event of injection site reaction to be mild and reasonably possibly attributable to the study drug. I concur.

- Subject (b) (6): 62-year-old White female who received study drug on Days 1, 101, and 245. On Day 245, the patient experienced an event of injection site rash; the patient recovered from the event of injection site reaction one month later. On Day 245, the patient discontinued from the study and study treatment due to the injection site rash. The investigator considered the event of injection site rash as mild and reasonably possibly attributable to study drug. I concur.
- Subject (b) (6): 52-year-old male who received study drug on Days 1 and 98. On Day 112, the patient developed injection site rash and permanently discontinued from the study treatment and the study due to this event. The investigator considered the event of injection site rash as mild and reasonably attributable to study drug. I concur.
- Subject (b) (6): 65-year-old White male who received study drug on Days 1, 100, 294, and 454. On Days 294 and 456, the subject experienced hypersensitivity, mild in severity; the 1st episode resolved. The patient discontinued from the study treatment due to this event. At the time of the report, the patient was recovering from a 2nd event of hypersensitivity. The investigator considered the event of hypersensitivity as reasonably possibly attributable to study drug. I concur.
- Subject (b) (6): 80-year-old Black female with PMH of DM, hyperlipidemia, hypertension, CHD, PAD, renal impairment, sciatica, and multiple other chronic illnesses who received study drug on Day 1. On Day 72, the patient developed a non-serious AE of arthralgia. The study treatment was permanently discontinued due to the event of arthralgia. The investigator considered the event of arthralgia as mild and reasonably possibly attributable to study drug. I think it is possible but not likely that the study drug was the cause of the arthralgia given the delay in symptoms from the date of injection and the multiple other conditions present at baseline.
- Subject (b) (6): 58-year-old White male with PMH of hyperlipidemia, hypertension, CABG, MI, and myotonic dystrophy who received study drug on Days 1, 91, and 331. On Day 331, the patient was noted to have blood CK increased (lab values not available). The patient discontinued from the study and study treatment due to this event. The investigator considered the event of blood CK increased as severe and reasonably possibly attributable to study drug. I agree that it is possible although the patient's myotonic dystrophy and atorvastatin use may also have contributed.
- Subject (b) (6): 80-year-old White male with PMH to include hyperlipidemia, hypertension, and PCI received drug on Days 1, 100, 270, 450, and 630. On Day 9, the patient presented with complaints of worsened abdominal pain. The patient was not well for 2-3 weeks prior to hospitalization. On the same day, computed tomography abdomen-pelvis was abnormal and showed mild pancreatic inflammation. White blood cell count was $12.5 \times 10^3/L$ (reference range: $4.5-11 \times 10^3/L$) and lipase was 95 U/L

(reference range: 12-70 U/L). The patient was diagnosed with acute pancreatitis. On Day 11, the patient recovered from the event of acute pancreatitis and was discharged. On Day 625, the patient presented to the emergency room with complaints of abdominal discomfort along with nausea and vomiting. White blood count was high $14.7 \times 10^3/\text{mCL}$ (reference range: $4.5\text{-}11.0 \times 10^3/\text{mCL}$) and lipase was 77 U/L (reference range: 11-82 U/L). The patient was diagnosed with gastroenteritis. The next day, the patient recovered from the event of gastroenteritis and was discharged with a prescription for ondansetron. The investigator considered the event of pancreatitis, but not gastroenteritis, as reasonably attributable to the study drug. It is not clear that study drug contributed to the event of pancreatitis as it looks like the abdominal symptoms started before study drug was administered and the patient stayed on drug for 2 years.

- Subject (b) (6): 66-year-old White female with multiple medical problems to include drug hypersensitivity. Her background medications included ezetimibe, acetylsalicylic acid, carbamazepine, mometasone, paracetamol, ramipril, and ranitidine. She received study drug at Days 1 and 85. On Day 86, the patient developed non-serious AE of myalgia and the study treatment was permanently discontinued. Six weeks later, the patient recovered from the event of myalgia. The investigator considered the event of myalgia as moderate and reasonably possibly attributable to study drug. This attribution to study drug is reasonable but the limited information makes it challenging to conclusively attribute this to study drug.
- Subject (b) (6): 70-year-old White female with multiple medical problems to include angioedema, COPD, and FH who received study drug on Day 1 only. On Day 1, the patient developed non-serious AE of dyspnea. The event resolved on the same day. The study treatment was permanently discontinued due to this event. The investigator considered the event of dyspnoea as moderate and reasonably possibly attributable to study drug. This attribution to study drug is reasonable but the limited information makes it challenging to conclusively attribute this to study drug.
- Subject (b) (6): 77-year-old White female with PMH of hyperlipidemia, hypertension, and tremor on metoprolol, propranolol, and rosuvastatin, who received study drug on Days 1, 90, and 272. On Day 48, the patient experienced the event of dyspnea. The study drug was permanently discontinued, and the patient was withdrawn from the study due to dyspnea, with the last dose of study drug received on Day 272. At the time of this report, the patient did not recover from the event of dyspnea. The investigator considered the event of dyspnea as moderate and reasonably possibly attributable to the study drug. This attribution to study drug is reasonable but the limited information makes it challenging to conclusively attribute this to study drug and not to an alternative diagnosis or contributing factor.

In the ISS Safety Population pool of ORION-9, -10, and -11, the incidence of AE leading to withdrawal of study treatment was 2.5% (45/1833) on inclisiran and 1.9% (35/1822) on placebo. The most common preferred term as a reason for withdrawal of treatment was ISR

(n=4, 0.2%) as compared to 0 patients on placebo. Other adverse reactions that led to withdrawal of treatment were in Neoplasms disorders and Musculoskeletal disorders with an approximately 0.2% greater incidence on inclisiran than placebo. With the exception of COVID-19 related AEs, the AEs leading to discontinuation in ORION-8 were similar to those seen in the original NDA submission.

Common TEAEs:

In ORION-8, the most common TEAEs (at least 2.0%) reported were diabetes mellitus (6.0%), arthralgia (4.7%), hypertension (4.4%), COVID-19 (4.0%), urinary tract infection (3.2%), back pain (3.1%), osteoarthritis (2.6%), injection site reaction (2.5%), upper respiratory infection (2.4%), nasopharyngitis (2.4%), angina pectoris (2.3%) and coronary artery disease (2.0%).

Overall, 54% of AEs were considered mild in severity, 38% were moderate, and 8% were severe.

In general, TEAEs occurred with similar incidence for both males and females in ORION-8. Notable exceptions are injection site reactions and urinary tract infections which occurred more frequently in women (see table below).

Table 15 ORION-8: Treatment Emergent Adverse Events by Sex (with at least Overall 2% Occurrence in Preferred Term) - Safety Population

System Organ Class Preferred Term	Female N=958 n(%)	Male N=2032 n(%)	Total N=2990 n(%)
Cardiac disorders	117 (12.2)	252 (12.4)	369 (12.3)
Angina pectoris	23 (2.4)	47 (2.3)	70 (2.3)
Coronary artery disease	20 (2.1)	40 (2)	60 (2)
General disorders and administration site conditions	145 (15.1)	173 (8.5)	318 (10.6)
Injection site reaction	54 (5.6)	22 (1.1)	76 (2.5)
Infections and infestations	266 (27.8)	399 (19.6)	665 (22.2)
COVID-19	47 (4.9)	74 (3.6)	121 (4)
Nasopharyngitis	21 (2.2)	50 (2.5)	71 (2.4)
Upper respiratory tract infection	30 (3.1)	43 (2.1)	73 (2.4)
Urinary tract infection	60 (6.3)	35 (1.7)	95 (3.2)
Metabolism and nutrition disorders	117 (12.2)	250 (12.3)	367 (12.3)
Diabetes mellitus	54(5.6)	126(6.2)	180 (6)
Musculoskeletal and connective tissue disorders	192 (20)	302 (14.9)	494 (16.5)
Arthralgia	50 (5.2)	90 (4.4)	140 (4.7)
Back pain	36 (3.8)	56 (2.8)	92 (3.1)
Osteoarthritis	31 (3.2)	48 (2.4)	79 (2.6)

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Vascular disorders	102 (10.6)	176 (8.7)	278 (9.3)
Hypertension	49(5.1)	84(4.1)	133(4.4)
UNCODED	76 (7.9)	147 (7.2)	223 (7.5)

Source: Reviewer created from JMP Clinical 8.1

In the placebo-controlled trials submitted with the initial NDA, the most common adverse reactions ($\geq 3\%$) in the inclisiran group, occurring more frequently than placebo, were ISR, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, and dyspnea.

In the Day 120 safety update for ORION-8 (cut-off date was January 31, 2020), where all subjects were on inclisiran, the most common TEAEs (at least 0.7%) were diabetes mellitus (1.9%), arthralgia (1.2%), back pain, hypertension, urinary tract infection and injection site reaction (0.9% for each PT), nasopharyngitis, coronary artery disease and osteoarthritis (0.8% for each PT), angina pectoris, injection site pain, upper respiratory tract infection and diarrhea (0.7% for each PT).

With the exception of COVID-19 AEs, the PTs seen in the May 2021 cut-off date for ORION-8 are similar to what was seen at the Day 120 safety update, are not unexpected in the context of the enrolled trial population, and do not suggest additional inclisiran-associated safety signals beyond what was observed in the original NDA submission.

AEs of Special Interest:

Injection Site Reactions (ISRs)

One hundred forty-six (146) out of 2990 (4.9%) subjects reported a TEAE at the injection site (using the MedDRA high-level term of injection site reactions). This incidence in ORION-8 was lower than the incidence of 8% in inclisiran-treated subjects within the ISS Safety Population (150/1833). A total of 5 (0.2%) subjects discontinued study drug due to ISRs (PTs of IS pruritus, IS rash, IS reaction).

The ISRs in ORION-8 include PTs of injection site reaction (76 subjects, 2.5%), injection site erythema (20 subjects, 0.7%), injection site rash (14 subjects, 0.5%), injection site pruritus (5 subjects, 0.2%), injection site cellulitis (2 subjects, 0.1%), and injection site vesicles (1 subject, <0.0%). The majority of subjects had mild AEs at the injection site (86%, 133/155); the remainder had moderate AEs (14%, 22/155). Medication was used to treat the AE at the injection site in 24% of cases. Two subjects (0.1%) had an AE of hypersensitivity.

Chemistry Abnormalities (ALT/AST/Creatinine/CK Elevations) and Hematology Abnormalities:

Table 16 ORION-8: Clinically Significant Chemistry Parameters - Safety Population

Parameter	Inclisiran n (%) N=2990
Subjects with at Least One Clinically Significant Chemistry Parameter	125 (4.2)
Alanine Aminotransferase (U/L)	
>3 and ≤5 × ULN	6 (0.2)
>5 × ULN	0
Aspartate Aminotransferase (U/L)	
>3 and ≤5 × ULN	6 (0.2)
>5 and ≤10 × ULN	1 (<0.1)
>10 × ULN	0
Alkaline Phosphatase (U/L)	
>2 × ULN	5 (0.2)
Total Bilirubin (mg/dL)	
>2 × ULN	6 (0.2)
Hy's Law: ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN	0
Serum Creatinine (mg/dL)	
≥50% increase from Baseline (not >2 mg/dL)	54 (1.8)
>2 mg/dL	40 (1.3)
≥50% increase from Baseline or >2 mg/dL	94 (3.1)
Creatine Kinase (U/L)	
>5 and ≤10 × ULN	12 (0.4)
>10 and ≤20 × ULN	1 (<0.1)
>20 × ULN	0

Data cut: May 10, 2021

For each test, the worst post-baseline value is used.

Clinically significant criteria are met when both of the following occur: post-baseline values meet the thresholds, and baseline values or any prior post-baseline values do not meet the thresholds.

Source: Reviewer created from supplement to safety update Table 14.3.3.1.2.2 and JMP Clinical 8.1

- Elevations in ALT (>3 and ≤ 5x ULN) were observed in 6 (0.2%) subjects. Elevations in AST

(>3x and ≤ 5x ULN) were observed in 6 (0.2%) subjects and (>5x and ≤ 10x ULN) was observed in 1 subject. In subjects who had AST/ALT data at a subsequent visit, most of these elevations normalized or improved. Five subjects (0.2%) had recent elevations in ALP (> 2x ULN). An increase in bilirubin > 2x ULN was reported in 6 subjects (0.2%). There were no Hy's law cases.

- Abnormal increases in serum creatinine (≥ 50% increase from baseline or > 2 mg/dL) were reported in 94 subjects (3.1%). For many of these subjects, they had elevated creatinine values at baseline that increased by 50% or more at Day 90; the creatinine levels decreased to some degree but did not return to baseline by Day 270. Many of these subjects have multiple underlying medical issues, such as DM, ASCVD, or hypertension, that can affect renal function over time, especially in an older population. Many had new medical issues or exacerbations of underlying medical issues that likely contributed to the increase in creatinine. Examples of some of these subjects are described in the next section.
- Abnormal increases in CK were reported in 13 subjects (0.4%) (> 5x to 10x ULN: 12; > 10x to 20x ULN: 1). In subjects who had CK data at a subsequent visit, all elevations normalized or significantly improved.

Additional information on notable subjects with abnormal chemistry parameters are described below:

1. Subject (b) (6), a 51-year-old male: Day 270 AST 6.7 x ULN, 15 days later was 0.5 x ULN. On Day 262, the patient was hospitalized due to a SAE of chronic pancreatitis exacerbation. This event likely contributed to the AST increase.
2. Subject (b) (6), a 48-year-old White female with PMH of DM, CAD, hyperlipidemia, hypertension, MI, PCI, and diabetic nephropathy had a normal alkaline phosphatase (ALP) at baseline. ALP increased to 4.4 x ULN at Day 270. This subject also had an increase in creatine > 50% from baseline and > 2 mg/dL at Day 270. On Day 255, the patient was hospitalized due to a SAE of cholelithiasis and had a cholecystectomy 4 days later. On Day 292, the patient was hospitalized for a diabetic ulcer that required amputation of a toe. On Day 311, the patient was hospitalized for localized foot infection and on Day 360 died from unknown causes. Lab abnormalities, particularly elevated ALP, are likely secondary to ongoing medical issues (status-post cholecystectomy) and unlikely related to study drug.
3. Subject (b) (6): 61-year-old White male with a PMH of CAD, MI, hyperlipidemia, chronic kidney disease, prior implantable defibrillator insertion had a total bilirubin of 2.1 and 2.3 x ULN on Days 90 and 270, respectively. The patient did not have significantly elevated AST/ALT or ALP at that time. The subject also had an elevated CK at Day 442. On Day 624, the patient was hospitalized due to a SAE of ventricular tachycardia, underwent synchronized shock via ICD, and had a scheduled ablation the following month.
4. Subject (b) (6): 62-year-old White male with PMH of hyperlipidemia,

hypertension, ischemic stroke, CVD, chronic cardiac failure, hypertensive encephalopathy, Gilbert's Syndrome with a baseline total bilirubin of 1.5. The subject had a total bilirubin of 3.4 x ULN on Day 90 that decreased to 1.3 on Day 270. Day 212 the patient was admitted for a radical prostatectomy for the treatment of prostate cancer. Elevated bilirubin likely due to Gilbert's Syndrome.

5. Subject (b) (6): 51-year-old Black female with PMH of DM, hyperlipidemia, hypertension, prior CABG, and prior MI who was hospitalized on Day 89 with worsening peripheral arterial occlusive disease. The AE of renal failure was also reported on Day 103. Baseline creatinine was 1.8 mg/dL which increased to 3.0 at Day 90 and decreased slightly to 2.7 at Day 270. Her underlying medical issues likely contributed to the increase in creatinine.
6. Subject (b) (6): 74-year-old White male with PMH of CHF, DM, hyperlipidemia, hypertension, ischemic stroke, MI, CVD, CHD, chronic kidney disease who experienced multiple AEs during the trial including hospitalization for CHF exacerbation on Days 187 and 253, and acute kidney injury on Day 281 with creatinine of 2.5 found on routine visit. Stress test and catheterization showed worsening CAD, and the subject underwent a CABG 2 weeks later. This subject had a baseline creatinine of 1.96 mg/dL, Day 90 value of 1.81 and Day 270 value of 2.55 mg/dL. His multiple underlying medical issues, including chronic kidney disease, likely contributed to the increase in creatinine.
7. Subject (b) (6): 72-year-old White female with PMH of CHF, DM, hyperlipidemia, hypertension, CABG, ischemic stroke, MI, PCI, chronic kidney disease, atrial fibrillation with pacemaker on the following medications: acetylsalicylic acid, amiodarone, amlodipine, atorvastatin calcium, bumetanide, escitalopram, glyceryl trinitrate, hydralazine, insulin glargine, levothyroxine, metoprolol tartrate, potassium chloride, and warfarin sodium. On Day 60, she had SAEs of fall at home and acute encephalopathy. Creatinine was 4.4 mg/dL and blood urea nitrogen was 48 mg/dL in the ER on Day 61. On Day 64, a repeat head CT revealed a SAE of small subdural hematoma. On Day 69, the patient recovered from encephalopathy, toxicity to various agents, and subdural hematoma and was discharged to an extended care facility. On Day 200, the patient was admitted with diagnosis of diarrhea (suspected *C. difficile* colitis) and acidosis. The patient experienced SAEs of severe septic shock, acute hypoxic respiratory failure, and urinary tract infection (UTI) and died on Day 201. She only received study drug on Days 1 and 90. Her underlying medical issues, including chronic kidney disease, and baseline medications likely contributed to the increase in creatinine.
8. Subject (b) (6), 58-year-old male: Day 270 CK 12.7 x ULN; 9 days later CK was 0.3 x ULN. This event is unlikely to be related to study drug which was continued.

There were no subjects with a clinically significant change in hematology parameters. However, as hematology and coagulation parameters were only tested at Day 1080 (≥ 90 days post final dose), few subjects (~20) in this on-going trial have data available for a Day 1080 assessment.

Anti-Inclisiran Antibodies:

In ORION-8, the planned LPLV date is at the end of February 2023. To date, ADA datasets are available for ORION-8 through the cut-off date of January 2020. As ADA samples for this trial are analyzed at specific milestones, additional long-term data will be available at the completion of this ongoing trial. For ORION-8, the majority of subjects had only reached the Day 90 visit in this trial at the most recent collection of ADA samples for evaluation (given the cut-off date of January 2020). Thus, the assessment of transient and persistent ADA response is not possible with only Day 90 visit data available. The percentage of subjects with treatment-induced ADA is summarized in the table below.

Table 17 Frequency (Percentage) Of Subjects with Treatment Induced ADA (ORION-8 Safety Population)

	Inclisiran (N=2967) n/m* (%)
Treatment Induced ADA response **	45/2965 (1.5%)
Not Treatment-Induced ADA response	2920/2965 (98.5%)

* n: # of subjects with anti-drug antibody (ADA) response; m: # of subjects tested for ADA.

** Treatment Induced ADA: 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 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: Tables 2-1, 2-2 and 2-3 from Novartis Responses to FDA Questions, dated November 2, 2021.

Two of the 45 (4.4%) subjects with treatment-induced ADAs had an associated hypersensitivity event. The hypersensitivity events consisted of the AEs of "allergic conjunctivitis" and "eczema". Both AEs were mild in severity, not serious, not suspected to be related to study drug, and fully resolved during the study. The treatment-induced ADA response in ORION-8 (45/2965, 1.5%) is low and similar to that seen in the pooled phase 3 trials (72/1830, 3.9%).

Reviewer's Conclusion: The overall safety profile for inclisiran in the phase 3 OLE trial ORION-8 was generally similar to that seen in the phase 3 trials included in the original NDA. No new safety concerns were identified.

In ORION-8, the most frequent SAEs reported were in the SOC cardiac disorders (coronary artery disease, angina pectoris, acute myocardial infarction, and ischemic stroke) and COVID-19 infections. With the exception of COVID-19 SAEs, these SAEs were similar to those reported at

the Day 120 safety update and the original NDA submission.

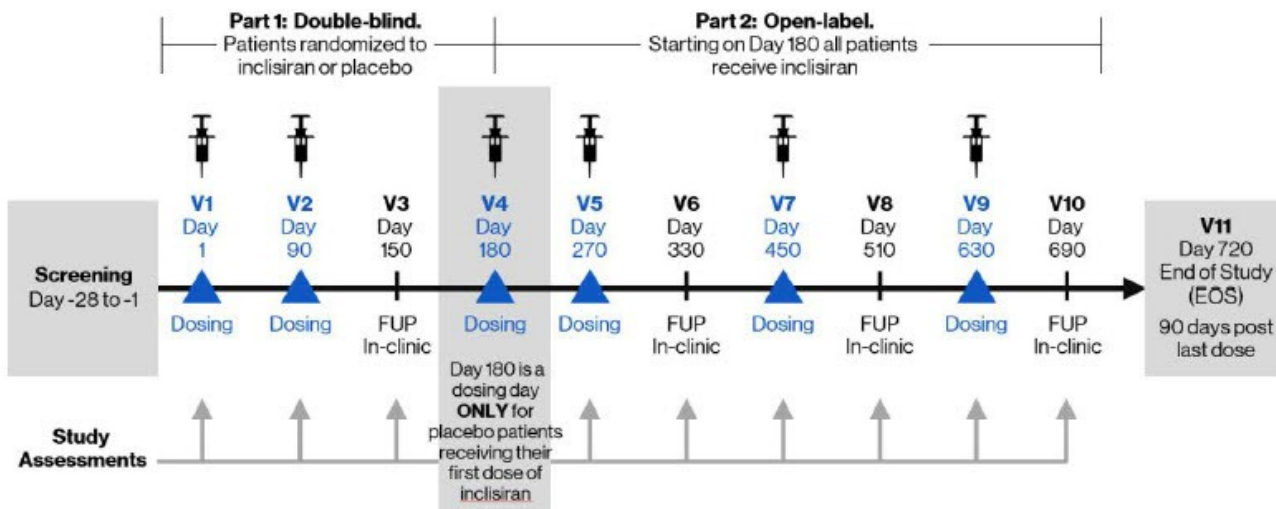
AEs that led to discontinuation included ischemic stroke, ISRs, COVID-19, myalgia, lung cancer, and dyspnea. The cases involving ISRs were considered reasonably attributable to study drug. With the exception of COVID-19 related AEs, the AEs leading to discontinuation in ORION-8 were similar to those seen in the original NDA submission.

The most common AEs reported in ORION-8 were diabetes mellitus, arthralgia, hypertension, COVID-19, urinary tract infection, back pain, osteoarthritis, and injection site reaction. With the exception of COVID-19 AEs, these AEs were similar to those reported at the Day 120 safety update. In the placebo-controlled phase 3 trials submitted with the initial NDA, the most common adverse reactions that occurred more frequently in the inclisiran group were injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, and dyspnea. The observed AEs were generally similar; however, diabetes mellitus was a common AE in ORION-8 but did not occur more frequently in the inclisiran group as compared to placebo in placebo-controlled data.

4.1.3. Phase 3 Trial: ORION-5

ORION-5 (CKJX839A12302) is an ongoing phase 3, two-part, double-blind, placebo-controlled followed by open-label, multicenter study evaluating the safety, tolerability, and efficacy of inclisiran in adult subjects with HoFH and elevated LDL-C despite maximum tolerated dose of LDL-C lowering therapies. The study has two sequential parts: part 1 (completed), a 6-month double-blind period in which subjects were randomized to inclisiran 300 mg or placebo, and part 2 (ongoing), an 18-month open-label follow-up period in which all subjects (including the placebo-treated subjects from part 1) are receiving inclisiran (see figure below).

Figure 3 ORION-5: Trial Design



Source: Figure 1-3 from safety_update_response and ORION-5 Study Protocol Figure 3-1
FUP=follow-up; V=visit

This study was initiated on February 6, 2019 and includes 56 subjects randomized 2:1 to either 300 mg inclisiran or placebo. The double-blind placebo-controlled portion of the trial (part 1) was completed in March 2020, and a total of 48 subjects are currently enrolled in the open-label part 2 of the trial with a final database lock planned in September 2021.

Safety data from the completed double-blind phase (part 1) of the ORION-5 study in adults with HoFH, along with open-label data accrued prior to the cut-off date from part 2, is included in this safety update. Safety data for ORION-5, which were not submitted as part of the NDA, includes all data up to the cut-off date of May 10, 2021 and includes:

- Part 1 (double-blind, placebo-controlled): Day 90 was the final dose of inclisiran or placebo, and the efficacy and safety endpoints were evaluated up to Day 180 (primary efficacy endpoint at Day 150).
- Part 2 (ongoing open-label phase): Starting on Day 180, subjects who received placebo started to receive inclisiran. Subjects who received inclisiran in part 1 continued to receive inclisiran every 6 months. Final inclisiran dosing of part 2 is on Day 630 and the last study visit is on Day 720.

Safety Assessments:

The translation of investigator-reported terms for the adverse event to preferred terms was examined by this reviewer. Overall, few errors in translation were identified, and no adverse events were reclassified. Based on comparing the reported term to the dictionary-derived preferred term, this reviewer believes that AEs were generally categorized appropriately. Overall, this safety data submission, in particular the patient narratives, was high-quality,

complete, and well-organized.

Refer to the Appendix for tables of study assessments for ORION-5.

- Physical examination: screening and Day 720 (90 days post final dose)
- Vital signs (heart rate and blood pressure): Days 1, 90, 150, 180, 270, 450, 630, and 720 (90 days post final dose)
- ECG: screening and Day 720 (90 days post final dose)
- Hematology and coagulation: Days 1, 150, and 720 (90 days post final dose)
 - Hemoglobin, hematocrit, erythrocytes, reticulocytes, MCH, MCV, MCHC, platelet count, white blood cell count with differential, PT, INR, and aPTT
- Full serum chemistry: Days 1 and 720 (90 days post final dose)
 - AST, ALT, ALP, GGT, TBIL, direct and indirect bilirubin, CK, lactate, bicarbonate, uric acid, creatinine, BUN, eGFR, sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), HbA1C, and hsCRP
- Limited serum chemistry: screening, Days 90, 150, 180, 270, 330, 450, 510, and 690
 - AST, ALT, ALP, GGT, TBIL, CK, creatinine, eGFR, fasting glucose, and HbA1C
- Urinalysis: screening, Days 1 and 720 (90 days post final dose)
 - Dipstick analyses at the investigational site to include nitrite, protein, glucose, ketone, urobilinogen, bilirubin, red blood cells/erythrocytes, white blood cells/leukocytes, pH, urine sediment (microscopic examination only performed in the event of abnormalities)
- Anti-inclisiran antibodies: collected on Days 1, 90, 150, 330, and 720 (90 days post final dose)

Safety Population: all subjects who received at least one dose of study drug. Treatment classification was based on the actual treatment received. This was the primary population for the safety analyses.

Adverse Event Assessment:

- AE Severity
 - 1 = Mild: Discomfort noticed, but no disruption to daily activity.
 - 2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.
 - 3 = Severe: Inability to work or perform normal daily activity.
- New onset of diabetes in subjects with no medical history of diabetes was reported when:
 - HbA1C becomes $\geq 6.5\%$ and/or
 - Two consecutive values of fasting plasma glucose that are ≥ 126 mg/dL
 - If a new concomitant medication for control of plasma glucose is added, further

information to assess for a diagnosis of new onset diabetes will be collected

- ‘Worsening of the glycemic control’ or ‘diabetic complications’ in subjects with a medical history of disease (HbA1C $\geq$ 6.5% at baseline) was reported when:
 - HbA1C increases from baseline $>$ 0.5% and/or
 - New concomitant medication or increase in dose of current antidiabetic therapy is initiated to improve the control of plasma glucose level.

Exposure and Disposition:

- Part 1: The median duration in the trial was 191 days (~0.5 years) for the inclisiran group and 188 days (~0.5 years) for the placebo group in ORION-5.
- Part 2: The median duration in the trial was 456 days (~1.4 years) for the inclisiran→inclisiran group and 440 days (~1.4 years) for the placebo→inclisiran group in ORION-5.

A total of 56 subjects with HoFH were randomized in part 1 of ORION-5 and a total of 48 subjects are currently in the ongoing open-label part 2 of the trial. Duration on study and subject dispositions for part 1 and part 2 for the ORION-5 trial are summarized in the following tables.

Table 18 ORION-5: Treatment Exposure and Subject Disposition in Part 1 - Safety Population

	Inclisiran N=37 n (%)	Placebo N=19 n (%)
Completed Day 180 visit (entered extension)	34 (91.9)	19 (100.0)
Discontinued before Day 180*	3 (8.1)	0
Withdrew Consent	2 (5.4)	0
Physician Decision	0	0
Lost to Follow-up	0	0
Death	0	0
Adverse Event	0	0
Initiation of protocol-prohibited approved PCSK9 inhibitor	0	0
Other	1 (2.7)	0
Duration on trial (Days)** - N	35	19
Mean $\pm$ SD	187.6 $\pm$ 11.6	187.8 $\pm$ 7.4
Median	191.0	188.0
Q1, Q3	180,196	182,192
Min, Max	161,217	175,205

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* Patients in Placebo – Inclisiran group were only injected placebo before Day 180, then transitioned to injection of Inclisiran since Day 180.

** Duration on trial is defined as the number of days from the first date of treatment to the date of last recorded contact/participation date in the database.

Source: Reviewer created from JMP Clinical 8.1 and supplement to safety update Table 14.1-1.1

Subject (b) (6) discontinued before Day 180 because of ‘other’ reason. Additional information was requested from and provided by the Applicant. This subject became pregnant, subsequently suffered a miscarriage, and withdrew from the study as this was a protocol deviation (the miscarriage occurred in (b) (6) and the subject withdrew consent in (b) (6)). The subject, a 41-year-old female, received only one dose of inclisiran, in (b) (6), while on the study. The patient has multiple risk factors for spontaneous abortion (diabetes, hypothyroidism, older age for pregnancy, concomitant treatments including statins). I agree with the Applicant’s and investigator’s assessment that from the available information, a causal association between the study medication could not be established.

Table 19 ORION-5: Treatment Exposure and Subject Disposition in Part 2 - Safety Population

	Inclisiran→Inclisiran N=37 n (%)	Placebo→Inclisiran N=19 n (%)	Total N=56 n (%)
Completed trial	0	0	0
Discontinued from trial	4 (10.8)	1 (5.3)	5 (8.9)
Ongoing	30 (81.1)	18 (94.7)	48 (85.7)
Discontinued from trial since Day 180*	4 (10.8)	1 (5.3)	5 (8.9)
Withdrew Consent	2 (5.4)	0	2 (3.6)
Physician Decision	0	0	0
Lost to Follow-up	0	0	0
Death	2 (5.4)	0	2 (3.6)
Adverse Event	0	0	0
Initiation of protocol-prohibited approved PCSK9 inhibitor	0	0	0
Other	0	1 (5.3)	1 (1.8)
Duration on trial (Days)** - N	35	19	54
Mean ± SD	425.7±131.1	457.1±83.1	436.7±116.6
Median	456.0	440.0	452.5
Q1, Q3	358,525	373,534	363,526
Min, Max	1,554	323,555	1,555

* Patients in Placebo – Inclisiran group were only injected placebo before Day 180, then transit to injection of Inclisiran since Day 180.
 ** Duration on trial part 2 is defined as the number of days from the first date of Part 2 to the date of last recorded contact/participation date in the database.
 Source: Reviewer created from supplement to safety update Table 14.1-1.2

Subject (b) (6) discontinued in part 2 because of 'other' reason. Additional information was requested from and provided by the Applicant. The subject was not able to receive two consecutive injections as there were 2 consecutive dosing visits missed in part 2 of the trial; both were related to the COVID-19 pandemic. As a result, the subject had been without open-label inclisiran treatment for more than a year and was discontinued from the study at the sponsor's request. The last known date of contact was (b) (6).

Reviewer Comment: The mean and median duration on trial in part 1 and in part 2 were similar in both groups. The percentage of subjects discontinuing from the trial was low in part 1 and increased slightly in part 2. Reasons included withdrawing consent, death, and 'other'.

Demographics:

The population studied in ORION-5 consisted of 61% female subjects, the mean age was 43 years, and 86% of subjects were White (see table below). Baseline demographics were reasonably well balanced between the inclisiran and placebo group, considering the small sample size for both groups.

Table 20 ORION-5: Baseline Demographics - Safety Population

	Inclisiran→Inclisiran N=37 n (%)	Placebo→Inclisiran N=19 n (%)	Total N=56 n (%)
Age (years)			
Mean ± SD	43.8±13.4	40.7±12.1	42.7±12.9
Median	42.0	37.0	41.0
Q1, Q3	32,53	30,50	32,52
Min, Max	22,70	23,62	22,70
Age Category (years)			
18 - <50	25 (67.6)	14 (73.7)	39 (69.6)
50 - <65	9 (24.3)	5 (26.3)	14 (25.0)
65 - <75	3 (8.1)	0	3 (5.4)
≥75	0	0	0
Gender			
Female	23 (62.2)	11 (57.9)	34 (60.7)
Male	14 (37.8)	8 (42.1)	22 (39.3)

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Weight (kg)			
Mean ± SD	73.9±11.1	70.9±13.8	72.9±12.0
Median	73.0	70.0	73.0
Q1, Q3	66,82	60,78	63,81
Min, Max	53,93	45,107	45,107
Height (cm)			
Mean ± SD	168.3±8.6	164.9±11.2	167.2±9.6
Median	169.0	164.0	167.5
Q1, Q3	162,175	160,171	160,174
Min, Max	150,182	140,186	140,186
BMI (kg/m ²)			
Mean ± SD	26.1±3.9	26.2±5.3	26.2±4.4
Median	26.2	26.2±5.3	26.2±4.4
Q1, Q3	24,28	24,28	24,28
Min, Max	18,39	18,39	18,39
Race			
American Indian or Alaska Native	0	0	0
Asian	6 (16.2)	2 (10.5)	8 (14.3)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	31 (83.8)	17 (89.5)	48 (85.7)
Ethnicity			
Not Hispanic or Latino	37 (100.0)	19 (100.0)	56 (100.0)
Country			
Hong Kong	1 (2.7)	0	1 (1.8)
Israel	4 (10.8)	3 (15.8)	7 (12.5)
Russia	7 (18.9)	3 (15.8)	10 (17.9)
Serbia	3 (8.1)	2 (10.5)	5 (8.9)
South Africa	3 (8.1)	1 (5.3)	4 (7.1)
Taiwan	4 (10.8)	1 (5.3)	5 (8.9)
Turkey	8 (21.6)	5 (26.3)	13 (23.2)
Ukraine	7 (18.9)	4 (21.1)	11 (19.6)
Source: Reviewer created from JMP Clinical 8.1 and supplement to safety update Table 14.1-2.1			

Treatment Compliance:

In part 1 of the trial, most subjects received inclisiran on both scheduled treatment days through Day 180 as follows: on Day 1 (100%; 37/37) and Day 90 (94.6%; 35/37). Two subjects (3.6%) missed one dose in part 1 of the trial; 5 subjects (8.9%) missed one dose and 1 subject (1.8%) missed two doses in part 2 of the trial. Overall, a total of 9 doses were missed over the entire duration of the trial. The dose administered was 300 mg in all the subjects. The majority

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(≥ 96.4%) of the injections were in the abdomen.

Safety Data:

The adverse events observed in parts 1 and 2 are summarized in the following tables. For subjects exposed to inclisiran in parts 1 and 2, 55% reported at least one AE and 20% reported at least one SAE. Two deaths occurred in part 2 of the trial when all subjects were on inclisiran. No subject discontinued study drug due to a TEAE in either parts 1 or 2 of the trial.

Table 21 ORION-5: Summary of Adverse Events in Part 1 – Safety Population

Category	Inclisiran n (%) N=37	Placebo n (%) N=19
Subjects Died	0	0
Subjects with at Least One TEAE	13 (35.1)	6 (31.6)
Subjects with at Least One Serious TEAE	2 (5.4)	1 (5.3)
Subjects Discontinued Study Drug Due to TEAE	0	0
Subjects Discontinued Study Drug Due to TESAE	0	0

TEAE=treatment emergent adverse event; TESAE= treatment emergent serious adverse event
 Source: Reviewer created from supplement to safety update Table 14.3.1-1.1

Table 22 ORION-5: Summary of Adverse Events in Part 1 (inclisiran only arm) and Part 2 – Safety Population

Category	Inclisiran→Inclisiran^a n (%) N=37	Placebo→Inclisiran^b n (%) N=19	Total ^c N=56 n (%)
Subjects Died	2 (5.4)	0	2 (3.6)
Subjects with at Least One TEAE	20 (54.1)	11 (57.9)	31 (55.4)
Subjects with at Least One Serious TEAE	8 (21.6)	3 (15.8)	11 (19.6)
Subjects Discontinued Study Drug Due to TEAE	0	0	0
Subjects Discontinued Study Drug Due to TESAE	0	0	0

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Subjects with Severe TEAE	3 (8.1)	2 (10.5)	5 (8.9)

^a For subjects assigned to inclisiran-inclisiran arm, the AEs/SAEs in the open-label extension (part 1 and part 2) were included.

^b For subjects assigned to placebo arm, only the AEs/SAEs in the open-label extension (part 2) were included.

^c Inclisiran Total includes the AEs/SAEs in part 1 on inclisiran arm only and in part 2 on both arms. TEAE=treatment emergent adverse event; TESAE= treatment emergent serious adverse event

Source: Reviewer created from JMP Clinical 8.1 and supplement to safety update Table 14.3.1-1.2

Deaths:

Two inclisiran→inclisiran treated subjects died during part 2 of the trial. The first subject was a 66-year-old Asian male with a prior medical history of smoking, angina pectoris, myocardial infarction, and PCI. The cause of death was reported as cardiogenic sudden death. I agree with the investigator that the event is likely not related to the study medication and is related to underlying coronary artery disease. The second case was a 54-year-old White female with coronary heart disease, who had experienced SAEs of colon cancer, endocarditis, and urinary tract infection in the previous year, who was admitted to the intensive care unit in multiple organ failure and bacterial pneumonia. Eight days after admission, cardiopulmonary resuscitation was initiated after a cardiac arrest; the subject did not recover. This event was also not reasonably attributable to inclisiran based on the subject’s underlying medical condition.

TESAEs:

TESAEs for part 1 (inclisiran versus placebo) and part 2 are summarized in the following two tables.

Table 23 ORION-5: Treatment Emergent Serious Adverse Events by Preferred Term - Safety Population – Part 1

Preferred term	Inclisiran n (%) N=37	Placebo n (%) N=19	Total N=56 n (%)
Subjects with at Least One Serious TEAE	2 (5.4)	1 (5.3)	3 (5.4)
Non-cardiac chest pain	1 (2.7)	0	1 (1.8)
Endocarditis	1 (2.7)	0	1 (1.8)
Adenocarcinoma of colon	1 (2.7)	0	1 (1.8)
Family stress	0	1 (5.3)	1 (1.8)

TESAE= treatment emergent serious adverse event

Source: Reviewer created from JMP Clinical 8.1 and supplement to safety update-Table 14.3.1-3.1

Table 24 ORION-5: Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term - Safety Population – Part 1 (Inclisiran only arm) and Part 2

System Organ Class Preferred term	Inclisiran→Inclisiran ^a n (%) N=37	Placebo→Inclisiran ^b n (%) N=19	Total ^c N=56 n (%)
Subjects with at Least One Serious TEAE	8 (21.6)	3 (15.8)	11 (19.6)
Cardiac disorders	3 (8.1)	0	3 (5.4)
Angina unstable	1 (2.7)	0	1 (1.8)
Aortic valve stenosis	2 (5.4)	0	2 (3.6)
Arteriosclerosis coronary artery	1 (2.7)	0	1 (1.8)
Coronary artery disease	1 (2.7)	0	1 (1.8)
General disorders and administration site conditions	2 (5.4)	0	2 (3.6)
Non-cardiac chest pain	1 (2.7)	0	1 (1.8)
Sudden cardiac death	1 (2.7)	0	1 (1.8)
Hepatobiliary disorders	0	1 (5.3)	1 (1.8)
Cholecystitis	0	1 (5.3)	1 (1.8)
Infections and infestations	2 (5.4)	1 (5.3)	3 (5.4)
Endocarditis	1 (2.7)	0	1 (1.8)
Pneumonia	1 (2.7)	0	1 (1.8)
Pneumonia viral	0	1 (5.3) ^e	1 (1.8)
Urinary tract infection	1 (2.7)	0	1 (1.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.7)	0	1 (1.8)
Adenocarcinoma of colon	1 (2.7)	0	1 (1.8)
Rectal cancer	1 (2.7)	0	1 (1.8)
Respiratory, thoracic and mediastinal disorders	1 (2.7)	0	1 (1.8)
Dyspnoea	1 (2.7)	0	1 (1.8)
Pulmonary oedema	1 (2.7)	0	1 (1.8)
NOT CODED ^d	2 (5.4)	1 (5.3)	3 (5.4)

^a For subjects assigned to inclisiran-inclisiran arm, the AEs/SAEs in the open-label extension (part 1 and part 2) were included.

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^b For subjects assigned to placebo arm, only the SAEs in the open-label extension (Part 2) were included.

^c Inclisiran Total consisted of the SAEs in Part 1 on inclisiran arm only and in Part 2 on both arms.

^d Study is ongoing, so some terms are yet to be coded

^e This case of viral pneumonia was confirmed to be due to COVID-19 in the subject narrative (Patient: (b) (6))

Source: Reviewer created from JMP Clinical 8.1 and supplement to safety update Table 14.3.1-3.2

In subjects treated with inclisiran in parts 1 and 2, 11 (20%) subjects reported a TESAE. The most frequent SAEs reported were in the SOC cardiac disorders (5.4%; 3/56) and the SOC infections and infestations (5.4%; 3/56). The majority of subjects experienced no more than one treatment emergent SAE. My review of these narratives did not find any events that are reasonably attributable to inclisiran.

TEAEs leading to study drug discontinuation:

No subject withdrew from treatment due to TEAEs in ORION-5.

TEAEs:

In part 1, there were few AEs that occurred in 2 or more subjects in either group (see table below).

Table 25 ORION-5: Treatment Emergent Adverse Events (in ≥ 2 Subjects Total) in Part 1 by Preferred Terms - Safety Population

Preferred Term	Inclisiran n (%) N=37	Placebo n (%) N=19	Total N=56 n (%)
Subjects with at Least One TEAE	13 (35.1)	6 (31.6)	19 (33.9)
Respiratory tract infection viral	2 (5.4)	2 (10.5)	4 (7.1)
Diarrhoea	2 (5.4)	0	2 (3.6)
Pyrexia	2 (5.4)	0	2 (3.6)
Tonsillitis	1 (2.7)	1 (5.3)	2 (3.6)

TEAE=treatment emergent adverse event

Source: Reviewer created from supplement to safety update Table 14.3.1-2.1.1

When comparing the groups based on SOC groupings, there were small imbalances in 'Gastrointestinal disorders' and 'General disorders and administration site conditions' but these were largely driven by a small imbalance in AEs of diarrhea and pyrexia, which was also seen when comparing individual preferred terms (see previous table). Otherwise, the adverse events were largely balanced between the two groups.

Table 26 ORION-5: Selected Treatment Emergent Adverse Events in Part 1 by System Organ Class - Safety Population

System Organ Class Preferred Term	Inclisiran n (%) N=37	Placebo n (%) N=19	Total N=56 n (%)
Gastrointestinal disorders	3 (8.1)	0	3 (5.4)
Abdominal pain	1 (2.7)	0	3 (5.4)
Diarrhoea	2 (5.4)	0	2 (3.6)
Mouth ulceration	1 (2.7)	0	1 (1.8)
General disorders and administration site conditions	3 (8.1)	1 (5.3)	4 (7.1)
Asthenia	0	1 (5.3)	1 (1.8)
Non-cardiac chest pain	1 (2.7)	0	1 (1.8)
Pyrexia	2 (5.4)	0	2 (3.6)

Source: Reviewer created from supplement to safety update Table 14.3.1-2.1.1

In part 2, angina pectoris was reported in 3 subjects who received inclisiran in part 1 and part 2 (inclisiran->inclisiran) vs. none in subjects who only received inclisiran in part 2 (placebo->inclisiran). As shown in the table below, aortic arteriosclerosis, aortic valve stenosis, diarrhea, pyrexia, and rhinorrhea were reported with a difference of 2 subjects (2 subjects vs. none in inclisiran->inclisiran vs. placebo->inclisiran). In general, the subjects in the 'inclisiran->inclisiran' group had 6 months greater duration of exposure to inclisiran than the 'transitioning from placebo to inclisiran' group. While diarrhea was also seen as a common TEAE in the placebo-controlled phase 3 trials and the placebo-controlled part 1 of ORION-5, some of the other AEs, such as angina pectoris, aortic arteriosclerosis, and aortic valve stenosis, more likely reflect the underlying high risk for CV events in this HoFH population. Imbalances in the AEs were not observed in placebo-controlled phase 3 data included with the original NDA submission.

Table 27 ORION-5: Treatment Emergent Adverse Events (in ≥ 2 subjects in Total column) in Part 1 (inclisiran only) and Part 2 by Preferred Terms - Safety Population

Preferred Term	Inclisiran->Inclisiran ^a n (%) N=37	Placebo->Inclisiran ^b n (%) N=19	Total ^c N=56 n (%)
Subjects with at Least One TEAE	20 (54.1)	11 (57.9)	31 (55.4)
Angina pectoris	3 (8.1)	0	3 (5.4)
Corona virus infection	2 (5.4)	1 (5.3)	3 (5.4)

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Nasopharyngitis	2 (5.4)	1 (5.3)	3 (5.4)
Respiratory tract infection viral	2 (5.4)	1 (5.3)	3 (5.4)
Aortic arteriosclerosis	2 (5.4)	0	2 (3.6)
Aortic valve stenosis	2 (5.4)	0	2 (3.6)
Diarrhoea	2 (5.4)	0	2 (3.6)
Pyrexia	2 (5.4)	0	2 (3.6)
Rhinorrhoea	2 (5.4)	0	2 (3.6)
Anaemia	1 (2.7)	1 (5.3)	2 (3.6)
Gastritis	1 (2.7)	1 (5.3)	2 (3.6)
Headache	1 (2.7)	1 (5.3)	2 (3.6)
Hypertension	1 (2.7)	1 (5.3)	2 (3.6)

^a For subjects assigned to inclisiran-inclisiran arm, the AEs/SAEs in the open-label extension (part 1 and part 2) were included.

^b For subjects assigned to placebo arm, only the AEs in the open-label extension (Part 2) were included.

^c Inclisiran Total consisted of the AEs in Part 1 on inclisiran arm only and in Part 2 on both arms.

Preferred terms are sorted descending by total count first, then inclisiran→ inclisiran, then placebo→ inclisiran. TEAE=treatment emergent adverse event

Source: Reviewer created from JMP Clinical 8.1 and supplement to safety update Table 14.3.1-2.2.2.

AEs of Special Interest:

- Injection Site Reactions (ISRs): In part 1, there were no AEs at the injection site. In Part 2, one subject in the inclisiran→ inclisiran group reported injection site erythema, mild in severity.

Chemistry Abnormalities:

In part 1, there was a greater percentage of subjects with at least one abnormal chemistry value in the placebo group (47%) compared to the inclisiran group (38%). There was no evidence of an increase in new-onset DM in the inclisiran treated group as compared to placebo (9% vs 11%).

When combining part 1 (inclisiran-treated only group) and part 2 (all subjects on inclisiran), 2 subjects had >3 and ≤5 x ULN increases in ALT, 1 subject had a >3 and ≤5 x ULN increase in AST, and 2 subjects had a ≥50% increase in serum creatinine from baseline (not >2mg/dL). Based on the prompt resolution of these elevations as well as concurrent events, this reviewer does not believe the lab abnormalities are likely to be primarily related to study drug.

For ALT/AST elevations:

- Subject (b) (6) (28-year-old Asian male with HoFH on rosuvastatin 20 mg and ezetimibe): ALT was 1.3 x ULN on Day 1. ALT was 3 x ULN at Day 510 but was 1.7 x ULN by next visit, Day 630. The subject was on treatment on Day 510 (drug was not stopped

as a result of the ALT elevation). Abnormal liver function test (mild) was recorded as an AE on Day 512, but no other AEs were recorded within a +/- 3-day window around the onset of the event. The investigator considered the AE to not be related to the study medication.

- Subject (b) (6) (59-year-old White male with HoFH, HTN, CHF, prior MI, chronic cholecystitis and pancreatitis on aspirin, carvedilol, ramipril, rosuvastatin 40 mg, and triamterene): ALT was 2 x ULN on Day 1. ALT was 4.2 x ULN at Day 180 and 3.3 x ULN 2 weeks later. ALT was 1.3 x ULN at ~ Day 230. This subject also had AST 2.3 x ULN at baseline, 3.2 x ULN at Day 180 and 2 weeks after. AST was 1.1 x ULN at ~ Day 230.

For creatinine elevations:

- Subject (b) (6): 41-year-old white female, baseline creatinine was 0.68 mg/dL, increased to 1.04 mg/dL at Day 270 and returned to baseline with 0.64 mg/dL at next visit, Day 450. Other notable events at that time were at Day 256, the patient was hospitalized due to a serious adverse event of angina unstable, underwent a coronarography which showed aortic valve stenosis, moderate aortic valve incompetence, and 85% stenosis and occlusion of the main left and right coronary artery. Approximately 2 months later, the subject was hospitalized for open-heart surgery because of stenotic coronary atherosclerosis and severe aortic valve stenosis.
- (b) (6): baseline creatinine was 0.65 mg/dL, increased to 1.03 mg/dL at Day 630, which was the last study visit prior to the DLP. Other notable events around that time were at Day 546, the patient was hospitalized due to a serious adverse event of degenerative aortic valve stenosis. The next day, transcatheter aortic valve implantation (TAVI) was performed. The procedure was complicated by development of a serious adverse event of pulmonary oedema. The patient was treated with sulzoncef, furosemide, propofol and methylprednisolone.

Table 28 ORION-5: Clinically Significant Chemistry Parameters - Safety Population – Part 1

Parameter	Inclisiran n (%) N=37	Placebo n (%) N=19	Total N=56 n (%)
Subjects with at Least One Clinically Significant Chemistry Parameter	14 (37.8)	9 (47.4)	23 (41.1)
Alanine Aminotransferase (U/L)			
>1 and ≤3 × ULN	0	0	0
>3 and ≤5 x ULN	0	1 (5.3)	1 (1.8)
>5 x ULN	0	0	0
Aspartate Aminotransferase (U/L)			

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>1 and ≤3 × ULN	0	0	0
>3 and ≤5 x ULN	0	1 (5.3)	1 (1.8)
>5 x ULN	0	0	0
Alkaline Phosphatase (U/L)			
>2 × ULN	0	0	0
Total Bilirubin (mg/dL)			
>2 × ULN	0	0	0
Hy's Law: ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN	0	0	0
Serum Creatinine (mg/dL)			
≥50% increase from Baseline or >2 mg/dL	0	0	0
Creatine Kinase (U/L)			
>5 × ULN	0	0	0
Fasting Glucose (mg/dL)			
Impaired ≥100 to <126 mg/dL	7 (18.9)	5 (26.3)	12 (21.4)
Diabetes ≥126 mg/dL	4 (10.8)	3 (15.8)	7 (12.5)
HbA1c (%)			
Impaired ≥5.7 to <6.5%	3 (8.1)	2 (10.5)	5 (8.9)
Diabetes ≥6.5%	1 (2.7)	0	1 (1.8)
Subjects Developed Diabetes during the Trial*	3/34 (8.8)	2/18 (11.1)	5/52 (9.6)

For each test, the most severe result in Part 1 is used for each subject.

Clinically significant criteria are met when both of the following occur: post-baseline values meet the thresholds, and baseline values or any prior post-baseline values do not meet the thresholds.

* The criteria for diagnosing diabetes are based on lab data only, when Fasting Glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% in patients with no diabetes at baseline.

Source: Reviewer created from JMP Clinical 8.1, supplement to safety update Tables 14.3.2-1.1 and 14.3.2-4.1

Table 29 Clinically Significant Chemistry Parameters - Safety population – Part 1 (inclisiran only) and Part 2

Parameter	Inclisiran→Inclisiran n (%) N=37	Placebo→Inclisiran * n (%) N=19	Total** N=56 n (%)

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Subjects with at Least One Clinically Significant Chemistry Parameter	26 (70.3)	10 (52.6)	36 (64.3)
Alanine Aminotransferase (U/L)			
>1 and ≤3 × ULN	0	0	0
>3 and ≤5 x ULN	1 (2.7)	1 (5.3)	2 (3.6)
>5 x ULN	0	0	0
Aspartate Aminotransferase (U/L)			
>1 and ≤3 × ULN	0	0	0
>3 and ≤5 x ULN	0	1 (5.3)	1 (1.8)
>5 x ULN	0	0	0
Alkaline Phosphatase (U/L)			
>2 × ULN	0	0	0
Total Bilirubin (mg/dL)			
>2 × ULN	0	0	0
Hy's Law: ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN	0	0	0
Serum Creatinine (mg/dL)			
≥50% increase from Baseline (not >2 mg/dL)	2 (5.4)	0	2 (3.6)
Creatine Kinase (U/L)			
>5 × ULN	0	0	0
Fasting Glucose (mg/dL)			
Impaired ≥100 to <126 mg/dL	17 (45.9)	8 (42.1)	25 (44.6)
Diabetes ≥126 mg/dL	5 (13.5)	2 (10.5)	7 (12.5)
HbA1c (%)			
Impaired ≥5.7 to <6.5%	6 (16.2)	7 (36.8)	13 (23.2)
Diabetes ≥6.5%	2 (5.4)	1 (5.3)	3 (5.4)
Subjects Developed Diabetes during the Trial***	5/34 (14.7)	1/18 (5.6)	6/52 (11.5)

For each test, the most severe result in Part 1 is used for each subject.

Clinically significant criteria are met when both of the following occur: post-baseline values meet the thresholds, and baseline values or any prior post-baseline values do not meet the thresholds.

* For subjects assigned to placebo arm, only the data in the open-label extension (Part 2) were included.

** Inclisiran Total consisted of the data in Part 1 on inclisiran arm only and in Part 2 on both arms.

*** The criteria for diagnosing diabetes are based on lab data only, when Fasting Glucose ≥ 126 mg/dL or HbA1c ≥ 6.5% in patients with no diabetes at baseline.

Source: Reviewer created from JMP Clinical 8.1, supplement to safety update Tables 14.3.2-1.2 and 14.3.2-4.2

Hematology Abnormalities:

There were no subjects with a clinically significant change in hematology parameters in Part 1 or 2.

In ORION-5, INR was only assessed at the screening visit, V1 (baseline), V3 (Day 150) and V11/EOS (Day 720). A total of 22 randomized subjects had at least one INR value $>1 \times$ ULN in the ORION-5 trial. Of these, nine subjects were on a vitamin K antagonist (such as warfarin) during the trial. Eight subjects had mild increase in INR values (sometimes at screening or at baseline) but these values all returned to normal by the end of study. Five subjects had INR values that remained elevated during the trial; additional information is provided on these 5 subjects:

- 2 subjects had an elevated INR at baseline that remained elevated throughout the trial (Subjects (b) (6) and (b) (6)). Neither one of the subjects was on a vitamin K antagonist. Subject (b) (6), was on inclisiran in parts 1 and 2, had a screening INR of 1.6 and values of 1.3 on Day 1, 1.8 on Day 150 (subject had an apheresis session 3 days prior to this assessment) and 1.6 on Day 720. Subject (b) (6), was on placebo in part 1 and inclisiran in part 2, had a screening INR of 1.3 and values of 1.4 on Day 1, 1.3 on Day 150 and 1.5 on Day 720.
- 2 apheresis-treated subjects had fluctuating increases in INR during the trial (Subjects (b) (6) and (b) (6)). Their highest INR values coincided with the start of apheresis treatments. Parameters of the coagulation system may be altered during apheresis by the mandatory use of anticoagulants (heparin) as well as the type of LDL apheresis columns used.^{16,17}
- Subject (b) (6) had an INR of 1.1 at Day 1 and 1.2 at Day 150. She had an abnormal INR value of 1.4 at Day 180 which was approximately 6 months following a single inclisiran injection in the entire study period. This subject, also discussed in the disposition section, had decided to withdraw from the trial approximately 2 months after a miscarriage.

Anti-Inclisiran Antibodies:

The ORION-5 trial had a recent database lock on October 22, 2021 with final and complete ADA datasets available for assessment. No subject in ORION-5 developed a treatment induced ADA response. This information represents the complete ADA data for this trial.

¹⁶ Khan TZ, Gorog DA, Arachchilage DJ et al (2019) Impact of lipoprotein apheresis on thrombotic parameters in patients with refractory angina and raised lipoprotein(a): Findings from a randomized controlled cross-over trial. *J Clin Lipidol* 13(5):788-796

¹⁷ Julius U, Siegert G, Gromeier S (2000) Intraindividual comparison of the impact of two selective apheresis methods (DALI and HELP) on the coagulation system. *Int J Artif Organs* 23(3):199-206

Reviewer's Conclusion: The overall safety profile for inclisiran in ORION-5 was generally similar to that seen in the phase 3 trials of the original NDA. No new safety issues were identified.

4.1.4. Phase 3 Trial: ORION-4

ORION-4 (CKJ839B12301): "Double-blind, Randomized, Placebo-controlled Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People with Atherosclerotic Cardiovascular Disease"

Open Session DMC Meeting Minutes for ORION-4 (CKJ839B12301):

- August 13, 2019: 1570 patients randomized.
 - The main reason for individuals failing screening is that total cholesterol (from desktop analyzer) is too low.
 - In the UK, there are plenty of eligible individuals that have been identified and clinic space/people are being expanding.
 - In the US, it has been difficult to identify those with high enough lipids. Sites will try to focus on individuals with more recent cholesterol measurements at pre-screening (as it is less likely they will have been started on LDL-C lowering therapy in the interim).
- February 4, 2020: 6400 patients randomized, 5300 in the UK and 1100 in the US.
 - Continued issues with many screening failures due to patients not meeting the lipid threshold.
 - There has been a low rate of dropout for intolerability during run-in and no SUSARs.
 - FDA requested that 70% of participants be on high-intensity LDL-C lowering therapy. Currently have 43% on high-intensity LDL-C lowering therapy. It is hoped that this requirement will be relaxed if a subgroup analysis by level of LDL-C lowering therapy is conducted.
- August 6, 2020: 6400 patients randomized.
 - Currently have 44% on high-intensity LDL-C lowering at baseline. A subgroup analysis by level of LDL-C lowering therapy (high-intensity, moderate-, low-intensity, or no statin) will be conducted (which would have 90% power in each of the categories).
 - Level of LDL control is the same in those on high-intensity LDL-C lowering therapy as those on medium- or low-intensity.
 - Impact of COVID-19:
 - Recruitment was paused in mid-March and face-to-face follow-up visits were suspended in both the UK and US.
 - Follow-up has continued remotely, but participants have been unable to receive study medication.

- Adjudication issue: receiving hospital documents with appropriate handling (redacting information etc.) when nurses are not in the hospital and not able to access records remotely.
- February 11, 2021: 7951 patients randomized.
 - Impact of COVID-19:
 - As of October 2020, there were around 4000 participants that had not been dosed in the last 6 months, but this has now been reduced to about 2100 participants.
 - New procedure for home administration of injections has been developed to allow all participants in UK to be able to receive study treatment.
 - IT infrastructure is now ready, but adjudication has not yet started due to the difficulty with getting access to records during the pandemic.

Reviewer's Conclusion: Inclusion criteria for the ORION-4 CVOT includes a baseline LDL-C of 100 mg/dL or greater threshold. The DMC meetings state that there are a large number of screening failures due to patients not meeting the lipid threshold. This is particularly true for the US (less of an issue in the UK). In addition, they are struggling to meet the requirement for 70% of participants to be on high-intensity LDL-C lowering therapy, as requested by FDA. As of August 2020, only 44% of enrolled subjects were on high-intensity LDL-C lowering therapy at baseline. Both issues (high numbers of screening failures and a reduced number of participants on high-intensity statin therapy may have been alleviated by having the baseline LDL-C threshold set at 70 mg/dL. However, the sponsor chose an LDL-C of 100 mg/dL in order to enroll subjects at higher baseline CV risk.

There are issues with enrollment, dosing, and a delay in adjudication due to COVID-19. However, there does not appear to be any notable safety issues due to inclisiran administration. Of note, based on the company's response to an FDA query, 19 (0.2%) subjects from October 30, 2018 to September 19, 2021 from ORION-4 discontinued study treatment due to use of other inhibitors of PCSK9, based on 8,185 randomized subjects to date. Six (0.1%) subjects are from the UK and 13 (0.8%) are from the US.

4.2. Safety in the Postmarket Setting

4.2.1. Safety Concerns Identified Through Postmarket Experience

The Applicant reports that the post-marketing safety reports received prior to the cut-off date of this submission (May 10, 2021) are very limited and do not reveal any new significant safety information. Nine non-serious post-marketing case reports were received (7 from Germany and 2 from Austria), and the adverse events reported in these nine cases are reportedly consistent with the experience in the phase 3 trials. None of the cases resulted in treatment

discontinuation.

4.2.2. Expectations on Safety in the Postmarket Setting

The use and administration of inclisiran in the postmarket setting is anticipated to be generally similar to its use and administration in clinical trials. Inclisiran was well-tolerated, and the most important safety issue observed in phase 3 trials was injection site reactions. Inclisiran will be administered by a health care provider in the clinic setting, as it was during the phase 3 trials. No additional risk management activities in the postmarket setting, e.g., REMS, are anticipated.

4.3. Integrated Assessment of Safety

ORION-3, -8, and -5 were well-executed and largely adhered to the protocol. The protocol amendments were reasonable and unlikely to have had a negative impact on the integrity of the trial or the interpretation of the results. There were no potential issues concerning the submitted data quality or integrity that raised questions about the safety results. Thus, these trials have generated data that are interpretable and supportive of the known safety profile of inclisiran.

Treatment emergent deaths and SAEs, with the exception of COVID-19-related SAEs, were similar to those reported in the original NDA and in the Day 120 safety update. Cardiovascular-related, neoplasms, and infection-related (COVID-19, pneumonia) SAEs were the most common. AEs that led to study drug discontinuation included ISRs, ischemic stroke, COVID-19-related, and malignancy-related AEs. The cases involving ISRs were likely attributable to inclisiran. Other causes of death, SAEs, and AEs leading to drug discontinuation (i.e., cardiovascular and malignancy) are not unexpected in a trial population of older subjects with established ASCVD or ASCVD risk equivalents.

Common AEs included diabetes mellitus, nasopharyngitis, COVID-19, hypertension, urinary tract infection, influenza, back pain, and arthralgia. An association with inclisiran was only established for urinary tract infection and arthralgia based on placebo-controlled phase 3 data. Other observed common AEs were not corroborated by placebo-controlled data, occur frequently even outside of clinical trials (e.g., back pain, nasopharyngitis), and are common for the enrolled trial population (e.g., diabetes mellitus, hypertension).

Injection site reactions were reported in 13.2% of ORION-3 subjects (49/371) and 4.9% of ORION-8 subjects (146/2990), compared to 8.2% of inclisiran-treated subjects (150/1833) in the safety pool of ORION-9, -10 and -11 (Safety Population of the original NDA; 1.8% (33/1822) of placebo-treated subjects reported ISRs). The higher incidence of ISRs in ORION-3 may be due to its longer study duration. Only one AE at the injection site (1/56, 1.8%) was reported in ORION-

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5 in the inclisiran-inclisiran treatment group. These AEs at the injection site in ORION-3, -8 and -5 were localized, predominantly mild or occasionally moderate, and transient in nature.

Clinically significant changes in laboratory parameters were observed at low frequency in the submitted open-label data but were mostly related to underlying disease and not corroborated by placebo-controlled data in the original NDA. There were no Hy's law cases.

In the phase 3 trials (ORION-9, -10, and -11), the incidence of subjects with a treatment-induced ADA response was 3.9% and titers were generally low. Approximately 2.2% of subjects had transient ADA, while 1.7% had persistent ADA. ADA presence did not appear to be associated with hypersensitivity events. The available data from ORION-3, -8, and -5 are consistent with those findings. There does not appear to be an association between the presence of transient or persistent ADA and hypersensitivity events. The observed frequencies for persistent ADA in ORION-3 and -5 and transient ADA in ORION-3, -8, and -5 are low and similar to those reported in the Safety Pool submitted in the original NDA.

Inclisiran was generally well-tolerated, and the most important safety issue was injection site reactions in the phase 2 and phase 3 trials. Few inclisiran treated subjects withdrew from treatment due to adverse reactions at the injection site.

Based on my review of new and updated safety data, the safety profile of inclisiran in subjects with ASCVD or HeFH and elevated LDL-C is consistent with that previously reported in the original NDA submission. Inclisiran continues to have an acceptable safety profile for its intended use in adults with ASCVD or HeFH.

5. Labeling Recommendations

5.1. Prescription Drug Labeling

The majority of labeling decisions were conveyed to the Applicant during the initial NDA review cycle. Refer to the initial primary clinical review document for this information (in DARRTS, dated November 6, 2020).

Additional issues discussed during this submission included the following:

1. proposed language for the Established Pharmacologic Class (EPC),
2. adding "none" to the Contraindications in highlights and Section 4,
3. inclusion of additional requested information on immunogenicity in Section 6.2, and
4. revision of information in Section 11 that clarifies the classification text that inclisiran sodium is a small interfering RNA (siRNA) (b) (4) PCSK9 (proprotein convertase subtilisin kexin type 9) mRNA.

6. Postmarketing Requirements and Commitments

Postmarketing Requirements

1. Conduct an efficacy and safety study evaluating inclisiran in patients with heterozygous familial hypercholesterolemia (HeFH) aged 12 years to less than 18 years. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 12-month, multicenter efficacy and safety study in 150 patients (randomized 2:1 to inclisiran and placebo), followed by a 12-month open-label extension with all patients assigned to inclisiran in pediatric patients aged 12 years to less than 18 years with HeFH on maximally tolerated, stable lipid-modifying therapy with LDL-C $\geq$ 130 mg/dL. Reference is made to the FDA Agreed initial Pediatric Study Plan (iPSP) dated November 28, 2018 and the FDA Written Request for inclisiran dated November 1, 2019 (DARRTS Reference ID: 4514598).
 - Final protocol for ORION-16 (CKJX839C12301) was submitted to FDA July 22, 2020. DDLO stated the final protocol was acceptable on January 5, 2021.
 - Study Completion: June 2025
 - Final Report Submission: December 2025
2. Conduct an efficacy and safety study evaluating inclisiran in patients with heterozygous familial hypercholesterolemia (HeFH) aged 6-7 if on plasma apheresis and 8 to <12 years of age. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 12-month, multicenter efficacy and safety study (b) (4), followed by a 12-month open-label extension with all patients assigned to inclisiran in pediatric patients aged 6-7 (if on plasma apheresis or meet eligibility criteria for lipid apheresis from their home country) and 8 years to less than 12 years with HeFH on maximally tolerated, stable lipid-modifying therapy (b) (4).
 - Draft Protocol Submission: December 2023
 - Final Protocol Submission: June 2024
 - Study Completion: June 2027
 - Final Report Submission: December 2027
 - The Applicant submitted new proposed milestone dates because of recruitment delays due to the ongoing COVID-19 pandemic in post-marketing study 1 which is currently ongoing in adolescent patients 12 to < 18 years of age. The FDA Written Request for the pediatric HeFH studies requests 1-year interim data from the ongoing adolescent study to better inform the dosing and safety in the younger pediatric patients, 8 to < 12 years of age. Due to the recruitment challenges in the adolescent study, 1-year interim data will be delayed impacting the lower pediatric age group study timelines.

3. Conduct a worldwide, descriptive study that collects prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.
 - Protocol Submission including first interim report: March 2022
 - Interim Study Report: March 2022 and annually
 - Study Completion: December 2030
 - Final Study Report: July 2031
 - The Applicant submitted new proposed milestone dates to reflect the ongoing status of the study globally. The study protocol has been finalized with other global health authorities to support commitments linked to inclisiran approval in other countries. Novartis has already initiated data collection from the countries where inclisiran has been approved. Novartis states that the revised timetable will allow them to keep the same timetable of annual interim report submissions already agreed to with other global health authorities worldwide.

Postmarketing Commitments

1. Validate the sensitivity and all other validation parameters except cutpoints for the ELISA method used to detect anti-inclisiran-reactive IgG/IgM antibodies in human serum, employing an affinity-purified anti-inclisiran antibody positive control (i.e., Rabbit Anti- KLH-TTRSC-2017 antiserum) to ensure that the assay is sensitive, specific, and selective for measurement of ADA responses. Validate the assay in accordance with the FDA Guidance for Industry entitled “Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection”.
 - Study Completion: August 2022
 - Final Report Submission: October 2022
2. Re-evaluate anti-inclisiran-reactive IgG/IgM antibodies in all clinical samples using the appropriately validated assay. Re-assess the impact of anti-inclisiran-reactive IgG/IgM antibodies on pharmacokinetics, efficacy, and safety.
 - Study Completion: July 2023
 - Final Report Submission: August 2023
 - The Applicant submitted new proposed milestone dates for these two PMCs. The Applicant states since inclisiran is a novel siRNA, there are many complexities to produce new antibody positive control (PC) reference material. The monoclonal antibodies production will likely be ready in the last quarter of 2021, however, the corresponding polyclonal antibodies positive control will not be available until the second half of

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2022. Due to the availability of the PC, the previously provided timelines are outdated and Novartis is requesting an extension.

7. Appendix

The tables below summarize the schedule of events and assessments for Group 1 (the inclisiran only arm) and Group 2 (evolocumab switching to inclisiran arm) in ORION-3, ORION-8, and ORION-5.

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Table 30 ORION-3 Schedule of Assessments (Group 1: Inclisiran Only Arm)

	Study Entry ^m	Observation Visits ^a	First Dose ^a	Treatment & Follow-Up (first 2 years) ^f												FU Visits (dosing) ^f	FU Visits (regular) ^f	EOS ^p	
				FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 540 (± 7)	FU10 570 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)				
Study Day		every 30 days (± 7)	Day 1													FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 870 FU16, 1080 FU18, 1260		
Informed consent	X																		
Inclusion / Exclusion Criteria	X																		
Physical Examination (including full neurological examination & weight)			X							X					X		X(D1080) ^e	X	
TSQM Questionnaire				X	X	X		X	X										
Vital Signs ^b	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12 Lead ECG ^c			X							X					X		X(D1080) ^e	X	
HbA1c ^a and serum glucose	X		X					X				X			X (D810 and 1350)	X (D1080)	X		
Hematology ^d	X	X	X						X					X		X (D1080)	X		
Coagulation ^d	X	X	X	X (S)	X (S)	X (S)		X (S)	X		X (S)	X (S)	X (S)		X	X (S)	X (S) / X (D1080)	X	
Full Chemistry ^d	X	X	X						X					X		X (D1080)	X		
Limited Chemistry				X	X	X		X		X	X	X	X		X	X (D 870, 1260)			
Urinalysis (local) ^g	X	X	X ^g		X	X		X	X		X	X		X	X	X	X	X	
Pregnancy test (local) ^h	X	X	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-inclisiran (ADA) antibodies ^l			X		X	X		X	X		X	X		X	X	X	X	X	
Stored samples ^k	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	
Efficacy parameters (LDL-C, lipids, PCSK9) ^l	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipoproteins ^l [Lp(a), ApoB]	X	X	X				X		X				X		X			X	
Study drug administration: inclisiran			X ^{o,q}			X			X			X			X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE/SAE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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ADA = anti-drug antibodies; AE = adverse event; ECG = electrocardiogram; FU=follow-up; EOS = end of study; HbA1c= glycated hemoglobin A1C; hsCRP=high sensitivity C-reactive protein; IL6=interleukin 6; IFN-γ=interferon gamma; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; S = Stored sample; SAE = serious adverse event; TNF-α=tumor necrosis factor alpha.

^a Observation visits every 30 days (±7 days) until study drug is available.

^b Vital signs: blood pressure and heart rate will be measured prior to injection. On Day 1 (vital signs will also be measured at 4 hours after injection).

^c ECG should be performed prior to the injection.

^d Hematology, chemistry (including glucose, liver and renal function, hsCRP, IL6, IFN-γ, and TNF-α), and coagulation testing (of which some will be collected and stored for future analyses).. Blood samples for determination of laboratory values will be performed prior to study drug injection. All laboratory testing will be performed with subjects in a fasted state. See [Section 7.1.6](#) for a list of laboratory parameters. Lab tests performed by study's designated Central Lab facility from entry into the study to EOS. On days when inclisiran is injected, if indicated, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logistically possible).

^e Physical and neurological examinations, weight, and ECG performed once yearly.

^f Visit windows are ± 2 days for the Day 30 visit, and ± 7 days from Day 90 onwards.

^g Urinalysis collection is prior to the injection on Day 1; supplies from the Central Lab must be used to perform the urinalysis.

^h Urine pregnancy test performed and results available prior to the injection on Day 1; supplies from the Central Lab must be used to perform the test.

ⁱ Women of childbearing potential will have a pregnancy test at each visit.

^j On Day 1 two ADA samples will be drawn: one before the injection and one 4 hours after the injection.

^k Plasma glucose and lactate will be collected at intervals throughout the study and stored for future analyses. See [Section 7.1.8](#) for details. Additional blood samples will be collected every 180 days and aliquots of plasma and serum stored for future analyses.

^l Efficacy parameters will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), C-reactive protein (CRP), and PCSK9. A standard lipid panel will be done at all visits (Day 1 to EOS) however some PCSK9 samples will be stored for future analyses and ultracentrifugation is to be done only at Day 1, Day 210, Day 360, Day 570, Day 720 and EOS.

^m Until study drug is available, subjects will attend a basic observation visit at 30 day intervals. These visits will include safety labs (hematology, chemistry, coagulation) and recording of AEs, SAEs, and concomitant medications.

ⁿ HbA1c assessed every 270 days. Therefore, HbA1C to be assessed at follow-up visits on Days 270, 540, 810, 1080, and 1350.

^o Subjects will be observed in the clinic for at least 4 hours post their first inclisiran injection before being discharged (Day 1 for subjects in Group 1; inclisiran only arm)

^p EOS will occur 90 days following the final administration of study drug. However, if the study ends early or if the subject discontinues the study, the EOS visit should occur at least 30 days following the final administration of study drug.

^q There should be a minimum of 7 days between Study Entry or last observation visit and Day 1.

Source: ORION-3 (MDCO-PCS-16-01) Global Protocol Amendment 4, Table 3

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Table 31 ORION-3 Schedule of Assessments (Group 2: Evolocumab Transition to Inclisiran Arm)

Study Day	Study Entry ^o	Observation Visits ^a	First Dose ^t	Treatment & Follow-Up (first 2 years) ^f												FU Visits (dosing) ^f	FU Visits (regular) ^f	EOS ^s	
				FU1 30 (± 2)	FU2 90 (± 7)	FU3 180 (± 7)	FU4 210 (± 7)	FU5 270 (± 7)	FU6 360 (± 7)	FU7 390 (± 7)	FU8 450 (± 7)	FU9 510 (± 7)	FU10 540 (± 7)	FU11 630 (± 7)	FU12 720 (± 7)				
		every 30 days (± 7)	Day 1														FU13, 810 FU15, 990 FU17, 1170 FU19, 1350	FU14, 900 FU16, 1080 FU18, 1260	
Informed consent	X																		
Inclusion / Exclusion Criteria	X																		
Physical Examination (including full neurological examination & weight)			X						X					X			X(D1080) ^e	X	
TSQM Questionnaire				X	X	X		X	X		X		X	X	X				
Adherence to self injection ^l				X	X	X		X	X										
Vital Signs ^a	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12 Lead ECG ^c			X						X					X			X(D1080) ^e	X	
HbA1c ^a and serum glucose	X		X					X					X		X (D810 and 1350)	X (D1080)	X		
Hematology ^d	X	X	X					X						X		X (D1080)	X		
Coagulation ^d	X	X	X	X (S)	X (S)	X (S)		X (S)	X		X (S)	X (S)		X (S)	X	X (S)	X (S) / X (D1080)	X	
Full Chemistry ^d	X	X	X					X						X		X (D1080)	X		
Limited Chemistry				X	X	X		X		X	X	X	X	X	X	X (D 900, 1260)			
Urinalysis (local) ^a	X	X	X ^h		X	X		X	X		X	X		X	X	X	X	X	
Pregnancy test (local) ^l	X	X	X ^h	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Anti-inclisiran (ADA) antibodies ^l									X		X		X	X	X	X	X	X	
Stored samples ^k	X	X	X	X	X	X		X	X		X	X		X	X	X	X	X	
Efficacy parameters (LDL-C, lipids, PCSK9) ^m	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Lipoproteins ^m [Lp(a), ApoB]	X	X	X				X		X			X		X				X	
Study drug administration: evolocumab ^{ln}			X ^t	Every 14 days through Day 336						X ^p									
Inclisiran									X ^r		X			X		X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE/SAE reporting	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

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ADA = anti-drug antibodies; AE = adverse event; ECG = electrocardiogram; FU= follow-up; EOS = end of study; HbA1c= glycated hemoglobin A1C; hsCRP=high sensitivity C-reactive protein; IL6=interleukin 6; IFN-γ=interferon gamma; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; S = Stored sample; SAE = serious adverse event; TNF-α=tumor necrosis factor alpha.

^a Observation visits every 30 days (±7 days) until study drug is available.

^b Vital signs: blood pressure and heart rate will be measured prior to injection. On Day 360 (transition visit), vital signs will also be measured at 4 hours after injection.

^c ECG should be performed prior to the injection.

^d Hematology, chemistry (including glucose, liver and renal function, hsCRP, IL6, IFN-γ, and TNF-α), and coagulation testing (of which some will be collected and stored for future analyses). Blood samples for determination of laboratory values will be performed prior to study drug injection. All laboratory testing will be performed with subjects in a fasted state. See [Section 7.1.6](#) for a list of laboratory parameters. Lab tests performed by study's designated Central Lab facility from entry into the study to EOS. On days when inclisiran is injected, if indicated, the investigator will need to collect a blood sample for tryptase within 30 minutes of the onset of anaphylaxis (or as soon as logistically possible).

^e Physical and neurological examinations, weight, and ECG performed once yearly.

^f Visit windows are ± 2 days for the Day 30 visit, and ± 7 days from Day 90 onward.

^g Urinalysis collection is prior to the injection on Day 1; supplies from the Central Lab must be used to perform the urinalysis.

^h Urine pregnancy test performed and results available prior to the injection on Day 1; supplies from the Central Lab must be used to perform the test.

ⁱ Women of childbearing potential will have a pregnancy test at each visit.

^j On Day 360 two ADA samples will be drawn: one before the injection and one 4 hours after the injection.

^k Plasma glucose and lactate will be collected at intervals throughout the study and stored for future analyses. See [Section 7.1.8](#) for details. Additional blood samples will be collected every 180 days and aliquots of plasma and serum stored for future analyses.

^l Diary cards should be turned in to study site coordinator at follow-up visits on Day 30, 90, 180, 270 and 360.

^m Efficacy parameters will include LDL-C, total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein (VLDL-C), C-reactive protein (CRP), and PCSK9. A standard lipid panel will be done at all visits (Day 1 to EOS) however some PCSK9 samples will be stored for future analyses and ultracentrifugation is to be done only at Day 1, Day 210, Day 360, Day 510, Day 720 and EOS.

ⁿ Day 1 in clinic; Days 14 through 336 to be self-injected according to label; for subjects in Transition 2; at Visit Day 360 in the clinic.

^o Until study drug is available, subjects will attend a basic observation visit at 30 day intervals. These visits will include safety labs (hematology, chemistry, coagulation) and recording of AEs, SAEs, and concomitant medications.

^p Only subjects in Transition 2 will receive a final dose of evolocumab at Visit Day 360 with the first dose of inclisiran.

^q HbA1c assessed every 270 days. Therefore, HbA1C to be assess at follow-up visits on Days 270, 540, 810, 1080, and 1350.

^r Subjects will be observed in the clinic for at least 4 hours post their first inclisiran injection before being discharged

^s EOS will occur 90 days following the final administration of study drug. However, if the study ends early or if the subject discontinues the study, the EOS visit should occur at least 30 days following the final administration of study drug.

^t There should be a minimum of 7 days between Study Entry or last observation visit and Day 1.

Source: ORION-3 (MDCO-PCS-16-01) Global Protocol Amendment 4, Table 3

Table 32 ORION-3 Criteria for Potentially Clinically Significant Abnormal Laboratory Tests

Parameter	Unit	Low Limit (LLN)	High Limit (ULN)
Hematology			
Hemoglobin	g/dL	≤10 g/dL	
Hematocrit	%	≤0.8 × LLN	
White Blood Cell Count	10 ³ /μL	≤2.8	≥16
Platelet Count	10 ³ / μL	≤75	≥700
IL6			≥100
TNF alpha			≥100
Hemoglobin A1C	%		≥6.5% + ≥0.5% change from baseline
Serum Chemistry			
Creatinine	mg/dL		>2
Creatine Kinase (CK)	U/L		>1 and ≤3 × ULN
Creatine Kinase (CK)	U/L		>3 and ≤5 × ULN
Creatine Kinase (CK)	U/L		>5 × and ≤10 × ULN
Creatine Kinase (CK)	U/L		>10 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L		>1 and ≤3 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L		>3 and ≤5 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L		>5 × ULN
Aspartate Aminotransferase (AST/SGOT)	U/L		>1 and ≤3 × ULN
Aspartate Aminotransferase (AST/SGOT)	U/L		>3 and ≤5 × ULN
Aspartate Aminotransferase (AST/SGOT)	U/L		>5 × ULN
Total Bilirubin	mg/dL		>2 × ULN
Alkaline Phosphatase			>2 × ULN

LLN=Lower limit of the standard reference (normal) range; ULN=Upper limit of the standard reference (normal) range.

Hemoglobin A1C criteria is stated in the table; all other criteria are met when both of the following occur: Post-baseline values meet the thresholds in the table and baseline values or any prior post-baseline values do not meet the thresholds.

Source: ORION-3 pcs-derivation-instruction

Table 33 ORION-8 Criteria for Potentially Clinically Significant Abnormal Laboratory Tests

Parameter	Unit	Lower Boundary	Upper Boundary
Hematology			
Hematocrit	%	$\leq 0.8 \times \text{LLN}$	N/A
Hemoglobin	g/dL	$\leq 10 \text{ g/dL}$	N/A
Platelet Count	$10^9/\text{L}$	$\leq 75^*$	$\geq 700^*$
White Blood Cell Count	$10^9/\text{L}$	≤ 2.8	≥ 16
Serum Chemistry			
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>1 and $\leq 3 \times \text{ULN}$
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>3 and $\leq 5 \times \text{ULN}^*$
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>5 and $\leq 10 \times \text{ULN}^*$
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	>10 and $\leq 20 \times \text{ULN}^*$
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	$>20 \times \text{ULN}^*$
Alkaline Phosphatase	U/L	N/A	$>2 \times \text{ULN}^*$
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>1 and $\leq 3 \times \text{ULN}$
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>3 and $\leq 5 \times \text{ULN}^*$
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>5 and $\leq 10 \times \text{ULN}^*$
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	>10 and $\leq 20 \times \text{ULN}^*$
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	$>20 \times \text{ULN}^*$
Creatine Kinase (CK)	U/L	N/A	>1 and $\leq 3 \times \text{ULN}$
Creatine Kinase (CK)	U/L	N/A	>3 and $\leq 5 \times \text{ULN}$
Creatine Kinase (CK)	U/L	N/A	$>5 \times$ and $\leq 10 \times \text{ULN}^*$
Creatine Kinase (CK)	U/L	N/A	>10 and $\leq 20 \times \text{ULN}^*$
Creatine Kinase (CK)	U/L	N/A	$>20 \times \text{ULN}^*$
Hemoglobin A1C	%	N/A	$\geq 6.5\%$ and $\geq 0.5\%$ change from baseline
Serum Creatinine	mg/dL	N/A	$\geq 50\%$ increase from Baseline or $>2 \text{ mg/dL}^*$
Total Bilirubin	mg/dL	N/A	$>2 \times \text{ULN}^*$

LLN=Lower limit of the standard reference (normal) range; ULN=Upper limit of the standard reference (normal) range.

*Clinically significant laboratory boundaries

Hemoglobin A1C criteria is stated in the table; all other criteria are met when both of the following occur: Post-baseline values meet the thresholds in the table and baseline values or any prior post-baseline values do not meet the thresholds.

Source: ORION-8 SAP Appendix 4

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Table 34 ORION-8 Schedule of Assessments

Study Day Visit window (± days)	Study Entry/ Double blind treatment	Open Label Treatment Phase		EOS ¹
	Day 1 ² (N/A)	Day 90 (First Dose) (±30)	Subsequent dosing visits ³ (i.e. Days 270, 450, 630, 810, 990) (±30)	Final Follow-up Day 1080 (≥ 90 days post final dose)
Informed consent	x			
Inclusion/exclusion Criteria	x			
Physical examination				x
Vital signs ⁴		x	x	x
Full serum chemistry ⁵				x
Limited serum chemistry ⁵		x	x	
Hematology and coagulation ⁶				x
Urinalysis (local) ⁷				x
Pregnancy test (local) ⁸		x	x	x
Lipids and lipoproteins		x	x	x
Sample for Anti-inclisiran (ADA) antibodies ⁹		x	x	x
Double blinded inclisiran or placebo ^{10, 11}	x			
Open label Inclisiran administration ¹¹		x	x	
Concomitant medications ¹²		x	x	x
AE/SAE reporting ¹²		x	x	x
Drug and device deficiencies (including AE/SAEs related to the drug or device deficiency)	x	x	x	x

AE = adverse event; EOS = end of study; SAE = serious adverse event

1. EOS visit should occur at least 90 days following the last inclisiran dose once a decision is made to end the study (either by the subject, investigator or sponsor). For subjects prematurely and permanently discontinued from study treatment, who are not willing to return within the 90 day timeframe, the EOS visit will be scheduled as soon as possible, or if decision to discontinue and not return is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.

2. Day 1 visit is the same as EOS visit in the previous qualifying ORION study. Aside from informed consent and eligibility, procedures will not be repeated but will be those captured during feeder study EOS visit except for subjects enrolled in Sweden. See Section 3.1 and Section 6.3 Sweden Specific Protocol Amendment 1 (to Global Amendment 1 version), dated 1 Nov 2018.

3. Dosing visits will occur every 180 days until the study ends for each respective subject. Visit windows have been extended to +/-2 months due to COVID-19.

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4. Vital signs: blood pressure and heart rate will be measured prior to injection on dosing days. When available, an automated BP device is recommended for collection of BP and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) is required per applicable visit.
5. See [Section 7.1.6.3](#) for details of specific tests to be analyzed
6. See [Section 7.1.6.1](#) and [Section 7.1.6.2](#) for details of specific tests to be analyzed
7. Urinalysis collection is prior to the injection; supplies from the central laboratory must be used to perform the urinalysis
8. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies and with results prior to injection; urine pregnancy test). Results of the pregnancy test from Day 540 of the feeder study will be used on Day 1 in ORION-8
9. ADA samples will be drawn prior to injection
10. Subjects who received blinded placebo in the feeder study will receive blinded inclisiran and subjects who received blinded inclisiran in the feeder study will receive blinded placebo on Day 1 in ORION-8. Subjects moving over from the ORION-3 trial will not receive any treatment at Day 1; all subjects were on inclisiran in the feeder trial and will receive their first dose of inclisiran in this study at day 90
11. Subjects will be observed in the clinic for 30 minutes post injection in order to have additional vital and/or laboratory assessments completed if needed. For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as logically possible).
12. Concomitant medications (relevant) and AE/SAE collection for this study will begin at time of consent and continue through EOS. Ongoing concomitant medications and AEs/SAEs from the feeder study will continue to be followed in this study until resolution.

Source: ORION-8 (MDCO-PCS-17-05) Protocol Amendment 2, Table 6-1

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Table 35 ORION-5 Schedule of Assessments

Visit	Screening	Randomization and Treatment	Treatment									EOS ¹³
	Day -28 to -1	V1 (baseline)	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11 (90 days post last dose)
Timelines		Day 1	Day 90	Day 150	Day 180	Day 270	Day 330	Day 450	Day 510	Day 630	Day 690	Day 720
Visit windows (+/-weeks)		1	3	3	3*	3*	3*	3*	3*	3*	3*	3*
Informed Consent	X											
Medical history and prior meds	X											
Assessment of eligibility ¹	X	X										
β-HCG pregnancy test ²	X	X	X	X	X	X	X	X		X	X	X
Study drug administration (inclisiran)		X	X			X		X		X		
Study drug administration (placebo; switch to inclisiran at Day 180)		X	X		X	X		X		X		
Physical examination ³	X											X
Neurological examination ⁴		X		X			X					X
Weight/Height/Waist circumference ⁵	X			X	X		X					X
Vital signs ⁶	X	X	X	X	X	X		X		X		X
12-lead ECG	X											X
Fasted lipid profile/biomarkers ⁷	X	X	X	X	X	X	X	X	X	X	X	X
Full serum chemistry ⁸		X										X
Limited serum chemistry ⁹	X		X	X	X	X	X	X	X	X	X	

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Hematology and coagulation ¹⁰	X	X		X								X
Urinalysis (local) ¹¹	X	X										X
Pharmacogenetic sample ¹²	X											
ADA assessment		X	X	X			X					X
Previous/concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X

β-HCG=beta-human chorionic gonadotrophic hormone; ADA=anti-drug antibodies; BP=blood pressure; CPK=creatin phosphokinase; CV=cardiovascular; ECG=electrocardiogram; eGFR=estimated glomerular filtration rate; EOS=end of study; HbA1C=glycated hemoglobin A1C; HDL-C=high density lipoprotein cholesterol; HR=heart rate; LDL-C=low density lipoprotein cholesterol; SC=subcutaneous; V=visit

*: The visit window is extended to +/- 2 months during the COVID-19 pandemic, to allow on-site visits (rather than remote visits) to occur as much as possible.

1. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
2. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies; urine pregnancy test).
3. Physical examination is the responsibility of the principal investigator or medically qualified designee.
4. Full neurological examination will be performed as described in Appendix C of the protocol
5. Height will be measured at baseline only and used to calculate body mass index.
6. On dosing days, vital signs will be measured prior to injection. When available, an automated BP device is recommended for collection of BP and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) is required per applicable visit
7. See Section 3.9 for details of specific tests to be analyzed
8. See Section 3.8.8.3 for details of specific tests to be analyzed
9. See Section 3.8.8.3 for details of specific tests to be analyzed
10. See Section 3.8.8.1 and Section 3.8.8.2 for details of specific tests to be analyzed
11. Performed locally using the central laboratory kit supplies
12. Sample may be taken during screening or anytime during study to be processed and stored, but only after separate consent has been signed.
13. For subjects prematurely and permanently discontinued from study treatment, EOS visit will be scheduled as soon as possible. If decision to discontinue is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.

Source: ORION-5 (MDCO-PCS-17-02) Statistical Analysis Plan, version 4.0, March 23, 2021, Table 2-1

Table 36 ORION-5 Criteria for Potentially Clinically Significant Abnormal Laboratory Tests

Parameter	Unit	Lower Boundary	Upper Boundary
Hematology			
Hematocrit	%	≤ 0.8 × LLN	N/A
Hemoglobin	g/dL	≤ 10 g/dL	N/A
Platelet Count	10 ⁹ /L	≤ 75*	≥ 700*
White Blood Cell Count	10 ⁹ /L	≤ 2.8	≥ 16
Serum Chemistry			
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 1 and ≤ 3 × ULN
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 3 and ≤ 5 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 5 and ≤ 10 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 10 and ≤ 20 × ULN*
Alanine Aminotransferase (ALT/SGPT)	U/L	N/A	> 20 × ULN*
Alkaline Phosphatase	U/L	N/A	> 2 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 1 and ≤ 3 × ULN
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 3 and ≤ 5 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 5 and ≤ 10 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 10 and ≤ 20 × ULN*
Aspartate Aminotransferase (AST/SGOT)	U/L	N/A	> 20 × ULN*
Creatine Kinase (CK)	U/L	N/A	> 1 and ≤ 3 × ULN
Creatine Kinase (CK)	U/L	N/A	> 3 and ≤ 5 × ULN
Creatine Kinase (CK)	U/L	N/A	> 5 × and ≤ 10 x ULN*
Creatine Kinase (CK)	U/L	N/A	> 10 and ≤ 20 × ULN*
Creatine Kinase (CK)	U/L	N/A	> 20 × ULN*
Hemoglobin A1C	%	N/A	≥ 6.5% and ≥ 0.5% change from baseline
Serum Creatinine	mg/dL	N/A	≥ 50% increase from Baseline or > 2 mg/dL*
Total Bilirubin	mg/dL	N/A	> 2 × ULN*

LLN=Lower limit of the standard reference (normal) range; ULN=Upper limit of the standard reference (normal) range.

Hemoglobin A1C criteria is stated in the table; all other criteria are met when both of the following occur: Post-baseline values meet the thresholds in the table and baseline values or any prior post-baseline values do not meet the thresholds.

Source: ORION-5 (MDCO-PCS-17-02) Statistical Analysis Plan, version 4.0, March 23, 2021, Table 10.4

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Clinical Review
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 NDA 214012
 LEQVIO™ (inclisiran)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	214012
Priority or Standard	Standard
Submit Date(s)	23 December 2019
Received Date(s)	23 December 2019
PDUFA Goal Date	23 December 2020
Division/Office	DDLO/OCHEN/CDER
Reviewer Name(s)	Eileen Craig, MD (efficacy) and Iffat Chowdhury, MD (safety)
Review Completion Date	4 November 2020
Established/Proper Name	Inclisiran
(Proposed) Trade Name	Leqvio
Applicant	The Medicines Company/Novartis Pharmaceuticals Co.
Dosage Form(s)	Subcutaneous (SC) injection
Applicant Proposed Dosing Regimen(s)	284 mg administered on Day 1, again at 3 months, then every 6 months.
Applicant Proposed Indication(s)/Population(s)	An adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

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Glossary

AC	advisory committee
ADA	anti-drug antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Apo-A1	apolipoprotein A1
ApoB	apolipoprotein B
aPTT	activated partial thromboplastin
AR	adverse reaction
ASCVD	atherosclerotic cardiovascular disease
ASGPR	asialoglycoprotein receptor
AST	aspartate aminotransferase
AUC	area under the curve
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHD	coronary heart disease
CK	creatinine kinase
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatinine phosphokinase
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computed tomography
CTA	Computed tomographic angiography

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CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CVD	cerebrovascular disease
dL	deciliter(s)
DMC	data monitoring committee
ECG	electrocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EOS	end of study
ETASU	elements to assure safe use
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FH	familial hypercholesterolemia
GalNAc	N-acetylgalactosamine
GCP	good clinical practice
GGT	gamma glutamyl transferase
GPV	Global Pharmacovigilance
GRMP	good review management practice
HbA1c	glycated hemoglobin A1C
HDL-C	high density lipoprotein cholesterol
HeFH	Heterozygous Familial Hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IFN- γ	interferon-gamma
IL6	interleukin 6
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISR	injection site reaction
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
LDL-C	low-density lipoprotein cholesterol
LDLR	low density lipoprotein receptor
LNP	lipid nanoparticles

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Lp(a)	lipoprotein(a)
Lp-PLA2	lipoprotein-associated phospholipase A2
MCH	mean cell hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	myocardial infarction
mITT	modified intent to treat
mL	milliliter(s)
mmHg	millimeters of mercury
mmol	millimole
MMRM	mixed-effect models for repeated measures
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NYHA	New York Heart Association
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAD	peripheral arterial disease
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	percutaneous coronary intervention
PCS	potentially clinical significant
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics
PEF	peak expiratory flow
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	prothrombin time
REMS	risk evaluation and mitigation strategy

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RISC	RNA-induced silencing complex
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SGE	special government employee
siRNA	short (small) interfering ribonucleic acid
SOC	standard of care or system organ class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal half-life
TBIL	total bilirubin
TC	total cholesterol
TEAE	treatment emergent adverse event
TNF- α	tumor necrosis factor-alpha
TTR	target transthyretin
ULN	upper limit of normal
US	United States
VLDL-C	very low-density lipoprotein cholesterol
WHO	World Health Organization

1. Executive Summary

1.1. Product Introduction

Inclisiran (proposed proprietary name of LEQVIO), a new molecular entity (NME), is a double-stranded short interfering ribonucleic acid (siRNA), which inhibits hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9). The reduction in intrahepatic PCSK9 levels leads to increased recycling and expression of the LDL-C receptor on the hepatocyte cell surface. This leads to increased LDL-C uptake and lowering of LDL-C levels in the circulation.

Inclisiran was developed as a single use prefilled syringe (300 mg inclisiran sodium in 1.5 mL aqueous solution containing 284 mg of inclisiran) for administration by a healthcare professional. Inclisiran is administered as a subcutaneous injection given at Day 1, again at 3 months, then every 6 months.

The applicant proposes the following indication: INCLISIRAN is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application contains substantial evidence that the drug is effective for its intended use. LDL-C is a valid surrogate endpoint for evaluating risk reduction of cardiovascular disease (CVD). Based on data showing robust LDL-C reductions and an acceptable safety profile, this reviewer recommends approval for the following indication:

- INCLISIRAN is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

It is important to note that the effect of inclisiran on cardiovascular morbidity and mortality has not been determined. Therefore, inclisiran is not indicated for the treatment of patients with primary hyperlipidemia without established clinical atherosclerotic CVD.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Inclisiran (proposed proprietary name of LEQVIO) is a double-stranded short interfering ribonucleic acid (siRNA) that lowers LDL-C levels in the circulation. The applicant proposes that inclisiran is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C). Based on data showing robust LDL-C reductions and an acceptable safety profile with inclisiran, this reviewer recommends approval of inclisiran as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL-C.

Hyperlipidemia, specifically an increase in LDL-C levels, is a major modifiable risk factor for the development of atherosclerosis and atherosclerotic cardiovascular disease (ASCVD). ASCVD continues to be the leading cause of death and disability worldwide. The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease. Patients with homozygous familial hypercholesterolemia (HoFH), a rare and life-threatening disorder, comprise a subpopulation whose disease is particularly severe and difficult to treat. This submission does not address the treatment of HoFH.

Current treatment guidelines emphasize reducing the risk of ASCVD through lipid management, based on an individualized approach which considers a patient's overall risk for a CV event. Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on their risk category. Ezetimibe and/or PCSK9 inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk (secondary prevention and HeFH) who require additional LDL-C reduction.

The phase 3 trials, ORION-9, ORION-10 and ORION-11, included a population of approximately 3500 patients with HeFH or ASCVD with elevated LDL-C despite maximally tolerated statin therapy who were treated with inclisiran sodium 300 mg administered subcutaneously at Day 1, Day 90, and every 6 months afterward for a duration of 18 months. The study population included relevant comorbidities such as increased age, renal impairment, hepatic impairment, hypertension and diabetes. The data from these 3 trials demonstrated durable, clinically meaningful LDL-C reduction (48-52%) with supportive results in total cholesterol, non-HDL-C and apo-B endpoints. The majority of subjects in the inclisiran group experienced a sizable LDL-C reduction at Day 510 compared to the placebo group. Consistent, statistically significant placebo-adjusted LDL-C percent changes from baseline to Day 510 were seen across various subpopulations defined by baseline demographic characteristics and disease comorbidities.

Inclisiran has a prolonged pharmacodynamic effect on LDL-C levels which allows for infrequent dosing, which may be preferable to some patients. It is possible, but not proven, that less frequent dosing with inclisiran may improve a patient's adherence. However, unlike alirocumab, evolocumab and statins, we do not have CV outcome data with inclisiran that confirms a reduction in CV morbidity and mortality, nor do we have the long-term safety data assessment that is possible from a CVOT that is several years in duration and enrolls thousands of patients. The lack of this data will limit the scope of the indication and thus supports a narrower indication than the applicant's proposed indication.

Patients that have defective LDL-C receptors and consequent diminution in LDL receptor activity, particularly patients with HoFH who are LDL receptor-negative, have a decreased LDL-C lowering response to drugs like statins and PCSK9 inhibitors that work through the LDL-C receptor. Inclisiran is therefore unlikely to show a sizable effect in these patients who have failed to show a meaningful LDL-C response to statins and PCSK9 inhibitor monoclonal antibodies.

Review of safety data identified few issues; these findings—either individually or collectively—do not outweigh efficacy in the intended population. More patients assigned to inclisiran reported and discontinued study drug due to injection site reactions compared with patients assigned to placebo, but no serious or severe reactions occurred. Other events with small imbalances greater in the inclisiran group included arthralgia and increases in blood glucose in patients with diabetes/impaired fasting glucose. The incidence of adverse events of concern, including hypersensitivity, neurocognitive events, renal events, increases in liver transaminase and ophthalmological events, were similar between the inclisiran and placebo groups. The incidence of persistent anti-drug antibodies was low and was not associated with attenuation of LDL-C lowering.

The benefit-risk analysis for inclisiran is favorable for an indication as an adjunct to maximally tolerated statin therapy in high-risk patients with clinical CVD or HeFH, who require additional LDL-C lowering. The data support approval for these conditions of use. The effect of inclisiran on cardiovascular morbidity and mortality has not been determined. Therefore, inclisiran is not indicated for the treatment of patients with non-familial hyperlipidemia without established clinical atherosclerotic CVD. The applicant will be issued postmarketing requirements (PMRs) to conduct phase 3 efficacy and safety studies evaluating inclisiran in patients with HeFH ages 8 years (or ≥ 6 years of age and on apheresis) to less than 18 years. In addition, the applicant will be issued a postmarketing commitment (PMC) to complete the ongoing randomized, double-blind, placebo-controlled multicenter trial in approximately 15,000 patients (randomized 1:1 to inclisiran and placebo) designed to assess the effects of inclisiran on the occurrence of major cardiovascular events.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Large burden of cardiovascular (CV) disease worldwide and in the US: • CVD prevalence in United States excluding hypertension (CHD, HF, and stroke only) is 9% overall (24.3 million in 2016)¹ • Leading cause of death in United States • \$351 billion annual cost of CVD and stroke in US (2015)¹ LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes: • Meta-analysis of statin trials demonstrated that an absolute reduction of 38.7 mg/dL (1 mmol/L) with statins is associated with a 22% relative risk reduction in 5-year incidence of major vascular events (non-fatal myocardial infarction, coronary death, ischemic stroke, or coronary revascularization).² • CV outcomes trials (CVOTs) of the two approved PCSK9 inhibitors, alirocumab and evolocumab, demonstrated that reducing LDL-C levels led to a reduction in risk of CV events.^{3,4} LDL-C reduction with other agents is used in high-risk patients who require additional LDL-C lowering:	LDL-C reduction with therapies targeting upregulation of the LDL-C receptor is the cornerstone of preventive treatment for CV disease. Statins are considered first-line, standard-of-care for lowering LDL-C with the goal of reducing CV risk. CVOTs of statins and monoclonal antibody PCSK9 inhibitors demonstrated that reducing LDL-C levels with these agents led to a reduction in risk of CV events.

¹ Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–528.

² Baigent, et al. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.

³ Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; 379: 2097-107.

⁴ Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- CVOT with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering⁵; (b) (4) - Other agents, such as colesevelam and bempedoic acid, may be used as adjuncts to statins, PCSK9 inhibitors, and ezetimibe, but the incremental effects on CV outcomes are uncertain. Patients with elevated LDL-C are treated for primary and secondary prevention of CV events: - Primary prevention: Reduce the risk for development of CV disease in patients at increased risk - Secondary prevention: Reduce the risk for additional CV events	
Current Treatment Options	<u>Treatment options</u> Monotherapy for LDL-C reduction - Statins: -22% [pravastatin 10 mg] to -63% [rosuvastatin 40 mg] - High-intensity statin, ≥50% reduction - Moderate-intensity statin, 30% to 49% reduction - Low-intensity statin, <30% reduction - Ezetimibe: -18% to -20% reduction Add-on therapy - Statin+ezetimibe: -12% to -19% additional lowering to statin - Statin+PCSK9 inhibitors: -46% to -71% additional lowering to statin - Statin+bempedoic acid: -17% to -18% additional lowering to statin	Current treatment guidelines emphasize reducing risk of atherosclerotic cardiovascular disease (ASCVD) through lipid management, based on an individualized approach which considers a patient’s overall risk for a CV event. In primary prevention, this is based on an ASCVD risk score and additional risk factors. Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on

⁵ Cannon, CP, Blazing, MA, Giugliano, RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Ezetimibe+bempedoic acid: -13% additional lowering to ezetimibe <u>Treatment recommendations, 2018 ACC/AHA Guidelines⁶</u> • Primary prevention ○ Moderate-intensity statin to reduce LDL-C by 30% to ≥50% depending on calculated CV risk ○ High-intensity statin in severe hypercholesterolemia (LDL-C level ≥190 mg/dl/heterozygous familial hypercholesterolemia [HeFH]) • Secondary prevention, high-risk for recurrence⁷ ○ High-intensity statin to reduce LDL-C by ≥50% +/- ezetimibe • Secondary prevention, very high-risk for recurrence⁸ ○ High-intensity statin to reduce LDL-C <70 mg/dL + ezetimibe +/- PCSK9 inhibitor Patient access to newer add-on therapies, such as PCSK9 inhibitors, has been challenging due to factors such as expense and refusal of payers	risk category. Low-intensity statins are not recommended for any population. Ezetimibe and/or PCSK9 inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk (secondary prevention and HeFH) who require additional LDL-C reduction. Statin reduce LDL-C by 25% to 60% depending on the statin intensity. PCSK9 inhibitors lower LDL-C by an additional 45% to 70%. Ezetimibe lowers LDL-C by an additional 15% to 20%. Other drug categories, such as fibrates or niacin, are not considered mainstays of LDL-C lowering therapy due to mild LDL-lowering ability and clinical trial data that shows no benefit in reducing CV morbidity or mortality among patients already treated with a

⁶ <https://www.ahajournals.org/doi/epub/10.1161/CIR.0000000000000625>

⁷ High-risk conditions are defined as age ≥65 years, heterozygous familial hypercholesterolemia (HeFH), prior coronary revascularization outside of the major ASCVD events, diabetes, hypertension, chronic kidney disease with estimated glomerular filtration rate 15-59 ml/min/1.72 cm², current smoker, and LDL-C ≥100 mg/dl despite maximally tolerated statin therapy and ezetimibe.

⁸ Very high risk for future ASCVD events includes a history of multiple major ASCVD events (ACS within 12 months, myocardial infarction, ischemic stroke, peripheral arterial disease defined as claudication with ankle-brachial index [ABI] <0.85, or previous revascularization or amputation, or one major event with multiple high-risk conditions).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to cover. ⁹	statin. ^{10,11} Additional agents may be used in patients who require additional LDL-C lowering despite optimum therapy.
Benefit	In patients with established ASCVD who take inclisiran for secondary prevention as add-on to background statin therapy, inclisiran lowers LDL compared to placebo: • At Day 510, -51% to -52% reduction In patients with HeFH who take inclisiran as add-on to background statin therapy, inclisiran lowers LDL compared to placebo: • At Day 510, -48% reduction A cardiovascular outcomes trial to evaluate the benefit of inclisiran as an adjunct to statin therapy is ongoing.	Inclisiran has a robust LDL-C lowering treatment effect. The LDL-C lowering treatment effect of inclisiran is similar to that achieved with alirocumab and evolocumab; however, alirocumab and evolocumab have both demonstrated CV risk reduction in outcomes trials. The LDL-C lowering treatment effect of inclisiran is greater than that of ezetimibe, bempedoic acid, and low-intensity statins; ezetimibe and low-intensity statins have been evaluated in CV outcomes trials. In the absence of outcomes data, the clinical benefit is uncertain. Nonetheless, inclisiran provides an additional option for patients who

⁹ Navar AM, Tayler B, Mulder H, et al. Association of Prior Authorization and Out-of-pocket Costs With Patient Access to PCSK9 Inhibitor Therapy. JAMA Cardiol. 2017 Nov 1;2(11):1217-1225.

¹⁰ AIM-HIGH Investigators, W.E. Boden, J.L. Probstfield, T. Anderson, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 365 (2011), pp. 2255-2267

¹¹ The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005.366:1849-1861.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		require LDL-C lowering despite optimized available therapies.
Risk and Risk Management	In phase 3 trials, inclisiran was associated with: • Injections site reactions (8.2% of patients) compared to placebo (1.8%) • Arthralgia (5.0% versus 4.0% in placebo) • Urinary tract infections (4.4% versus 3.6% in placebo) • Diarrhea (3.9% versus 3.5% in placebo) • Bronchitis (4.3% versus 2.7% in placebo)	Inclisiran is associated with injection site reactions (ISR) that were mild to moderate in severity and transient in nature. The risk for ISR is monitorable, and can be adequately addressed through labeling. Other adverse events with imbalances were infrequent and included small increases in blood glucose in patients with diabetes/ impaired glucose tolerance. However, new onset diabetes incidence was similar to placebo. Adverse events of special interest, including hypersensitivity, hepatic events, renal events, neurological/ neurocognitive events, and ophthalmological events, demonstrated rates similar to placebo.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☒	Patient-focused drug development or other stakeholder meeting summary reports <i>The applicant comments that patient-focused drug development studies show that patients describe a preference for infrequent (6 monthly) over more frequent (2 weekly) injections to lower cholesterol over and above statins (data on file as per applicant). In addition, patients reportedly believe that such preference will drive improved adherence and preference. However, the applicant has no direct evidence to prove the veracity of these assertions.</i>	Module 2.5, Section 6.3 in Clinical Overview of applicant's submission
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Hypercholesterolemia, specifically an increase in low-density lipoprotein cholesterol (LDL-C) levels, is a major modifiable risk factor for the development of atherosclerosis and atherosclerotic cardiovascular disease (ASCVD). ASCVD comprises a variety of diseases with similar pathophysiology (atherosclerosis) of the heart and blood vessels, including coronary heart disease (CHD), acute coronary syndrome (ACS), and stroke.

ASCVD continues to be the leading cause of death and disability worldwide.¹² On the basis of NHANES 2013 to 2016 data, the prevalence of CVD (comprising CHD, HF, stroke, and hypertension) in adults ≥ 20 years of age is 48% overall (121.5 million in 2016) and increases with age in both males and females. CVD prevalence excluding hypertension (CHD, HF, and stroke only) is 9% overall (24.3 million in 2016).¹ In the United States, heart disease is the leading cause of death for men and women, including most racial and ethnic groups.¹³ Approximately 647,000 Americans die from heart disease each year.¹⁴ The average annual direct and indirect cost of CVD and stroke in the United States was an estimated \$351.2 billion in 2014 to 2015.¹⁵

Many large-scale, randomized trials have shown that reducing LDL-C levels with statins reduces the risk of CHD, with a direct relationship between LDL-C levels and CHD events. One meta-analysis concluded that lowering LDL-C by 1 mmol/L (38.7 mg/dL) for 4 to 5 years reduces the risk of major vascular events (non-fatal myocardial infarction, coronary death, ischemic stroke, or coronary revascularization) by 22%¹⁶. Several trials have shown that statin regimens using higher doses or more-potent agents, which both yield greater reductions in LDL-C, reduce the risk of vascular events more than less-intensive

¹² Foreman KJ, Marquez N, Dolgert A et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet*. 2018; 392: 2052-90.

¹³ Heron, M. Deaths: Leading causes for 2017. *National Vital Statistics Reports*;68(6). Accessed May 1, 2020.

¹⁴ <https://www.cdc.gov/heartdisease/facts.htm>. Accessed May 1, 2020.

¹⁵ Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics—2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–528.

¹⁶ Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. *Lancet* 2010;376:1670-1681.

statin regimens in patients at very high cardiovascular risk.^{17,18,19,20} More recently, CV outcomes trials of the two approved monoclonal antibody PCSK9 inhibitors, alirocumab and evolocumab, also demonstrated that reducing LDL-C levels with these agents led to a reduction in risk of CV events.^{21,22}

A CVOT with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering²³. (b) (4)

Other agents, namely colesvelam and bempedoic acid, may be used as adjuncts to statins, PCSK9 inhibitors, and ezetimibe, but the incremental effects on CV outcomes are uncertain.

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease. For LDL-C lowering therapies, in the absence of cardiovascular outcomes data, contemporary decisions to approve novel LDL-lowering therapies are influenced by the direction and magnitude of drug-induced changes in LDL-C, the mechanism of action of the novel agent, as well as the effects of the drug on other lipid parameters, markers of cardiometabolic risk and any evidence for off-target toxicity. In the case of the monoclonal antibody PCSK9 inhibitors, evolocumab and alirocumab, approval was granted in 2015, prior to the completion of their cardiovascular outcomes trials (CVOTs). However, the initial indication was restricted to a higher CV risk population, namely as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL-C. The indication was broadened after the successful completion of their CVOTs, which incorporated

¹⁷ Cannon CP, Braunwald E, McCabe CH, Rader D J, Rouleau JL, Belder R et al., for the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators*. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. *N Engl J Med* 2004; 350(15): 1495-504.

¹⁸ LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC et al; Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352:1425–35.

¹⁹ Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I et al., on behalf of the Incremental Decrease in End Points through Aggressive Lipid Lowering Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. The IDEAL study: a randomized controlled trial. *JAMA* 2005; 294:2437– 45. Erratum in: *JAMA*. 2005 Dec 28;294(24):3092.

²⁰ Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol*. 2006;48(3):438-45.

²¹ Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med* 2018; 379: 2097-107.

²² Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713-22

²³ Cannon, CP, Blazing, MA, Giugliano, RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.

important safety assessments, demonstrating CV benefit associated with LDL-C reduction, and reassuring long-term safety data.

ORION-4 (Study CTSU-MDCO-PCS-17-01), titled “A Double-blind, Randomized, Placebo-controlled Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People with Atherosclerotic Cardiovascular Disease”, an ongoing cardiovascular outcome trial with inclisiran, is being conducted in the hyperlipidemic (non-HoFH) population but results will not be known for several years. The phase 3 HPS-4/TIMI 65/ORION-4 trial (NCT03705234) will be conducted at approximately 180 clinical sites in the UK and the US. Approximately 15,000 participants aged 55 years or older with atherosclerotic cardiovascular disease will be randomized between inclisiran sodium 300 mg and matching placebo (given by subcutaneous injection on the day of randomization, at 3 months and then every 6-months) in a 1:1 ratio for a planned median duration of about 5 years. The US centers are planned to enroll approximately 3,000 of the 15,000 subjects in this trial. All participants will be followed until death, withdrawal of consent for follow-up, or the scheduled end of the study (even if they have a study outcome or discontinue study treatment for any reason). The estimated primary completion date is December 2024,²⁴ with results expected by 2025.

2.2. Analysis of Current Treatment Options

Current treatment guidelines emphasize reducing the risk of atherosclerotic cardiovascular disease (ASCVD) through lipid management, based on an individualized approach which considers a patient’s overall risk for a CV event. In primary prevention, this is based on an ASCVD risk score and additional risk factors.

Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on risk category. Low-intensity statins are not recommended for any population. Ezetimibe and/or PCSK9 inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk (secondary prevention and HeFH) who require additional LDL-C reduction.

Statin reduce LDL-C by 30% to 60% depending on the statin intensity. PCSK9 inhibitors lower LDL-C by an additional 50% to 70%. Ezetimibe lowers LDL-C by an additional 15% to 20%. Other drug categories, such as fibrates or niacin, are not considered mainstays of LDL-C lowering therapy due to mild LDL-lowering ability and clinical trial data that shows no benefit in reducing

²⁴ <https://clinicaltrials.gov/ct2/show/NCT03705234>

CV morbidity or mortality among patients already treated with a statin.^{25,26}

The following drugs are currently approved for patients with primary hyperlipidemia or HeFH:

- Statins (HMG-CoA reductase inhibitors) and statin fixed-dose combinations (rosuvastatin, atorvastatin, simvastatin, pitavastatin, lovastatin, fluvastatin, pravastatin, atorvastatin/ezetimibe, simvastatin/ezetimibe);
- Cholesterol absorption inhibitor (ezetimibe);
- Peroxisome proliferator receptor alpha (PPAR- α) activators (fenofibric acid, fenofibrate, choline fenofibrate)
- Bile acid sequestrants (cholestyramine, colestipol, colesevelam);
- Niacin extended-release; and
- PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitors (alirocumab and evolocumab)
- Adenosine triphosphate-citrate lyase (ACL) inhibitor (bempedoic acid and bempedoic acid/ezetimibe)

Statins are considered the standard-of-care for lowering LDL-C with the goal of reducing CV risk. The FDA-approved LDL-C-lowering therapies that are indicated to treat patients with hyperlipidemia when administered in addition to background statin therapy include colesevelam, ezetimibe, simvastatin/ezetimibe, atorvastatin/ezetimibe, evolocumab, alirocumab, bempedoic acid and bempedoic acid/ezetimibe (designated by bold font in table below).

²⁵ AIM-HIGH Investigators, W.E. Boden, J.L. Probstfield, T. Anderson, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*, 365 (2011), pp. 2255-2267

²⁶ The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005.366:1849-1861.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Indications
Statins (HMG-CoA inhibitors)						
Lovastatin (Mevacor, Altoprev) NDA (21316)	Adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb)	1987 2002	20, 40, and 60 mg tablets, PO once daily	60 mg dose: mean % change in LDL-C: -41%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of MI, revascularization procedures, and angina in patients without CHD, but with multiple risk factors Slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower Total-C and LDL-C
Simvastatin (Zocor) NDA 19766	Adjunctive therapy to diet to reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (HeFH) and mixed dyslipidemia	1991	5, 10, 20, 40 and 80 mg tablets, PO once daily	40 mg dose: mean % change in LDL-C: -31% 80 mg dose: mean % change in LDL-C: -36%	Skeletal muscle effects (myopathy/rhabdomyolysis) with increased risk with 80 mg dose, liver enzyme abnormalities, hypersensitivity	Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia (HoFH) Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with HeFH after failing an adequate trial of diet therapy
Pravastatin (Pravachol) NDA 19898	Adjunctive therapy to diet to reduce elevated Total-C,	1991	20, 40 and 80 mg tablet; PO once daily	80 mg dose: mean % change in	Skeletal muscle effects (myopathy/	Reduce the risk of MI, revascularization, and cardiovascular mortality in hypercholesterolemic patients without clinically evident CHD

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	LDL-C, ApoB, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia			LDL-C: -37%	rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of total mortality by reducing coronary death, MI, revascularization, stroke/TIA, and the progression of coronary atherosclerosis in patients with clinically evident CHD Reduce elevated serum TG levels in patients with hypertriglyceridemia Treat patients with primary dysbetalipoproteinemia who are not responding to diet Treat children and adolescent patients ages 8 years and older with HeFH after failing an adequate trial of diet therapy
Fluvastatin (Lescol, Lescol XL) NDA 20261, 21192	Adjunctive therapy to diet to reduce elevated TC, LDL-C, Apo B, and TG and increase HDL-C in adult patients with primary hyperlipidemia and mixed dyslipidemia	1993	20, 40 and 80 mg tablet; PO once daily	80 mg dose: mean % change in LDL-C: -35%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce elevated TC, LDL-C, and Apo B levels in boys and postmenarchal girls, 10 to 16 years of age, with HeFH after failing an adequate trial of diet therapy Reduce the risk of undergoing revascularization procedures in patients with clinically evident CHD Slow the progression of atherosclerosis in patients with CHD
Atorvastatin (Lipitor) NDA 20702	Adjunct therapy to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (HeFH and	1996	Tablets: 10, 20, 40, and 80 mg PO once daily	80 mg dose: mean % change in LDL-C: -60%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with

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	nonfamilial) and mixed dyslipidemia					CHD Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia Reduce total-C and LDL-C in patients with HoFH Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH after failing an adequate trial of diet therapy
Rosuvastatin (Crestor) NDA 21366	Adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDLC in patients with primary hyperlipidemia and mixed dyslipidemia	2003	5, 10, 20 and 40 tablets, PO once daily	40 mg dose: mean % change in LDL-C: -63%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Patients with hypertriglyceridemia Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) Patients (ages 7 to adult) with HoFH to reduce LDL-C, total-C, and ApoB Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C Pediatric patients 8 to 17 years of age with HeFH to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy Risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors
Pitavastatin (Livalo) NDA 22363	Adjunctive therapy to diet to reduce elevated TC, LDL-C, Apo B, TG, and to	2009	Tablets: 1 mg, 2 mg, and 4 mg; PO once daily	4 mg dose: mean % change in LDL-C: -43%	Skeletal muscle effects (myopathy/rhabdomyolysis),	none

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	increase HDL-C in patients with primary hyperlipidemia or Mixed dyslipidemia				liver enzyme abnormalities, hypersensitivity	
Simvastatin /ezetimibe (Vytorin) NDA 21687	Adjunctive therapy to diet to reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (HeFH and non-familial) hyperlipidemia or mixed hyperlipidemia	2004	Tablets (ezetimibe mg/simvastatin mg): 10/10, 10/20, 10/40, 10/80; PO once daily	10/80 mg dose: mean % change in LDL-C: -60%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments
Atorvastatin/ezetimibe (Liptruzet) NDA 200153	Adjunctive therapy to diet to reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (HeFH and non-familial) hyperlipidemia or mixed hyperlipidemia	2013	Tablets (ezetimibe mg/atorvastatin mg): 10/10, 10/20, 10/40, 10/80 PO once daily	10/80 mg dose: mean % change in LDL-C: -61%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments
Bile acid sequestrants						
Colestipol	Adjunctive therapy	1977	5-30g PO		May reduce	none

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hydrochloride (Colestid granule, Colestid tablet) NDA 17563	to diet for the reduction of elevated serum total and LDL-C in patients with primary hypercholesterolemia who do not respond adequately to diet		once daily or in divided doses		absorption of folic acids and fat-soluble vitamins such as A, D and K. Increased bleeding, constipation.	
Cholestyramine (Questran, Prevalite) NDA 16640, ANDA 73263	Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet	1977 1996	8 to 24 grams anhydrous cholestyramine resin PO divided into two doses	mean reduction in LDL-C: -10%	Increased bleeding tendency due to hypoprothrombinemia associated with Vitamin K deficiency. Constipation.	Relief of pruritus associated with partial biliary obstruction
Colesevelam Hydrochloride (Welchol tablet, Welchol for oral suspension) NDA 22362	Adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with a statin	2000	Tablets 625 mg; 3.75 g pwd pkts.; 3.75 g PO once daily	3.75 g dose: mean % change in LDL-C: -15%	May reduce absorption of folic acids and fat-soluble vitamins such as A, D and K. Constipation.	Reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH as monotherapy or in combination with a statin after failing an adequate trial of diet therapy Improve glycemic control in adults with type 2 diabetes mellitus
Peroxisome proliferator receptor alpha (PPAR-α) activators						
Fenofibric acid	Adjunct to diet to reduce elevated	1993	Oral Tablets: 35 mg and	105 mg dose: mean	Skeletal muscle effects	To reduce TG in adult patients with severe hypertriglyceridemia

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(Fibracor) NDA 22418	TC, LDL-C, TG and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia		105 mg, PO once daily	% change in LDL-C: -21%	(myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	
Fenofibrate (Tricor, Antara, Triglide, Lipofen, Fenoglide) NDA 21203	Adjunct to diet to reduce elevated LDL-C, Total-C, TG and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia	1993	Capsules, 48-160 mg/day, PO once daily	160 mg dose: mean % change in LDL-C: -21%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	To reduce TG in adult patients with severe hypertriglyceridemia
Choline fenofibrate (Trilipix) NDA 22224	Adjunct to diet to reduce elevated LDL-C, Total-C, TG and Apo B, and to increase HDL-C in patients	2008	Tablets: 45 and 135 mg; PO once daily	135 mg dose: mean % change in LDL-C: -21%	Skeletal muscle effects (myopathy/rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	To reduce TG in patients with severe hypertriglyceridemia
PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitors						
Evolocumab (Repatha) PCSK9 inhibitor antibody BLA 125522	Adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with	2015	140 mg SC every 2 weeks OR 420 mg SC injection once monthly	140 mg SC every 2 weeks: mean % change in LDL-C: -55% to -71%	Allergic reactions (angioedema, rash, urticaria)	To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C

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	primary hyperlipidemia (including HeFH) to reduce LDL-C					
Alirocumab (Praluent) PCSK9 inhibitor antibody BLA 125559	Adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C	2015	75 to 150 mg SC injection every 2 weeks OR 300 mg SC injection once monthly	150 mg SC injection every 2 weeks: mean % change in LDL-C: -58%	Allergic reactions (pruritus, rash, urticaria) and serious hypersensitivity reactions	To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease
Other Therapies						
Extended release niacin (Niaspan) NDA 20381	To reduce elevated TC, LDL-C, Apo B and TG, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia	1997	Tablets: 500, 750, 1000 mg; Dose range: 500 mg to 2000 mg PO once daily	3000 mg dose: mean % change in LDL-C: -14%	Rhabdomyolysis, liver dysfunction, hypersensitivity reactions	To reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia In combination with a bile acid binding resin: - slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hyperlipidemia - as an adjunct to diet to reduce elevated TC and LDL-C in adult patients with primary hyperlipidemia To reduce TG in adult patients with severe hypertriglyceridemia
Ezetimibe	Adjunct to diet to	2002	10 mg tablet	10 mg dose:	Elevations in	Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C

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(Zetia) Intestinal cholesterol/ phytosterol absorption inhibitor NDA 21445	reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with a statin		PO once daily	mean % change in LDL-C: -18%	liver enzymes, myopathy/ rhabdomyolysis	in patients with mixed hyperlipidemia in combination with fenofibrate Reduce elevated total-C and LDL-C in patients with HoFH, in combination with atorvastatin or simvastatin Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)
Bempedoic acid (Nexleto) adenosine triphosphatase (ACL) inhibitor NDA 211616	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C.	2020	180 mg tablet PO once daily	180 mg dose: mean % change in LDL-C: -17 to -18%	Hyperuricemia, gout, tendon rupture, musculoskeletal side effects, elevations in liver enzymes	
Bempedoic acid (Nexlizet) ACL inhibitor and Intestinal cholesterol/ phytosterol absorption inhibitor NDA 211617	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C	2020	180 mg bempedoic acid/10 mg ezetimibe tablet PO once daily	180 mg/10 mg dose: mean % change in LDL-C: -38%	Hyperuricemia, tendon rupture, musculoskeletal side effects, elevations in liver enzymes	

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Source: Individual drug prescribing information

Note: Bold text indicates FDA-approved LDL-C-lowering therapies that are indicated to treat patients with hyperlipidemia when administered in addition to background statin therapy

Abbreviations: ACL=adenosine triphosphate-citrate lyase; HeFH=heterozygous familial hypercholesterolemia; HoFH= homozygous familial hypercholesterolemia; PO=by mouth

(<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Inclisiran is a new molecular entity (NME) and it is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

Excerpts of Pre-submission Regulatory History:

December 17, 2015: Pre-IND Meeting:

The clinical team provided comments regarding safety monitoring for future trials, such as: assess for any potential relatedness of new-onset diabetes to ALN-PCSSC use; evaluate for the incidence and severity of injection site reactions, hypersensitivity, and immunogenicity; subjects should be on maximally tolerated statin therapy; subjects who achieve two consecutive LDL-C values < 25 mg/dL should be monitored more closely; neurological examinations should be incorporated into the protocol for all subjects; all subjects need to be followed until the drug is no longer significantly pharmacodynamically active; and include older subjects in the trials. (b) (4)

October 7, 2016: FDA Request for Information regarding revusiran

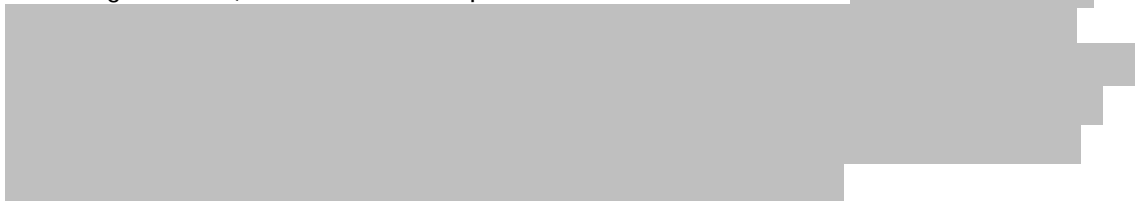
FDA request for information regarding the relevance of the findings from the Alnylam revusiran program. Alnylam Pharmaceuticals, Inc. had recently announced discontinuation of development of revusiran, another investigational RNA interference (RNAi) therapeutic that was being developed for the treatment of hereditary ATTR amyloidosis with cardiomyopathy (hATTR-CM). According to their press release, an imbalance of mortality and peripheral neuropathy were noted in the Phase 3 program. FDA requested updated safety data for ALN-PCSSc, including an assessment for neuropathy, lactic acidosis, myopathy, liver-related adverse events/chemistries as well as any potential safety signals identified to date. Response with the requested information was submitted on October 24, 2016 (S-0022).

April 24, 2017: FDA EOPII Meeting minutes

FDA provided written feedback following the April 6, 2017 EOPII meeting. The meeting topics centered on alignment of the key aspects of the proposed Phase III program. Some clinical recommendations included:

- (b) (4)
For the populations the applicant has identified, the majority of subjects should be on

high-intensity statin therapy, such as atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg.

- Eligibility criteria should be as inclusive as possible. Recommend including subjects with history of hemorrhagic stroke; liberalize AST/ALT cut-offs; include patients with stable heart failure, especially those with ischemic cardiomyopathy; if the data from the renal impairment study (ORION-7) support it, include patients with eGFR <30 mL/min/1.73m² into all Phase III trials.
- The eligibility criteria included a history of ASCVD or ASCVD-risk equivalents. We advised the applicant that with our current regulatory approach to LDL-C-lowering drugs, the (b) (4) indication for inclisiran would likely be similar to that granted for evolocumab and alirocumab (i.e., as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C) unless there are positive results from a CVOT. (b) (4)

- Assessments and pre-specified definitions for new-onset diabetes or worsening of pre-existing diabetes mellitus should be detailed in the protocols.
- The neurologic exams should be comprehensive and include peripheral sensory and motor evaluation, and an assessment of gait, pain, position, strength and reflexes.
- Size of the safety database at the time of NDA submission: At least 1500 patients should be exposed to inclisiran for approximately 18 months, in order to include the safety data from at least 4 injections. The vast majority of these subjects should be exposed to the to-be-marketed doses and formulation of inclisiran in double-blind, controlled trials. The long-term experience in controlled trials needs to include a heterogeneous population with respect to demographics, high- and moderately-high risk for CVD, concomitant high- and moderate-high intensity statin therapy, diabetes, established cardiovascular disease, and CHF or ischemic cardiomyopathy to ensure sufficient representation from the types of patients expected to use inclisiran if approved.
 - Of note, the applicant has submitted in the Controlled Phase III Studies pool, 1822 subjects treated with placebo and 1833 with inclisiran, with 1666 receiving all 4 doses of inclisiran. This meets and exceeds what the FDA requested at the EOP II meeting.
- Detailed recommendations were given regarding the (b) (4) ORION-4 CVOT, which are not relevant for this submission.

October 26, 2017: FDA feedback on Phase III protocols

FDA provided feedback on the draft Phase III protocols, SAP and dose regimen rationale. Response and revised protocols addressing FDA feedback submitted on November 21, 2017 (S-0086) and November 30, 2017 (S-0087). Some of the issues raised include:

- In ORION-9 and ORION-10, in addition to being on a maximally tolerated dose of statin, the majority of subjects with HeFH should also be on chronically administered ezetimibe.
- Subjects with New York Heart Association (NYHA) class III heart failure are excluded from the trial; recommend including these patients in the phase 3 trials and CVOT, since patients with NYHA class III ischemic cardiomyopathy would likely be treated with LDL-C-lowering therapy.
- In ORION-9, ORION-10, and ORION-11, one of the secondary endpoints is “mean maximum reduction in LDL-C levels”. [REDACTED] (b) (4) [REDACTED] providing an average of maximum reductions would not accurately reflect the effect of the drug throughout the dosing interval.
- The percentage change in LDL-C from baseline to Day 510 is the primary endpoint in this study. The time adjusted % change in LDL-C from baseline between Day 90 and Day 540 will be considered a secondary endpoint.
- For serious adverse events and adverse events of special interest, FDA recommends prospectively planned analyses that compare treatment groups with respect to risk, e.g., with a rate ratio, risk difference, hazard ratio, or relative risk, along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison (no hypothesis testing is necessary).

December 8, 2017: FDA feedback on ORION-10 final protocol

FDA recommended that if patients discontinue study medication to initiate a protocol-prohibited lipid-lowering-therapy (e.g., an approved PCSK9 inhibitor), collect the reason that the new therapy was initiated. Response and feedback incorporated into the ORION-10 protocol amendment #1 submitted on January 16, 2018 (S- 0100)

April 19, 2019: FDA feedback on format and content of the NDA

FDA recommendations included:

- In the ISS, Adverse Event (AE) tables should provide analyses by multiple levels of the MedDRA hierarchy, i.e., System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), and preferred term (PT).
- Include data tables of adverse events of special interest (AESIs), including injection site reactions, hypersensitivity reactions, immune-mediated reactions, new onset diabetes mellitus, and cancer.
- ISRs: In the safety tables, provide a row that includes the number and percentage of subjects that experienced an injection site reaction (ISR) using the MedDRA High Level Term: ‘Injection site reaction’; also breakdown the HLT by the relevant PTs so that no potential ISRs are missed.

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- Provided feedback on what should be included in the narrative summaries for deaths and adverse events leading to drug or study discontinuation.
- Provide the minutes of all DSMB and steering committee meetings. Include a chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

September 13, 2019: FDA feedback on Integrated SAP and ORION-11 SAP

FDA provided feedback on the classification of high intensity statin (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg) and definition of Hy's Law.

3.3. Foreign Regulatory Actions and Marketing History

Inclisiran is not authorized for marketing in any country. We asked the applicant to provide, at NDA submission, the important regulatory actions and substantive communications in other countries. The applicant provided a summary of meeting minutes from the European Medicines Agency in application Section 1.6.3 Correspondence Regarding Meetings: EMA Scientific Advice.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

According to Dr. Cynthia Kleppinger's Office of Scientific Investigations (OSI) clinical inspection summary (in DARRTS dated 9/24/2020; Reference ID: 4675108), the inspection for this NDA consisted of two domestic clinical investigator sites and one foreign clinical investigator site in addition to the NDA sponsor (Novartis Pharmaceuticals Corporation in East Hanover, NJ). As Dr. Kleppinger notes in her review, the COVID-19 pandemic significantly limited the Office of Regulatory Affairs' ability to conduct onsite good clinical practice (GCP) inspections; planned foreign onsite inspections could not be completed. At the inspection of Novartis Pharmaceuticals, the FDA inspector observed that there were 4 subjects in ORION-9, 23 subjects in ORION-10, and 34 subjects in ORION-11 that did not have an in-person EOS visit, and are presumed to have not been given the terminal EOS ECG. This finding is not expected to change the overall results of this application as ECG findings were not an issue with inclisiran and the number of subjects potentially missing the EOS ECG across the three trials, involving a total of 3660 subjects, is small. In conclusion, based on the inspections of the two domestic clinical sites, the sponsor, and the remote regulatory assessment of one foreign site, the inspectional findings support the validity of data as reported by the sponsor under this NDA.

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Reviewer Note: One investigator (Dr Captain; Site (b) (6)) was terminated from the study due to protocol and GCP non-compliance. This site randomized (b) (6) in ORION-9; the results for (b) (6) are not expected to impact the overall results.

4.2. Product Quality

The drug substance, inclisiran sodium, is a synthetic, chemically modified double-stranded small interfering ribonucleic acid (siRNA) oligonucleotide, covalently connected to a ligand containing three N-acetylgalactosamine (GalNAc) residues (to facilitate uptake by hepatocytes). The sense strand contains 21 nucleotides and the antisense strand contains 23 nucleotides; it was designed to match the human messenger ribonucleic acid transcripts for proprotein convertase subtilisin kexin type 9 (PCSK9). The manufacturer of the drug substance is (b) (4). FDA concluded that the drug substance information is adequate to control the identity, purity, strength, and quality of the drug substance used for manufacturing the drug product. The proposed drug substance specifications are consistent with batches used in clinical, nonclinical, and registration stability studies (for additional details, refer to Dr. Jensen's CMC review dated 7/16/2020 in Panorama).

The inclisiran injection drug product is a single dose sterile, preservative-free, clear, and colorless to pale yellow solution in a prefilled syringe (PFS). Each PFS unit contains 284 mg inclisiran (equivalent to 300 mg inclisiran sodium salt) in 1.5 mL water for injection. It may include sodium hydroxide and/or phosphoric acid for pH adjustment to target 7. FDA concluded that the proposed specification is adequate to support the quality of the proposed product (for additional details, refer to Dr. Carver's drug product review dated 9/4/2020 in Panorama).

The composition of inclisiran injection used throughout all clinical development was the same and the applicant proposes the same for marketing. Initially, a 2 mL vial (batches manufactured at (b) (4)) was filled to deliver either 100 mg (0.5 mL) of inclisiran sodium or 300 mg (1.5 mL) of inclisiran sodium. Subsequently, a prefilled syringe (batches manufactured at (b) (4)) delivering the identical 300 mg of inclisiran sodium (1.5 mL) was developed as the commercial presentation and was used in the second half (doses 3 and 4) of one of the Phase III clinical trials (ORION-10). The drug product used in the phase 3 clinical trials is the same as the 'to be marketed' product.

The applicant proposes a prefilled syringe containing 300 mg inclisiran sodium solution, transported and stored at room temperature, and administered by a healthcare professional, as the to-be-marketed presentation.

The OPQ recommends a complete response (CR) action due to Office of Pharmaceutical Manufacturing Assessment (OPMA) recommending a 'withhold approval' because of deficiencies related to the (b) (4) drug product manufacturing site in (b) (4) (refer to CDER Clinical Review Template

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review by Dr. Ramaswamy, in DARRTS dated 10/1/20; Reference ID: 4679598 and Dr. Janoria's facility review in Panorama dated 9/30/2020). This CR action will allow for (b) (4) and Novartis to complete studies and provide updated accurate information to the NDA for assessment.

Dr Ramaswamy concludes that there currently are no outstanding deficiencies related to the drug substance, drug product, process, microbiology, environmental analysis, and container/carton label sections of the NDA. Due to outstanding manufacturing facility related deficiencies, OPQ overall recommendation for NDA 214012 is a complete response action.

4.3. Clinical Microbiology

The applicant states that Inclisiran Injection is a preservative-free sterile solution presented in a 2.25 mL prefilled syringe for single use. Inclisiran Injection is tested for endotoxin and container closure integrity on stability throughout the shelf-life, which assures the microbiological quality of the drug product.

4.4. Nonclinical Pharmacology/Toxicology

Inclisiran was administered via SC injection in all toxicology studies, consistent with the clinical route of administration. The pivotal toxicology studies involved once monthly dosing which is more frequent than the phase 3 clinical trials where dosing was on Day 1, Day 90, and then every 6 months. The nonclinical toxicology repeat dose studies were 4 weeks, 15 weeks and 29 weeks duration in rats and 4 weeks, 15 weeks and 40 weeks duration in monkeys. As described in the applicant's submission, these studies included analysis of inclisiran in plasma and in tissues including the liver which is the target organ of effect, the kidney which is the main organ of elimination of inclisiran from plasma, and the heart, a non-target tissue. The pharmacology/toxicology team (refer to review by Dr. Braithwaite, in DARRTS dated 9/30/20; Reference ID: 4678631) confirms that inclisiran was well-tolerated in repeat dose studies up to 29-weeks of duration in rats and 40-weeks of duration in monkeys.

Because inclisiran will be co-administered with statins in the real world setting and in clinical trials, a study was conducted in monkeys to determine the potential toxicity of administering inclisiran in combination with atorvastatin. When both atorvastatin and inclisiran were administered together, further decreases (compared to monotherapy of either agent) in cholesterol, LDL and triglycerides were seen, but were less than additive. Maximal reduction of PCSK9 was seen in monkeys treated with inclisiran alone. This may be due to the finding that statins cause an increase in PCSK9 levels when compared to pretreatment values and likely accounts for the reduced degree of PCSK9 lowering compared to inclisiran treatment alone. The FDA pharmacology/toxicology team confirms that no new or exacerbated toxicity were observed when inclisiran was administered in combination with atorvastatin for 85 days. The NOAEL in the pivotal rat and monkey studies were 250 mg/kg/28 days (8-fold the 300 mg

recommended clinical dose based on BSA comparison/dose) and 300 mg/kg/28 days (19- fold the 300 mg recommended clinical dose based on BSA comparison/dose), respectively.

The development of anti-drug antibodies (ADA) was evaluated in repeat dose studies in rats and monkeys. Inclisiran did not stimulate proinflammatory cytokines in mice or monkeys, or activate complement in monkeys. There were some incidences of the development of ADA, but they were generally low titer responses in a small number of animals, were not dose related, and did not impact PCSK9 or LDL-C parameters. Dr. Braithwaite notes that delayed or absent IgM immune response to KLH antigen were observed in monkeys at doses ≥ 100 mg/kg/28 days (16-fold the 300 mg recommended clinical dose based on BSA comparison/dose). Reduced IgG response to KLH antigen was observed several days after immunization at the 300 mg/kg/28-day dose (19- fold the 300 mg recommended clinical dose based on BSA comparison/dose). However, these findings were reversible.

Development and reproductive toxicity studies were conducted in rats and rabbits. Inclisiran did not show positive signals for selective reproductive toxicity in fertility and early embryonic development studies conducted in rats, embryo-fetal development studies conducted in rats and rabbits, and pre- and postnatal development study conducted in rats. Dr. Braithwaite confirms that inclisiran did not have an adverse impact on reproduction or development in rats and rabbits.

Genotoxicity studies were conducted including a bacterial mutagenicity assay, an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assay in rats. Dr. Braithwaite confirms that inclisiran tested negatively for genotoxicity in a standard battery of OECD-compliant tests and did not promote neoplastic transformations in TgRasH2 mice or Sprague Dawley rats.

The applicant's off-target analysis involved a bioinformatics search against the human transcriptome and was used to identify a set of transcripts based on partial sequence homology to PCSK9 that would potentially be inhibited by inclisiran. Twenty genes were identified whose expression may be impacted by inclisiran. To measure off-target inhibition, the response of endogenously expressed transcripts to inclisiran was determined by quantitative polymerase chain reaction in a dose response study in Hep3B cells. The results showed a ≥ 45 -fold difference between the "on-target" inhibition of PCSK9 and the inhibition of any of the predicted off-target transcripts, supporting the specificity of inclisiran for PCSK9.

The pharmacology/toxicology team recommends approval of inclisiran for the indicated population.

4.5. Clinical Pharmacology

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The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data submitted under NDA 214012 and recommends approval (refer to the Clinical Pharmacology review by Sang Chung, Ph.D., Justin Earp, Ph.D., and Jayabharathi Vaidyanathan, Ph.D., in DARRTS dated 10/13/2020; Reference ID: 4684702). Important recommendations and comments from their review are summarized below:

Dosing in patient subgroups

There was an increase in inclisiran exposure in patients with severe renal impairment (2.5-fold) or moderate hepatic impairment (2.1-fold). However, the pharmacodynamic markers including PCSK9 and LDL-C changes in these patients were comparable to those with normal renal or hepatic function.

- Renal impairment: No dose adjustment is necessary in patients with mild, moderate or severe renal impairment. Inclisiran was not studied in patients with end stage renal disease.
- Hepatic impairment: No dose adjustment is needed in patients with mild or moderate hepatic impairment. Inclisiran was not studied in patients with severe hepatic impairment.
- Other demographics: No dose adjustments are needed for differences in age, body weight, sex, or race.

The to-be-marketed drug product (formulation and device) was used in the pivotal and supportive Phase 3 trials.

Mechanism of action

Inclisiran is a chemically modified double-stranded 21-23mer small interfering RNA, conjugated on the sense strand with triantennary GalNAc to facilitate uptake by hepatocytes. In hepatocytes, the antisense strand is incorporated in the RNA-induced silencing complex (RISC) and directs catalytic breakdown of mRNA for PCSK9, thereby inhibiting translation of PCSK9 protein. The reduction of intrahepatic PCSK9 levels increases LDL-C receptor recycling and expression on the hepatocyte cell surface, leading to an increase in LDL-C uptake and lowering LDL-C levels in the systemic circulation.

Pharmacokinetics

Absorption

At the proposed inclisiran dose of 284 mg, the T_{max} was approximately 4 hours post dose with a mean C_{max} of 509 ng/mL. Concentrations reached undetectable levels after 24 to 48 hours post dosing.

Distribution

Inclisiran is 87% bound to human plasma proteins at clinically relevant plasma concentrations

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(0.5 µg/mL, mean C_{max} following 300 mg SC injection). As shown in nonclinical studies, inclisiran distributes primarily into the liver, which is the target organ of effect, followed by the kidney. In animals, elimination of radioactivity from liver was slow, and the half-life for all tissues were greater than 190 hours.

Metabolism

Inclisiran is extensively metabolized by non-specific nucleases to shorter nucleotides of varying length.

Elimination

The clin-pharm team states that the apparent terminal half-life is approximately 7 hours (range 5-7 h) following 300 mg dose. Approximately 17% (range 9% - 31%) of dose is eliminated as unchanged inclisiran in urine. Renal clearance of inclisiran is reduced with decreasing renal function.

Drug-drug interactions

Inclisiran is not a substrate for and is not an inducer or inhibitor of CYP450 enzymes or common drug transporters. Thus, inclisiran exposure is unlikely to be influenced by other drugs. In addition, inclisiran does not influence drug metabolizing enzymes or transporters, and is unlikely to be the source of drug interactions.

- Inclisiran is not an in vitro inhibitor or inducer of cytochrome P450 (CYP450) enzymes. The applicant tested inclisiran's ability to inhibit CYP450 enzymes using human liver microsomes. Inclisiran reportedly did not exhibit direct or time dependent inhibition towards CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5, with half maximal inhibitory concentrations. No induction of CYP450 enzymes was observed at inclisiran concentrations up to 37-fold above the clinical 300 mg dose C_{max} .
- Inclisiran is not an in vitro substrate or inhibitor of common drug transporters including organic anion transporters (OAT1, OAT3), organic cation transporters (OCT1, OCT2, OCT3), organic anion transporting polypeptides (OATP1B1, OATP1B3), multi-drug and toxin extrusion proteins (MATE1, MATE2k), multi-drug resistance 1 (MDR1), bile salt export pump (BSEP) and the breast cancer resistance protein (BCRP) transporter.

Inclisiran PK was not significantly impacted by the co-administration of statin drugs in one small study. In study ALN-PCCS-001, inclisiran PK was compared between groups of subjects who were treated with inclisiran alone (N = 3 to 5), and inclisiran in combination with statins (N=6). Subjects on statins had similar inclisiran exposures as subjects not on statins, both on the first and last dose of inclisiran administration.

Statin PK (atorvastatin and rosuvastatin) was not significantly impacted by the co-administration of inclisiran based on sparse statin PK data collected in ORION-10. The PK of statins in subjects in the inclisiran group was similar to the PK of statins in the placebo group.

In conclusion, there is a low likelihood of clinically significant drug-drug interactions with inclisiran.

Pharmacodynamics

Inclisiran is cleared from plasma relatively quickly but has a prolonged PD effect on LDL-C and PCSK9 levels. As PK and PD profiles were not temporally linked, dose selection was based on PD findings and PD modeling, rather than PK. Refer to Section 7.1.4 for additional details.

Hepatic Impairment

ORION-6 was a Phase I, open-label study to evaluate the PK, PD, safety, and tolerability of a single dose of inclisiran administered SC in subjects with mild to moderate hepatic impairment (based on Child-Pugh assessment) compared with matched subjects with normal hepatic function. Subjects with Child-Pugh Class A (5 to 6 points) and Class B (7 to 9 points) were classified as mild and moderate hepatic impairment, respectively. Subjects with severe hepatic impairment were not studied.

Twenty-eight subjects were enrolled in the study: 10 subjects with mild hepatic impairment, 6 subjects with moderate hepatic impairment, and 12 subjects with normal hepatic function.

Pharmacokinetics: Inclisiran plasma exposures increased in subjects with moderate hepatic impairment. Inclisiran plasma concentrations reached maximum concentrations approximately 5 hours to 6 hours after dosing, followed by declining concentrations until undetectable levels were observed after 48 hours in the majority of subjects. The C_{max} geometric mean ratios (90% CI) between subjects with mild and moderate hepatic impairment compared to subjects with normal HF were 1.1 (0.8, 1.5) and 2.1 (1.5, 3.0), respectively. The AUC_{0-inf} geometric mean ratios (90% CI) were 1.3 (1.1, 1.7) and 2.0 (1.6, 2.6) for subjects with mild and moderate hepatic impairment, respectively.

The mean baseline LDL-C levels were 133, 97, and 160 mg/dL in subjects with normal HF, mild and moderate hepatic impairment, respectively. All groups had decreases in LDL-C compared to baseline. The greatest decreases were observed in subjects with mild hepatic impairment and normal hepatic function. LDL-C percentage changes from baseline on Day 60 were 52%, 53%, and 40% in subjects with normal HF, mild and moderate hepatic impairment, respectively. On Day 180, LDL-C levels were reduced by 40%, 37%, and 24% for subjects with normal HF, mild and moderate hepatic impairment, respectively. The applicant proposes the following labeling:

“8.7 Hepatic Impairment

No dose adjustment is necessary in patients with mild to moderate hepatic impairment. INCLISIRAN has not been studied in patients with severe hepatic impairment [see *Clinical Pharmacology* (12.3)].”

Renal Impairment

ORION-7 was a Phase I, single-dose, open-label study to evaluate the safety, tolerability, PK, and PD of a single dose of 300 mg inclisiran sodium administered SC to subjects with renal impairment (mild, moderate, severe) compared with matched subjects with normal renal function. The effect of ESRD on inclisiran PK was not evaluated. The effect of hemodialysis on inclisiran was not investigated during inclisiran development. The applicant states that as inclisiran is eliminated renally, hemodialysis is anticipated to remove inclisiran from plasma.

Thirty-one subjects were enrolled and received inclisiran: 8 subjects each with normal, mildly impaired, and moderately impaired renal function and 7 subjects with severely impaired renal function. Median CrCl was 103 mL/min in subjects with normal renal function and 69 mL/min, 33 mL/min, and 20 mL/min in subjects with mild, moderate, and severe renal impairment, respectively.

Pharmacokinetics: Inclisiran plasma exposures increased with renal impairment. Inclisiran plasma concentrations reached maximum concentrations around 4 hours to 8 hours after dosing and were at undetectable levels between 48 and 96 hours. The C_{max} geometric mean ratios (90% confidence interval [CI]) between renal impairment groups and healthy subjects were 2.3 (1.5, 3.6), 2.0 (1.3, 3.1), and 3.3 (2.1, 5.2) for mild, moderate, and severe renal impairment, respectively. The AUC from time 0 to 48 hours geometric mean ratios (90% CI) were 1.6 (1.2, 2.1), 1.8 (1.4, 2.4), and 2.3 (1.8, 3.1) for mild, moderate, and severe renal impairment, respectively.

The mean baseline LDL-C levels were 136, 139, 113, and 95 mg/dL in subjects with normal renal function and in subjects with mild, moderate, and severe renal function impairment, respectively. Maximum LDL-C percentage changes from baseline of 58%, 35%, 53%, and 51% were observed from Day 30 to Day 60 in the normal renal function group and the mild, moderate, and severe renal impairment groups, respectively. The applicant proposes the following labeling:

“8.6 Renal Impairment

No dose adjustments are necessary for patients with mild, moderate, severe renal impairment (b) (4) [see *Clinical Pharmacology* ([12.3](#))]. (b) (4)

”

Reviewer comment:

(b) (4)

The C_{max} geometric mean ratio (90% confidence interval [CI]) between healthy subjects and patients with severe renal impairment was 3.3 (2.1, 5.2). The AUC from time 0 to 48 hours geometric mean ratios (90% CI) was 2.3 (1.8, 3.1) for severe renal impairment.

In the QT study, at the inclisiran mean C_{max} observed in this study (2888 ng/mL), the model-predicted $ddQTcF$ was 1.9 msec (90% CI 0.6, 3.2 msec). At the maximum individual inclisiran concentration observed in this study (8430 ng/mL), the model-predicted $ddQTcF$ was 5.7 msec (90% CI 1.1, 10.3 msec). At the mean C_{max} observed in ORION-7 at the therapeutic dose of 300 mg in severe renal impairment (1760 ng/mL), the model-predicted $ddQTcF$ was 1.1 msec (90% CI 0.3, 1.9 msec). The applicant concludes that inclisiran had no clinically significant effect on $QTcF$ at systemic exposures that significantly exceeded those likely to be obtained at therapeutic doses.

The 900 mg dose in the QTc study is a similar exposure increase to that of severe renal impairment.

QT Study

ORION-12 was a randomized, double-blind, placebo- and positive-controlled, 3-way crossover study in 48 healthy subjects. Each subject received a single SC injection of inclisiran sodium 900 mg (3-times the recommended dose), placebo, and a single oral dose of moxifloxacin 400 mg (active control) at various timepoints.

The QT consultation review by Dr Begum (in DARRTS dated 5/13/20; Reference ID: 4607664) notes that the mean peak concentrations of 2890 ± 1360 ng/mL ($T_{max} \sim 4$ h) were observed following a 900 mg inclisiran injection. The peak concentrations of inclisiran observed in the study were higher than those observed with therapeutic doses (300 mg) in healthy subjects (C_{max} : 509 ng/mL) and in subjects with severe renal impairment (C_{max} : 1760 ng/mL; Study ORION-7). None of the subjects experienced $QTcF$ values greater than 480 msec in the inclisiran 900 mg group. Similarly, none of the subjects experienced $\Delta QTcF$ values greater than 30 msec in the inclisiran 900 mg group. The applicant's by-time analysis, which the FDA agreed with, showed that inclisiran 900 mg excluded the 10 msec threshold at the suprathreshold dose level for $\Delta\Delta QTcF$ [C_{max} at 4 hours: FDA analysis: 2.9 msec (90% CI 0.5, 5.2 msec); applicant analysis: 2.5 msec (90% CI 0.6, 4.5 msec)].

Thus, at a single dose of 900 mg, inclisiran had no clinically significant effects on $QTcF$ or other ECG variable at systemic exposures that significantly exceed those likely to be achieved with a therapeutic dose.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

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4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

See below for the table of clinical trials that are pertinent to the evaluation of efficacy and safety for this review.

Table 2. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled; Male/Female; Age Range	Study Population	No. of Centers, Countries and (Sites)
<i>Controlled Studies to Support Efficacy and Safety</i>								
ORION-9	03397121	Phase III, placebo-controlled, Double-blind, randomized, multicenter trial	284 mg inclisiran or placebo; Dosing: Day 1, Day 90, Day 270 and Day 450; subcutaneous injection	mean % change in LDL-C from baseline to Day 510 and time adjusted % change in LDL-C from baseline after Day 90 and up to Day 540	540 days (18 months)	482 227/255 21-80	Subjects with HeFH and elevated LDL-C on maximally tolerated statin	47 centers; Canada (3) Czech Republic (3) Denmark (6) Netherlands (5) South Africa (9) Spain (6) Sweden (3) United States (11)
ORION-10	03399370	Phase III, placebo-controlled, Double-blind, randomized, multicenter trial	284 mg inclisiran or placebo; Dosing: Day 1, Day 90, Day 270 and Day 450; subcutaneous injection	mean % change in LDL-C from baseline to Day 510 and time adjusted % change in LDL-C from baseline after Day 90 and up to Day 540	540 days (18 months)	1561 1083/478 35-90	Subjects with ASCVD and elevated LDL-C on maximally tolerated statin	145 centers; United States (145)

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ORION-11	03400800	Phase III, placebo-controlled, Double-blind, randomized, multicenter trial	284 mg inclisiran or placebo; Dosing: Day 1, Day 90, Day 270 and Day 450; subcutaneous injection	mean % change in LDL-C from baseline to Day 510 and time adjusted % change in LDL-C from baseline after Day 90 and up to Day 540	540 days (18 months)	1617 1160/457 20-88	Subjects with ASCVD or ASCVD-risk equivalents and elevated LDL-C on maximally tolerated statin	72 centers; Czech Republic (2) Germany (5) Hungary (4) Poland (19) South Africa (8) Ukraine (9) United Kingdom (24)
<i>Studies to Support Safety</i>								
ORION-12		Phase I, randomized, double-blind, double-dummy, placebo- and positive-controlled, crossover study	3 SC injections of 300 mg Inclisiran and 1 placebo tablet; 3 SC injections of placebo and 1 placebo tablet; 400 mg oral moxifloxacin and 3 SC injections of placebo	assess the effect of a supra-therapeutic dose of inclisiran on cardiac repolarization as assessed by the QTc interval corrected for HR using the QTcF.	30 days	48 33/15 20-59	Healthy subjects	1 center; United States
ORION-3		Phase II, open label, long term extension study with an active comparator (evolocumab)	Group 1 (Inclisiran Only Arm): Inclisiran 300 mg on Day 1 and every 180 days until Day 720, an	Evaluate the effect of inclisiran on LDL-C at Day 210 compared to	4 years (ongoing)	374	Subjects with ASCVD or ASCVD risk equivalents and elevated LDL-C	Canada (12) Germany (6) Netherlands (14) United Kingdom (14) United States (8)

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			additional dose on Day 810, then every 180 day dosing until EOS; SC injection Group 2 (Switching Arm): Evolocumab 140 mg on Day 1 and every 14 days until Day 336 or Day 360; subcutaneous injection. At Day 360, switch to inclisiran every 180 day dosing until EOS; SC injection	Baseline of ORION-1 in Group 1 (inclisiran only arm).			despite maximum tolerated dose of LDL-C lowering Therapy who have completed ORION-1 (dose-finding study)	
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>								
ORION-6		Phase I, single-dose, open-label, parallel-group study	284 mg inclisiran; single dose; subcutaneous injection	assess the PK, PD and safety of Inclisiran in subjects with hepatic impairment compared to	180 days	28 16/12 29-74	Subjects with mild, moderate, and normal hepatic function	1 center; United States

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				subjects with normal hepatic function				
ORION-7		Phase I, single-dose, open-label, parallel-group study	284 mg inclisiran; single dose; subcutaneous injection	assess the PK of Inclisiran in subjects with renal impairment compared to subjects with normal renal function	Day 60 or subjects LDL-C returned to within 50% of the absolute reduction from Baseline	31 22/9 24-78	Subjects with normal renal function and subjects with mild, moderate and severe renal impairment	2 centers; New Zealand

5.2. Review Strategy

The primary focus of this review is the three pivotal phase III studies: ORION-9, -10 and -11. Eileen Craig, MD focused on the regulatory history and efficacy section of the clinical review; Iffat Chowdhury, MD focused on the safety portion of the clinical review. Section 8 presents the safety review which focused on the pooled data (Safety Pool) from ORION -9, -10, and -11. The applicant's analysis was verified and supplemented with the clinical reviewer's analysis, where applicable.

The clinical reviewers collaborated with reviewers from the Office of Biotechnology Products (OBP), Division of Biotechnology Review and Research IV (DBRRIV) on the review of the antibody assay validation and inclisiran immunogenicity (refer to the review by Dr. Takahashi in DARRTS dated 8/14/2020; Reference ID: 4656320).

Dr. Jennifer Clark, Office of Biometrics II, conducted an independent review of the efficacy of inclisiran. Please refer to her review for the FDA's statistical analysis of efficacy (in DARRTS dated 7/29/2020; Reference ID: 4648765). Sections 6 and 7 of this review will present the results of the applicant's efficacy analyses with the clinical reviewer's commentary, where relevant.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. ORION-9 (MDCO-PCS-17-03)

6.1.1. Study Design

Overview and Objective

Title of Study: A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (LDL-C)

The primary objective was to evaluate the effect of inclisiran treatment on LDL-C levels at Day 510. Other objectives included an assessment of the safety and tolerability profile of inclisiran.

Trial Design

ORION-9 was a Phase III, placebo-controlled, double-blind, randomized trial in approximately 400 subjects with HeFH and elevated LDL-C, despite maximum tolerated dose of LDL-C lowering therapies. The purpose of the trial was to evaluate the efficacy, safety, and tolerability of 4 subcutaneous inclisiran injections over a period of 18 months. Screening occurred approximately 2 weeks prior to randomization. Subjects were randomized 1:1 to inclisiran sodium 300 mg or placebo. Treatment allocation was stratified by country and by current use of statins or other lipid-modifying therapies. Each subject would receive four subcutaneous injections of blinded inclisiran or placebo on Day 1, Day 90, Day 270, and Day 450. The end of study (EOS) visit would be conducted on Day 540. Subjects who withdrew from study drug treatment were asked to continue follow-up for safety and efficacy using the protocol-specified visit schedule and procedures.

Pharmacodynamic assessments were scheduled at various visits and included LDL-C levels as well as other lipids and lipoproteins (e.g., total cholesterol, triglycerides, HDL-C, non-HDL-C, very low-density lipoprotein cholesterol [VLDL-C], apolipoprotein A1 [Apo-A1], apolipoprotein B [ApoB], lipoprotein(a) [Lp(a)], high sensitivity C-reactive protein [hsCRP], and PCSK9). All subjects were offered to have pharmacogenetic analyses done, unless underlying causal mutations of HeFH were well documented by a validated specialized laboratory.

LDL-C Assessment for Efficacy

Subjects were in a fasted state for all efficacy laboratory assessments of lipids/lipoproteins/biomarkers. LDL-C using ultracentrifugation was done additionally at baseline and at Day 510. Calculated LDL-C used the Friedewald calculation ($LDL-C = TC - HDL-C - TG/5$), which is typically used in clinical practice and is generally considered reliable within <0.5 mg/dL of directly-measured LDL. The Friedewald equation loses accuracy in subjects with elevated triglycerides or low LDL-C values. Thus, the primary endpoints used a reflexive LDL-C approach: either calculated LDL-C (based on the Friedewald formula) was used, or if the calculated LDL-C was less than 40 mg/dL or triglycerides were greater than 400 mg/dL, or calculated LDL-C was missing, directly measured (using ultracentrifugation) LDL-C was used, if it was available (non-missing).

Safety assessments including adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), concomitant medications, and safety laboratory parameters were collected during the study. Formation of anti-drug antibodies (ADA) and further characterization of ADA were evaluated.

The independent Data Monitoring Committee (IDMC) reviewed safety data after the first 40 subjects received the first SC injection of inclisiran or placebo and had completed 1 month follow-up. Thereafter the IDMC reviewed safety data every 3 months until the end of study (EOS) unless requested otherwise by the IDMC.

Key Inclusion Criteria:

- Male or female subjects ≥ 18 years of age.
- History of HeFH with a diagnosis of HeFH by genetic testing; and/or a documented history of untreated LDL-C of >190 mg/dL, and a family history of FH, elevated cholesterol or early heart disease that may indicate FH (Simon Broome Diagnostic criteria for HeFH²⁷)
- Serum LDL-C ≥ 100 mg/dL at screening
- Fasting triglyceride <400 mg/dL at screening.
- Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized local clinical methodology.
- Subjects on statins should be receiving a maximally tolerated dose. Maximum tolerated dose is defined as the maximum dose of statin that can be taken on a regular basis without intolerable adverse events. Intolerance to any dose of any statin must be documented as historical AEs attributed to the statin in question in the source documentation and on the Medical History page of the electronic case report form (eCRF).
- Subjects not receiving statins must have documented evidence of intolerance to all doses of at least two different statins: one statin at the lowest available daily dose AND another statin at any dose. A subject may participate in the study with documentation of intolerance to only one statin if there is a documented history of rhabdomyolysis attributed to that statin.
- Subjects on lipid-lower therapies (such as a statin and/or ezetimibe) should be on a stable dose for ≥ 30 days before screening with no planned medication or dose change during study participation.

Key Exclusion Criteria:

- Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study, and/or put the subject at significant risk or might interfere with interpretation of the clinical study results.
- New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction $<25\%$.
- Cardiac arrhythmia within 3 months prior to randomization that is not controlled by medication or via ablation.
- Major adverse cardiovascular event within 3 months prior to randomization.
- Uncontrolled severe hypertension: systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg prior to randomization despite antihypertensive therapy.

²⁷ Austin, MA, Hunter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: A HuGE prevalence review. American Journal of Epidemiology. 2004;160:407-420.

- Active liver disease defined as any known current infectious, neoplastic, or metabolic pathology of the liver or unexplained elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), >3x the upper limit of normal (ULN), or total bilirubin >2x ULN at screening confirmed by a repeat abnormal measurement at least 1 week apart.
- History of malignancy that required surgery (excluding local and wide-local excision), radiation therapy and/or systemic therapy during the three years prior to randomization.
- Females who are pregnant or nursing, or who are of childbearing potential and unwilling to use at least two methods of highly effective contraception for the entire duration of the study.
- Males who are unwilling to use an acceptable method of birth control during the entire study period (ie, condom with spermicide).
- Known history of alcohol and/or drug abuse within the last 5 years.
- Treatment with other investigational products or devices within 30 days or five half-lives of the screening visit, whichever is longer.
- Planned use of other investigational products or devices during the course of the study
- Treatment (within 90 days of screening) with monoclonal antibodies directed towards PCSK9.

Dose Rationale

Previous studies²⁸ have shown that a 300 mg dose of inclisiran sodium is reasonably well tolerated and provides maximum efficacy (i.e., doses higher than 300 mg did not provide additional efficacy in LDL-C lowering). The applicant used modelling and simulation studies to further explore this dose and dosing regimen to confirm that it will provide sustained reductions in PCSK9 and LDL-C.

Test Product, Dose and Mode of Administration: Inclisiran sodium 300 mg (inclisiran sodium includes 284 mg inclisiran and 16 mg sodium) will be administered as a single SC injection on Day 1, Day 90, Day 270, and Day 450.

Reference Therapy, Dose, and Mode of Administration: Placebo will be administered as SC injections of saline solution. Placebo volume will be matched to test product volume within each dose and injection; the 300 mg dose will be administered as 1.5 mL of placebo.

²⁸ ALN-PCSSC-001: Doses up to 800 mg as a single dose and two doses or more doses up to 500 mg were administered. ORION-1: Up to 500 mg as a single dose on Day 1 or two doses on Day 1 and Day 90 (100 mg, 200 mg or 300 mg) were administered.

The study drug should be administered under aseptic conditions by clinical study site staff. The site of injection was the abdomen, alternating sides for each injection.

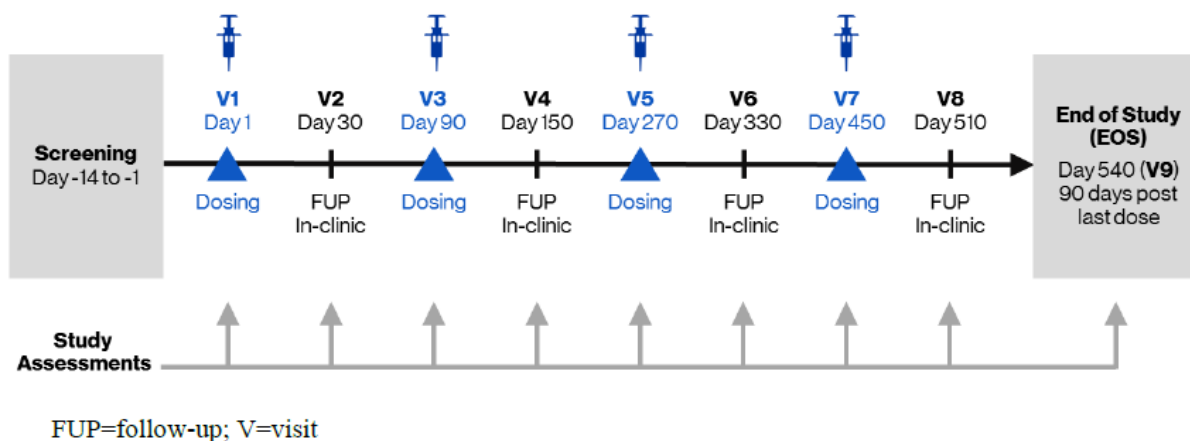
Prohibited Concomitant Medications

- Medications prescribed to lower LDL-C (e.g., statins, ezetimibe, lomitapide, mipomersen, niacin, colesvelam, bile acid absorption inhibitors, monoclonal antibodies directed towards PCSK9).
- Any medication taken for the purpose of lipid lowering, including over-the-counter or herbal therapies.

Permitted Concomitant Medications

- Hormone replacement therapy
- Lipid-lower medications; subjects already on a stable (≥ 30 days before screening) lipid-lower medications (such as statins and/or ezetimibe) should remain on the dose that they have received during participation in the original protocol unless clinically indicated
- Prescription medications prescribed to treat preexisting medical conditions such as diabetes and hypertension
- Prescription or nonprescription medications, when necessary to treat an AE, and at the discretion of the investigator

Figure 1. Study Design of ORION-9



Source: Applicant's Figure 1, ORION-9 Protocol Amendment #4

Study Endpoints

Primary Efficacy Endpoints:

- Percentage change in LDL-C from baseline to Day 510

- Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. This is the average percentage change in LDL-C from baseline over the period after Day 90 and up to Day 540. (The applicant states that this analysis assesses the effect on LDL-C levels seen with a more chronic dosing regimen. The Day 90 dose is the start of the 6-monthly dosing regimen.)

Key Secondary Efficacy Endpoints:

- Absolute change in LDL-C from baseline to Day 510
- Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C

Safety Endpoints: Adverse event, SAEs, vital signs, clinical laboratory values (hematology, coagulation testing, chemistry, and urinalysis), ADA testing and electrocardiograms (ECGs) will be collected at specified visits through the EOS visit (Day 540).

Blinded Study: This was a double-blind, placebo-controlled study. Study medication was blinded prior to distribution to the site. Inclisiran may be visually distinguishable from placebo; therefore, blinded syringes were provided to all study sites and used to maintain the blind. Each investigational product vial, inclisiran or placebo, was covered in a yellow shroud to blind the vial. Randomization via automated interactive response technology (IRT) was used to assign subject to blinded investigational product kits.

Reviewer Comments: The design of this trial was similar to other recent trials for agents that are intended to be used as an add-on to statin in higher CV risk populations. One feature that was different was the 18-month duration of the phase III trials rather than the more typical 12 months. Because inclisiran is administered only 3 times in the first year and 2 times per year afterward, this 18-month duration allowed for subjects to be exposed to 4 injections of inclisiran, which is important to more completely assess the safety profile, particularly injection site reactions (ISRs) and other hypersensitivity reactions. The infrequent administration of inclisiran also impacted when the assessment for the primary endpoint for efficacy would be taken. For lipid-lowering agents that are administered more frequently and steady-state lipid lowering is reached within a few weeks, the primary endpoint for LDL-C reduction is usually done around Week 12. For inclisiran, the primary endpoint for percentage change in LDL-C from baseline was assessed at Day 510. While this gives one a good assessment of steady-state and durable LDL-C reduction, one would anticipate that there may be more missing data with an endpoint assessed 17 months into the trial rather than 3 months.

The primary endpoint was percentage change in LDL-C from baseline to Day 510. Reduction of LDL-C is a surrogate endpoint for CV risk reduction and has been used as the basis for approval in previous trials of lipid-lowering drugs.

Key secondary endpoints that are relevant to clinical practice included percent change in non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC) and apolipoprotein B (Apo-B) from baseline to Day 510. The Hochberg procedure was applied to control the family-wise type I error rate at a 2-sided significance level of $\alpha=0.05$ for the key secondary endpoints.

Other endpoints of interest to practicing clinicians were changes from baseline in triglycerides (TG), HDL, lipoprotein (a) [Lp(a)], and hsCRP. The applicant did not include these biomarkers as prespecified secondary endpoints; however, the review team evaluated them as exploratory endpoints.

The applicant made reasonable efforts to blind study medication from subjects and investigators. However, if a patient wanted to try and unblind their treatment assignment and, for example, had an LDL-C assessment done at a health fair that showed a significant decrease (such as > 40%) in LDL-C, they may have been able to guess their treatment assignment to inclisiran.

The FDA clinical team encouraged the applicant to make the eligibility criteria as inclusive as possible, such as including older subjects (the applicant removed the upper age limit); including those with a history of hemorrhagic stroke or stable heart failure, especially those with ischemic cardiomyopathy; liberalizing AST/ALT cut-offs; and, if the data from the renal impairment study supported it, including patients with eGFR <30 mL/min/1.73m² into all Phase III trials. The applicant did agree to broaden many of the eligibility criteria. The subjects in this trial should thus represent patients that will be treated in real world conditions.

This trial was placebo-controlled, which was justified as subjects were receiving a background of maximum tolerated statin therapy (ideally high-intensity statin) and/or other lipid-lowering therapies, such as ezetimibe. At the time these trials were conducted, PCSK9 monoclonal antibody inhibitors (i.e., alirocumab, evolocumab) were not widely available to patients.

The FDA clinical team made extensive recommendations regarding the baseline lipid-lowering regimen that patients should be on, specific safety assessments, the size of the safety database, the duration of the trials, data collected if patients discontinue study medication, what should be included in the safety analyses, etc. The applicant agreed to the majority of FDA requests in a timely, thoughtful and thorough manner.

Statistical Analysis Plan

Sample Size and Power: The sample size calculation was performed with the assumption (which was based on the observed results from a Phase II study) that the difference in change from

baseline between the active dose group and the placebo group for LDL-C would be no less than 30 mg/dL, with a standard deviation of 20 mg/dL. A sample size of at least 380 evaluable subjects would provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025.

Primary Endpoint Analysis: The family-wise type I error rate was controlled at one-sided significance level of $\alpha=0.025$ by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 was tested first. If the null hypothesis were rejected at one-sided significance level of $\alpha=0.025$ and superiority of inclisiran over placebo were claimed, then the time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 would be tested, also at one-sided significance level of $\alpha=0.025$. Mixed-effect models for repeated measures (MMRM) would be performed on the percent change in LDL-C from baseline to Day 510 to test the superiority of inclisiran over placebo. The model included fixed effect for treatment, visits, baseline value, interaction between treatment and visits, and current use of statins or other lipid-modifying therapies.

Time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 were calculated from the MMRM with imputed data. Linear combinations of the estimated means after Day 90 and up to Day 540 were used to compare treatments. Results were combined using Rubin's method.

Key Secondary Endpoint Analysis: The secondary efficacy endpoints would not be tested if either one of the co-primary efficacy endpoints' null hypothesis failed to be rejected. The Hochberg procedure was applied to control the family-wise type I error rate at one-sided significance level of $\alpha=0.025$ for the key secondary endpoints. The key secondary endpoints were analyzed using the same methods as in the primary efficacy analysis.

Missing Data: The applicant attested that they would diligently follow up with each subject during the study through Day 540 ± 14 days on all efficacy laboratory assessments of lipids/lipoproteins/biomarkers to keep missing data to a minimum regardless of whether the subject remained on study treatment, used ancillary therapies, experienced an adverse event, or adhered to the protocol. However, if missing data, defined as data not available from either scheduled (within the protocol defined visit window) or unscheduled visits, occurred for the primary or any of key secondary efficacy endpoints then that data would be imputed.

Primary and key secondary efficacy endpoints had missing data imputed using multiple imputation techniques (a primary method and sensitivity/exploratory methods).

A multiple imputation washout model was utilized for the primary efficacy analysis of the percentage change in LDL-C from baseline to Day 510 endpoint. The washout model, a modified control-based Pattern-Mixture Model (PMM), was used to explore the possibility of data

missing not at random (MNAR) for subjects who discontinued the study early. For subjects who discontinued the study early, their missing values were imputed under the assumption that their outcome would be similar to those in the placebo group with similar background characteristics. For subjects in the inclisiran group only missing Day 510 values were imputed. For subjects in the placebo group their missing values over all visits after early termination were imputed based on the missing at random (MAR) assumption. Multiple imputation was used to account for uncertainty in the imputation process and results from the imputed datasets were combined using Rubin's method.

One sensitivity technique included using control-based pattern mixture models which utilize placebo data for monotone missing inclisiran sodium 300 mg treatment data. Additional sensitivity data imputation techniques were utilized. Retrieved data were analyzed in all analyses where possible.

Interim Analysis: No interim analysis were performed in this study.

Analysis Populations

- Intent-to-Treat (ITT) Population
The intent-to-treat (ITT) population comprises all subjects randomized into the study. Treatment classification was based on the randomized treatment. The ITT population was used for analysis of the primary and secondary endpoints.
- Full Analysis Set (FAS)
The FAS comprises all subjects who are randomized into the study, take any study medication and have at least one post treatment lipid data measured. Treatment classification was based on the randomized treatment.
- Modified Intent-to-Treat (mITT) Population
The mITT population comprises all randomized subjects who receive at least one dose of investigational product and have both the baseline and the 510-day follow-up LDL-C assessment. Treatment classification was based on the randomized treatment.
- Safety Population
All subjects who received at least one dose of investigational product. Treatment classification was based on the actual treatment received. This is the primary population for the safety analyses.

Reviewer comment: The FDA clinical and statistical teams provided feedback on the SAPs for ORION-9, -10, -11, and the integrated summary (ISS) of safety and efficacy (ISE). The final SAP for ORION-11 was submitted 6/20/2019 and was found acceptable. An updated SAP for ORION-11 was submitted 8/12/2019, and we issued a letter on 9/13/2019 clarifying what statins and doses meet the definition of high-intensity statin, and that an assessment of Hy's law should be presented for subjects without regard to their baseline lab parameters. On 9/13/2019, final SAPs for ORION-9 and ORION-10 were submitted. On 9/27/2019, addendums to the SAPs for

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ORION-9, -10, and -11 were submitted and FDA found these SAPs acceptable on 11/5/19. The SAP for the ISS and ISE was found acceptable on 10/17/19.

Table 3. Schedule of Assessments for ORION-9

Visits	Screening	Randomization	Treatment							EOS ¹
		V1 (baseline)	V2	V3	V4	V5	V6	V7	V8	V9 (90 days post last dose)
Timelines	Day -14 to -1	Day 1	Day 30	Day 90	Day 150	Day 270	Day 330	Day 450	Day 510	Day 540
Visit windows (± days)			±2	±30	±30	±30	±30	±30	±30	±14
Informed consent	X									
Assessment of eligibility	X	X ²								
Demographics and medical history	X									
Pregnancy test	X ³	X ³		X ³		X ³		X ³	X ³	X ³
Randomization		X								
Investigational product administration		X ^{4,5}		X ^{4,5}		X ^{4,5}		X ^{4,5}		
Physical examination	X									X
Neurological examination		X								X
Weight/height/waist circumference	X ⁶									X
Vital signs ⁷	X	X		X		X		X		X
12-lead ECG	X	X								X
Fasted lipid profile/biomarkers ⁸	X	X		X	X	X	X	X	X	X
ADA		X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹
Full Serum chemistry ¹⁰		X								X
Limited serum chemistry ¹⁰	X			X	X	X	X	X	X	
Urinalysis (local) ¹¹	X	X								X
Hematology and coagulation ¹²	X	X			X					X
Pharmacogenetic sample ¹³	X									
Previous/concomitant medications	X	X	X	X	X	X	X	X	X	X
AEs/SAE reporting	X	X	X	X	X	X	X	X	X	X

ADA=anti-drug antibodies; AE=adverse event; ECG=electrocardiogram; EOS=end of study; V=visit; SAE=serious adverse event

1. For subjects who decide to prematurely and permanently discontinue from study treatment and who decline further follow-up visits, EOS visit will be scheduled as soon as possible. If decision to discontinue is made at a specific visit, this visit will become the EOS visit and EOS visit procedures should be followed.
2. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
3. Only in women of childbearing potential (performed locally, prior to any dosing, using central laboratory kit supplies; urine pregnancy test)

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4. Subjects will be observed in the clinic for at least 4 hours following the first injection only (Randomization visit) and 30 minutes for each subsequent visit in order to have additional vital and/or laboratory assessments completed if needed.
5. For any suspected episode of anaphylaxis, the investigator will need to collect a blood sample for tryptase within 30 minutes of an onset of anaphylaxis (or as soon as logically possible).
6. Height will be measured at baseline only and used to calculate body mass index.
7. On Day 1 vital signs will be measured prior to injection and 4 hours post injection; all other visits, vital signs will be measured only prior to injection. When available, an automated BP device is recommended for collection of BP and the result recorded to the nearest mmHg. The subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) is required per applicable visit.
8. See Section 7.2 for details of specific tests to be analyzed.
9. ADA serum samples will be collected on Day 1 prior to injection and 4 hours after injection. At all other visits, ADA serum samples will be collected prior to injection only, if an injection is scheduled for that visit. As presented in Section 6, serum samples for analysis are collected at every visit but assessment of ADA will only occur for samples collected at the following visits: Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510. Samples will be stored for assessment (if needed) for samples collected at the following visits: Randomization (after injection), Day 90, Day 270, Day 450, End of Study Visit.
10. See Section 7.1.8.3 for details of specific tests to be analyzed.
11. See Section 7.1.8.5 for details of specific tests to be analyzed.
12. See Section 7.1.8.1 and Section 7.1.8.2 for details of specific tests to be analyzed.
13. Sample may be taken during screening or anytime during study to be processed and stored, but only after separate consent has been signed.

Source: Applicant's ORION-9 submission, Table 3

Hematology blood draws include:

- Hemoglobin, hematocrit, erythrocytes, reticulocytes, mean cell hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet count, white blood cell count with differential.

Coagulation blood draws include:

- Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin (aPTT).

Chemistry blood draws vary based on visit day as follows:

- Full serum chemistry - Baseline (Day 1) and EOS (Day 540): AST, ALT, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (TBIL), direct and indirect bilirubin, creatine phosphokinase (CPK), lactate, bicarbonate, uric acid, creatinine, urea (BUN), estimated glomerular filtration rate (eGFR), sodium, potassium, calcium, inorganic phosphate, chloride, albumin, total protein, glucose (fasting), glycated hemoglobin A1C (HbA1C), and tryptase (as required).
- Limited serum chemistry - Screening, Days 90, 150, 270, 330, 450 and 510: ONLY: AST, ALT, ALP, GGT, TBIL, CPK, creatinine, eGFR, fasting glucose, HbA1C (not at Day 150, 330 and 510) and tryptase (as required).

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Fasted lipid profile/biomarkers include:

- Total cholesterol (TC), triglycerides, LDL-C, HDL-C, non-HDL-C, VLDL-C, Apo-A1, ApoB, lipoprotein (a) [Lp(a)], hsCRP, and PCSK9.

Protocol Amendments

Protocol Amendment #1 (dated 21 Nov 2017): Changes were made to address comments received from an FDA review of the study. These clarifications were related to exclusion criterion #3, site training requirements and statistics: All sites were conducted under the US IND; FDA requested to allow NYHA class III heart failure subjects into the trial; participating study sites would be trained on the importance of completing study follow-up procedures and collecting the documentation required for missing data values; appendix detailing full neurological examination was added; clarification of HbA1C analyses; and sensitivity analysis would be performed on the primary and key secondary efficacy endpoints to assess the impact of missing values.

Protocol Amendment #2 (dated 08 Jan 2018): Changes were made to the Withdrawal criteria: i.e. collect data if patients withdraw because they have initiated protocol-prohibited lipid-lowering therapy (e.g., an approved PCSK9 inhibitor); the amendment also clarified standards for vital sign measurements based on FDA comments: an automated BP device was recommended for collection of BP and the result recorded to the nearest mmHg. The revision specified that a subject should be sitting at rest for at least 5 minutes prior to these assessments. One assessment for each vital sign (HR, BP) was required per applicable visit.

Protocol Amendment #3 (dated 30 Aug 2018): Administrative changes and minor edits.

Protocol Amendment #4 (dated 30 Jan 2019): Changes to include refinement in the description of time adjusted analyses of LDL-C, clarify the plan to test for ADA and to align the approach to missing data handling with Health Authority feedback.

Reviewer comment: The clinical team agreed with the applicant's protocol amendments and do not believe that these modifications had a negative impact on the integrity of the trial or our interpretation of the results

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted in compliance with the protocol, The Medicines Company's standard operating procedures and/or guidelines and any vendor partners where applicable, the US FDA regulations, the International Conference on

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

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Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and other local regulations, in operation at the time of the study.

Financial Disclosure

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.²⁹

The Medicines Company has employed the following steps to minimize bias of the clinical study results:

- Use of multiple clinical sites
- Clinical site monitoring
- Clinical site audits
- Independent and centralized assessment of efficacy response data

The efficacy and safety studies used multiple investigators (none of whom have a disclosable interest), blinding, objective endpoints, or measurements of endpoints by someone other than the investigator to minimize bias.

Refer to Section 13.2 Financial Disclosure for additional information.

Patient Disposition

The study was conducted in 47 centers in 8 countries: Canada (3 centers), Czech Republic (3 centers), Denmark (6 centers), Netherlands (5 centers), South Africa (9 centers), Spain (6 centers), Sweden (3 centers), and USA (12 centers).

A total of 617 subjects were screened and 482 were randomized. In ORION-9, approximately 22% of screened subjects were screen failures. The most common inclusion/exclusion criteria not met was the triglycerides inclusion criterion (fasting triglyceride <400 mg/dL at screening) in 15% (93/617) of subjects. The second most common inclusion/exclusion criteria not met was the statin intolerance inclusion criterion (subjects not receiving statins must have documented evidence of intolerance to all doses of at least two different statins...) in 2% (13/617) of subjects.

The 482 randomized subjects were enrolled in 46 sites from 8 countries (no subjects were enrolled from 1 site in the USA). South Africa enrolled the most subjects (177, 37%), followed by Spain (84, 17%), US (65, 13%) and Denmark (49, 10%).

²⁹ See [web address].

As shown in the table below, at Day 510 approximately 98% of the ITT Population were still in the study and at Day 540 (EOS Visit) approximately 97% were still in the study. A total of 3.8% (9/240) of placebo-treated subjects discontinued the study. The most common reason for discontinuation from the study was withdrawal of consent (1.7%; 4/240). There was 1 discontinuation from the study due to death in both treatment groups. A total of 2.9% (7/242) of inclisiran-treated subjects discontinued the study. The most common reason for discontinuation from the study was other (2.1%; 5/242); other reasons included subject moved to a new house and screen failure (accidentally randomized).

Table 4. ORION-9: Patient Disposition for ITT Population

	Placebo (N=240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Completing the Day 510 visit	234 (97.5)	238 (98.3)	472 (97.9)
Completing the Day 540 visit	231 (96.3)	235 (97.1)	466 (96.7)
Discontinued	9 (3.8)	7 (2.9)	16 (3.3)
Death	1 (0.4)	1 (0.4)	2 (0.4)
Adverse event	0	0	0
Withdrew consent	4 (1.7)	0	4 (0.8)
Physician decision	0	0	0
Lost to follow-up	2 (0.8)	1 (0.4)	3 (0.6)
Initiation of PCSK9 inhibitor	1 (0.4)	0	1 (0.2)
Other	1 (0.4)	5 (2.1)	6 (1.2)
Duration on study (days)*			
Mean ± SD	534.6±54.2	537.5±47.4	536.0±50.8
Median	541	542	541
Q1, Q3	533, 547	535, 548	534, 548

Abbreviations: ITT=intent-to-treat; PCSK9= proprotein convertase subtilisin/kexin type 9

* Duration on study is defined as the number of days from the first date of treatment to the date of last recorded visit in the database.

Source: Applicant's ORION-9 submission, Tables 14.1.2.1 and 14.1.7.1. and FDA OCS Analysis Studio, Custom Table Builder. Columns - Dataset: Demographics; Filter: ITTFL = 'Y'. Table Section 1 - Dataset: Disposition; Filter: None.A

Protocol Violations/Deviations

Protocol deviations were similar between the treatment groups (see table below). The most common protocol deviations were prohibited concomitant medication/change in baseline statin or other lipid-lowering therapy dose and inclusion and/or exclusion criteria violation.

Table 5. ORION-9: Protocol Deviations – ITT Population

	Placebo (N=240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Subjects with at least 1 protocol deviation	30 (12.5)	25 (10.3)	55 (11.4)
Inclusion and/or exclusion criteria violation	8 (3.3)	8 (3.3)	16 (3.3)
Laboratory assessments not drawn at Days 1, 510 or 540 (EOS) Visits	0	7 (2.9)	7 (1.5)
Mis-Dosing for any reason other than subject safety or withdrawal*	6 (2.5)	5 (2.1)	11 (2.3)
Prohibited concomitant medication/change in baseline statin or other lipid-lowering therapy dose	14 (5.8)	9 (3.7)	23 (4.8)
SAE form not reported to applicant within 24 hours	2 (0.8)	1 (0.4)	3 (0.6)
Informed consent not signed prior to study entry	2 (0.8)	0	2 (0.4)

Abbreviations: ITT=intent-to-treat; EOS=end of study; SAE=serious adverse event

* Defined as missing dose or a dose delayed by more than 30 days

Source: Applicant's ORION-9 submission, Tables 14.1.5.1 and 14.1.6.1.

Table of Demographic Characteristics

Table 6. ORION-9: Demographic and Baseline Characteristics of the ITT Population

Demographic Parameters	Placebo Control Group (N= 240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Sex			
Male	115 (47.9)	112 (46.3)	227 (47.1)
Female	125 (52.1)	130 (53.7)	255 (52.9)
Age			
Mean years (SD)	55.0 (11.8)	54.4 (12.5)	54.7 (12.1)
Median (years)	56.0	56.0	56.0
Min, max (years)	21, 80	22, 79	21, 80
Age Group			
18 - < 65 years	185 (77.1)	189 (78.1)	374 (77.6)
≥ 65 years	55 (22.9)	53 (21.9)	108 (22.4)
18 - < 75 years	233 (97.1)	234 (96.7)	467 (96.9)
≥ 75 years	7 (2.9)	8 (3.3)	15 (3.1)
Weight			
Mean, kg (SD)	84.2 (18.3)	83.7 (18.6)	83.9 (18.4)
BMI (kg/m ²)			
Mean, kg (SD)	28.8 (5.1)	29.0 (5.7)	28.9 (5.4)
Race			
White	227 (94.6)	226 (93.4)	453 (94.0)
Black or African American	7 (2.9)	8 (3.3)	15 (3.1)
Asian	5 (2.1)	7 (2.9)	12 (2.5)
American Indian or Alaska Native	0	1 (0.4)	1 (0.2)
Native Hawaiian or other Pacific Islander	1 (0.4)	0	1 (0.2)
Ethnicity			
Hispanic or Latino	8 (3.3)	7 (2.9)	15 (3.1)
Not Hispanic or Latino	232 (96.7)	235 (97.1)	467 (96.9)
Region			
United States	32 (13.3)	33 (13.6)	65 (13.5)
Rest of the World			
Canada	11 (4.6)	12 (5.0)	23 (4.8)
Czech Republic	5 (2.1)	7 (2.9)	12 (2.5)
Denmark	26 (10.8)	23 (9.5)	49 (10.2)
Netherlands	19 (7.9)	19 (7.9)	38 (7.9)
Spain	42 (17.5)	42 (17.4)	84 (17.4)
South Africa	89 (37.1)	88 (36.4)	177 (36.7)
Sweden	16 (6.7)	18 (7.4)	34 (7.1)
Baseline GFR Category (mL/min/1.73 m ²)			

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Demographic Parameters	Placebo Control Group (N= 240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
≥15 to <30	0	0	0
≥30 to <60	20 (8.3)	17 (7.0)	37 (7.7)
≥60 to <90	138 (57.5)	131 (54.1)	269 (55.8)
≥90	82 (34.2)	94 (38.8)	176 (36.5)
ASCVD	73 (30.4)	59 (24.4)	132 (27.4)
Diabetes Mellitus	28 (11.7)	20 (8.3)	48 (10.0)
Smoking (current or former)	102 (42.5)	84 (34.7)	186 (38.6)
Hypertension	101 (42.1)	102(42.1)	203 (42.1)
Baseline LDL-C (mg/dL)			
Mean (SD)	154.7 (58.1)	151.4 (50.4)	153.0 (54.3)
Median (mg/dL)	138.0	139.0	138.5
Min, max (mg/dL)	57, 460	69, 322	57, 460
Baseline HDL-C (mg/dL)			
Mean (SD)	50.8 (13.1)	51.5 (15.1)	51.1 (14.2)
Median (mg/dL)	49.0	50.0	50.0
Min, max (mg/dL)	19, 93	14, 100	14, 100
Baseline Total Cholesterol (mg/dL)			
Mean (SD)	232.4 (62.8)	230.0 (54.6)	231.2 (58.8)
Median (mg/dL)	214.0	218.5	216.0
Min, max (mg/dL)	119, 540	140, 410	119, 540
Baseline Triglycerides (mg/dL)			
Mean (SD)	134.4 (65.6)	135.4 (72.9)	134.9 (69.3)
Median (mg/dL)	119.0	120.0	119.0
Min, max (mg/dL)	31, 428	42, 482	31, 482
Baseline non-HDL-C (mg/dL)			
Mean (SD)	181.5 (62.5)	178.5 (55.4)	180.0 (59.0)
Median (mg/dL)	158.0	167.5	163.5
Min, max (mg/dL)	85, 505	86, 374	85, 505
Baseline Apolipoprotein B (mg/dL)			
Mean (SD)	124.5 (34.8)	123.8 (33.2)	124.1 (34.0)
Median (mg/dL)	116.0	118.0	117.0
Min, max (mg/dL)	64, 304	66, 254	64, 304
Baseline Lipoprotein-a (nmol/L)			
Mean (SD)	118.3 (135.8)	123.2 (140.3)	120.8 (137.9)
Median (mg/dL)	54.0	57.0	55.0
Min, max (mg/dL)	2, 700	3, 840	2, 840
Baseline PCSK9 (µg/L)			
Mean (SD)	429.1 (135.3)	452.2 (131.2)	440.7 (133.6)
Median (mg/dL)	413.5	448.4	432.9

Demographic Parameters	Placebo Control Group (N= 240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Min, max (mg/dL)	137, 1156	125, 1004	125, 1156
Baseline C Reactive Protein (mg/L)			
Mean (SD)	3.2 (5.7)	2.4 (4.5)	2.8 (5.1)
Median (mg/dL)	1.4	1.2	1.3
Min, max (mg/dL)	0.1, 45.0	0.1, 58.1	0.1, 58.1

Abbreviations: GFR=glomerular filtration rate; SD=standard deviation; ASCVD=Atherosclerotic Cardiovascular Disease

Source: Applicant's ORION-9 submission, Tables 14.1.8.1, 14.1.9.1, 14.2.15.1 and 14.3.3.1.1; response to FDA IR (3/12/2020)

Reviewer comment: The demographic and baseline characteristics were balanced between the two treatment groups, especially for sex, age, race and region. The study primarily enrolled white subjects so there is very limited representation of non-white and Hispanic or Latino patients. The study population included appropriate representations of female sex and relevant comorbidities such as renal impairment, hypertension and, to a lesser degree, diabetes. There were small imbalances between treatment groups in some comorbid conditions such as ASCVD, diabetes and smoking status that should not impact the interpretation of efficacy.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

In ORION-9, 432 subjects (89.6%) consented to genetic testing. Fifty-nine percent (256 of 432) of these subjects, who consented to genetic testing, had single low-density lipoprotein receptor (LDLR) mutation. Of these 256 subjects, 168 (65.6%) had LDLR negative mutations, 28 (10.9%) subjects had LDLR defective mutations and 60 (23.4%) had LDLR mutations that were unclassified. Twenty-three of these 432 subjects (5.3%), who consented to genetic testing, had mutations in the APOB gene and one subject (0.2%) had a PCSK9 gain of function mutation. In 37 out of 432 subjects (8.6%), who consented to genetic testing, 2 or more mutations were identified. According to the applicant, the subjects with LDLR negative mutations had the highest baseline LDL-C (167 mg/dL). The table below presents this data for the entire ITT population.

Table 7. ORION-9: Genetic Mutation Profile of the ITT Population

Genetic variant group	Placebo Control Group (N= 240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Two or more mutations	15 (6.3)	22 (9.1)	37 (7.7)
Single LDLR mutation	131 (54.6)	125 (51.7)	256 (53.1)

Genetic variant group	Placebo Control Group (N= 240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Negative	87/131 (66.4)	81/125 (64.8)	168/256 (65.6)
Defective	11/131 (8.4)	17/125 (13.6)	2 /256 (10.9)
Unknown	33/131 (25.2)	27/125 (21.6)	60/256 (23.4)
ApoB	11 (4.6)	12 (5.0)	23 (4.8)
PCSK9 GOF	0	1 (0.4)	1 (0.2)
None Identified	54 (22.5)	61 (25.2)	115 (23.9)
No genetic testing	29 (12.1)	21 (8.7)	50 (10.4)

Abbreviations: ApoB=apolipoprotein B; GOF=gain of function; LDL-R=low density lipoprotein receptor; PCSK9=proprotein convertase subtilisin/kexin type 9
Source: Applicant's ORION-9 submission, Table 14.1.8.1

At baseline, use of lipid modifying therapy (LMT) was reasonably balanced between the treatment groups (see table below). Overall, 94.4% (455/482) of subjects received LMT, 90.5% (436/482) of subjects received statin therapy, and 55.4% (267/482) received other LMT and 3.9% (19/482) received other LMT and no statin. Overall, 73.9% (356/482) were on a high intensity statin, 14.5% (70/482) were on a moderate intensity statin and 1.9% (9/482) were on a low intensity statin at baseline. Approximately half (52.3%; 252/482) of subjects were treated with ezetimibe.

Table 8. ORION-9: Baseline Concomitant Medications of the ITT Population

Baseline Medications	Placebo Control Group (N= 240) n (%)	Inclisiran (N=242) n (%)	Total (N=482) n (%)
Baseline Lipid Modifying therapy			
None	14 (5.8)	13 (5.4)	27 (5.6)
Non-statin (other LMT) only	9 (3.8)	10 (4.1)	19 (3.9)
Statins only	86 (35.8)	102 (42.1)	188 (39.0)
Other LMT used ($\pm$ statin)	140 (58.3)	127 (52.5)	267 (55.4)
Statins used ($\pm$ other LMT)	217 (90.4)	219 (90.5)	436 (90.5)
High Intensity*	171 (71.3)	185 (76.4)	356 (73.9)
Moderate Intensity**	40 (16.7)	30 (12.4)	70 (14.5)
Low Intensity	4 (1.7)	5 (2.1)	9 (1.9)

Abbreviations: LMT= lipid modifying therapy

* High-Intensity: Atorvastatin 40-80mg; ezetimibe/simvastatin 80mg; rosuvastatin 20-40 mg; simvastatin 60-80 mg

** Moderate Intensity: Atorvastatin 10-20mg; ezetimibe/simvastatin 20-40mg; rosuvastatin 5mgQOD- <20 mg QD; simvastatin 20-40 mg; fluvastatin 80mg; pitavastatin 2mg; pravastatin 40-80 mg

Source: Applicant's ORION-9 submission, Table 14.1.16.2.1

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Reviewer comment: The majority of participants were on background high-intensity statin therapy, which is appropriate, as inclisiran, if approved, would be most clinically relevant in patients with HeFH or at higher CV risk not adequately controlled by maximally tolerated statin therapy. The enrolled population adequately reflects the intended clinical population.

Approximately 25% (122/482; 26.7% placebo:24.0% inclisiran) of subjects reported either partial or complete intolerance to statins. The most common symptoms of statin intolerance (partial or complete) were muscle ache (75%; 91/122), other symptoms (36%; 44/122), and cramping (22%; 27/122). Approximately 12% (14/122) of these subjects had at least one documented abnormal lab (7% CK level, 3% hepatic [mainly ALT], 2% other lab).

Treatment Compliance and Concomitant Medications

Treatment Compliance

All study drugs were administered subcutaneously by clinical study site staff, primarily in the abdominal region (doses on Day 1, Day 90, Day 270, and Day 450). Overall, 96.7% (232/240) of placebo-treated subjects and 95.4% (230/241) of inclisiran-treated subjects received all 4 planned SC doses. Approximately 97% of placebo-treated and inclisiran-treated subjects received 3 of the 4 planned SC doses.

Reviewer comment: Over 95% of study subjects received all 4 doses of study drug. This high level of treatment compliance will allow for a good assessment of steady-state and durable LDL-C reduction.

Changes in Lipid-Modifying Therapy (LMT) During Trial

Six percent (14/240) of subjects in the placebo group and 3% (8/242) in the inclisiran group had changes in LMT use during the trial. One subject (0.2%) in the placebo group began therapy with a PCSK9 monoclonal antibody (evolocumab); no subject in the inclisiran group began therapy with a PCSK9 monoclonal antibody.

Shifts from baseline in statin intensity were minimal in both treatment groups. Most subjects remained on their statin intensity category (high, moderate, low or none) throughout the trial.

New or changed concomitant medications during the study were similar between the placebo and inclisiran treatment groups.

Efficacy Results – Primary Endpoint

The applicant's co-primary endpoints for this trial are:

- Percentage change in LDL-C from Baseline to Day 510.

- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540. The applicant states that this provides the average LDL-C between the dosing intervals and reflects LDL-C effect at a steady state. The Day 90 dose is the start of the every 6-month dosing regimen.

Percentage change in LDL-C from Baseline to Day 510:

The placebo-adjusted change in LDL-C from baseline to Day 510 using observed values was -49.5% (p<0.0001). The primary analysis used a prespecified washout model to account for missing data.³⁰ The placebo-adjusted change in LDL-C from baseline to Day 510 using the imputed values was -47.9% (p<0.0001).

Table 9. ORION-9: Primary Efficacy Endpoint – ITT Population

Primary Endpoint	Placebo (N= 240)	Inclisiran (N=242)	p-value
Percentage Change in LDL-C from Baseline to Day 510 (Observed values)			
LS Mean (95% CI)	8.4 (4.0,12.8)	-41.2 (-44.5, -37.8)	
LS Mean Difference (95% CI) from Placebo		-49.5 (-55.0, -44.0)	<.0001
Percentage Change in LDL-C from Baseline to Day 510 (Washout – Imputed values)			
LS Mean (95% CI)	8.2 (4.3, 12.2)	-39.7 (-43.7, -35.6)	
LS Mean Difference (95% CI) from Placebo		-47.9 (-53.5, -42.3)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant’s ORION-9 submission, Tables 15, 14.2.1.1, 14.2.2.1.1 and 14.2.15.1

Reviewer comment: In a HeFH population, inclisiran lowers LDL-C to a clinically meaningful degree, -40% from baseline and -48% from baseline as compared to the placebo group.

Sensitivity Analyses

Three additional, prespecified sensitivity analyses (PMM, MMRM, ANCOVA with country and current use of statins or other LMT as fixed effects) for handling missing values were used to

³⁰ A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. This modified model assumed missing Day 510 missing-at-random (MAR) for Inclisiran subjects if they received all 4 doses and had data observed at Day 540. Analysis of covariance (ANCOVA) on each of the 100 datasets was performed by including fixed effects for treatment, and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin’s Method.

analyze the percentage change from baseline at Day 510. Similar, statistically significant ($p < 0.0001$), placebo-adjusted differences were seen for the primary endpoint, regardless of sensitivity analysis used for missing values.

Table 10. ORION-9: Primary Efficacy Endpoint-Percentage Change in LDL-C from Baseline to Day 510 Sensitivity Analyses – ITT Population

Primary Endpoint	Placebo (N= 240)	Inclisiran (N=242)	p-value
Control-Based Pattern-Mixture Model (PMM)*			
LS Mean (95% CI)	8.3 (4.3, 12.2)	-39.7 (-43.7, -35.7)	
LS Mean Difference (95% CI) from Placebo		-48.0 (-53.4, -42.4)	<.0001
Mixed Model for Repeated Measures (MMRM)**			
LS Mean (95% CI)	8.1 (4.2, 12.0)	-40.8 (-44.6, -36.9)	
LS Mean Difference (95% CI) from Placebo		-48.8 (-54.3, -43.3)	<.0001
ANCOVA from Multiple Imputation Washout Model Including Country and Current Use of Statin/LMT***			
LS Mean (95% CI)	7.8 (0.1, 15.6)	-40.1 (-47.4, -32.7)	
LS Mean Difference (95% CI) from Placebo		-47.9 (-55.5, -40.3)	<.0001

Source: Applicant's ORION-9 submission, Table 14.2.2.1.1

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's Method.

** A MMRM analysis that assumes missing data are MAR was performed. The model included fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. The Restricted Maximum Likelihood (REML) estimation approach was used with the covariance structure set as Unstructured. A linear contrast at Day 510 was used to compare treatment groups.

*** A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. This modified model assumed missing Day 510 MAR for Inclisiran subjects if they received all 4 doses and had data observed at Day 540. Analysis of covariance (ANCOVA) on each of the 100 datasets was performed by including fixed effects for treatment, current use of statins or other lipid-modifying therapies(y/n), country, interaction between treatment and country, and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin's Method.

As shown in the following table, results examined by region were reasonably consistent. The placebo-adjusted change in LDL-C from baseline to Day 510 ranged from -43% in North America to -51% in South Africa ($p < 0.0001$).

Table 11. ORION-9: Primary Efficacy Endpoint-Percentage Change in LDL-C from Baseline to Day 510 by Study Center Region – ITT Population

Percentage Change in LDL-C from Baseline to Day 510*	N	LS Mean (95% CI)	LS Mean Difference (95% CI) from Placebo	p-value
North America				
Inclisiran	45	-38.3 (-46.7, -29.9)	-42.9 (-54.9, -30.9)	<.0001
Placebo	43	4.6 (-4.0,13.2)		
Europe				
Inclisiran	109	-37.1 (-43.5, -30.7)	-46.9 (-55.8, -38.0)	<.0001
Placebo	108	9.8 (3.6,15.9)		
South Africa				
Inclisiran	88	-43.2 (-49.5, -36.8)	-50.9 (-59.8, -42.0)	<.0001
Placebo	89	7.7 (1.5, 14.0)		

Source: Applicant’s ORION-9 submission, Table 14.2.1.1.20

*A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. This modified model assumed missing Day 510 MAR for Inclisiran subjects if they received all 4 doses and had data observed at Day 540. Analysis of covariance (ANCOVA) on each of the 100 datasets was performed by including fixed effects for treatment, and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin’s Method.

Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540

Compared to placebo, the time-adjusted percentage change from baseline after Day 90 and up to Day 540 was -44.3% (p<0.0001) (see table below).

Table 12. ORION-9: Co-Primary Efficacy Endpoint – Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540 ITT Population

Primary Endpoint	Placebo (N= 240)	Inclisiran (N=242)	p-value
Time-Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540*			
LS Mean (95% CI)	6.2 (3.3,9.2)	-38.1 (-41.0, -35.1)	
LS Mean Difference (95% CI) from Placebo		-44.3 (-48.5, -40.1)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant’s ORION-9 submission, Tables 16 and 14.2.1.1

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a

covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.

As shown in the following table, results examined by region were reasonably consistent. The time-adjusted percentage change in LDL-C from baseline after Day 90 to Day 540 ranged from -40% in North America to -49% in South Africa (p<0.0001).

Table 13. ORION-9: Primary Co-Primary Efficacy Endpoint- Time Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540 by Study Center Region – ITT Population

Time Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540*	N	LS Mean (95% CI)	LS Mean Difference (95% CI) from Placebo	p-value
North America				
Inclisiran	45	-39.7 (-45.6, -33.8)	-39.8 (-48.3, -31.2)	<.0001
Placebo	43	0.1 (-6.1,6.2)		
Europe				
Inclisiran	109	-34.0 (-38.8, -29.3)	-42.0 (-48.7, -35.4)	<.0001
Placebo	108	8.0 (3.3, 12.7)		
South Africa				
Inclisiran	88	-42.0 (-46.6, -37.3)	-48.7 (-55.2, -42.1)	<.0001
Placebo	89	6.7 (2.1,11.3)		

Source: Applicant's ORION-9 submission, Table 14.2.1.1.20

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.

Data Quality and Integrity

The study was well executed and largely adhered to the protocol. The protocol amendments were reasonable and unlikely to have had a negative impact on the integrity of the trial or our interpretation of the results. Protocol deviations were similar between the treatment groups and were not believed to have a negative impact on study results. Subject retention was excellent (97%). The applicant made reasonable efforts to blind study medication from subjects and investigators. There were no notable financial conflicts of interest. Datasets were complete, generally straightforward to navigate, and of high quality. There were no potential issues concerning the submitted data quality or integrity that raise questions about the

purported efficacy results. Thus, the study has generated data that are robust, interpretable, and persuasive in supporting the proposed indication.

Efficacy Results – Key Secondary Endpoints

Three key secondary endpoints were defined in the protocol and statistical analysis plan:

- Absolute change in LDL-C from Baseline to Day 510.
 - The placebo-adjusted absolute change from baseline to Day 510 in LDL-C levels was -68.9 mg/dL (p<0.0001).
- Time-adjusted absolute change in LDL-C from Baseline after Day 90 and up to Day 540.
 - Compared to placebo, the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was -62.7 mg/dL (p<0.0001).
- Percentage change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C.
 - The placebo-adjusted percentage change in PCSK9 from baseline to Day 510 was -78.3% (p<0.0001).
 - The placebo-adjusted percentage change in TC from baseline to Day 510 was -31.8% (p<0.0001).
 - The placebo-adjusted percentage change in Apo-B from baseline to Day 510 was -36.1% (p<0.0001).
 - The placebo-adjusted percentage change in non-HDL-C from baseline to Day 510 was -42.4% (p<0.0001).

Table 14. ORION-9: Key Secondary Efficacy Endpoints-ITT Population

Key Secondary Efficacy Endpoints	Placebo (N= 240)	Inclisiran (N=242)	p-value
Absolute Change in LDL-C (mg/dL) from Baseline to Day 510; Control-Based Pattern-Mixture Model (PMM)*			
LS Mean (95% CI)	9.9 (4.1, 15.8)	-59.0 (-64.8, -53.2)	
LS Mean Difference (95% CI) from Placebo		-68.9 (-77.1, -60.7)	<.0001
Time-Adjusted Absolute Change in LDL-C (mg/dL) from Baseline After Day 90 and up to Day 540; PMM*			
LS Mean (95% CI)	6.2 (1.7, 10.6)	-56.6 (-61.0, -52.2)	
LS Mean Difference (95% CI) from Placebo		-62.7 (-69.0, -56.5)	<.0001
Percentage Change from Baseline to Day 510 in PCSK9; PMM*			
LS Mean (95% CI)	17.7 (13.9, 21.4)	-60.7 (-64.4, -57.0)	
LS Mean Difference (95% CI) from Placebo		-78.3 (-83.7, -73.0)	<.0001

Percentage Change in TC from Baseline to Day 510; PMM*			
LS Mean (95% CI)	6.7 (4.0,9.4)	-25.1 (-27.8, -22.4)	
LS Mean Difference (95% CI) from Placebo		-31.8 (-35.6, -28.0)	<.0001
Percentage Change in Apo-B from Baseline to Day 510; PMM*			
LS Mean (95% CI)	2.9 (0.1, 5.7)	-33.1 (-35.9, -30.4)	
LS Mean Difference (95% CI) from Placebo		-36.1 (-40.0, -32.1)	<.0001
Percentage Change in non-HDL-C from Baseline to Day 510; PMM*			
LS Mean (95% CI)	7.4 (3.9, 10.9)	-34.9 (-38.5, -31.4)	
LS Mean Difference (95% CI) from Placebo		-42.4 (-47.3, -37.4)	<.0001

Source: Applicant's ORION-9 submission, Tables 14.2.3.1, 14.2.4.1, 14.2.5.1, 14.2.6.1, 14.2.7.1, and 14.2.8.1
 Abbreviations: Apo-B=apolipoprotein B; CI=confidence interval; HDL-C = high density lipoprotein cholesterol; ITT=intent-to-treat; LDL-C = low density lipoprotein cholesterol; LS=least squares; MAR=missing at random
 * A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's Method.

Reviewer comment: The results of the key secondary efficacy endpoints are consistent and supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. This is expected as LDL-C is a major component of TC and non-HDL-C, and apolipoprotein B is the primary apolipoprotein of LDL-C. In addition, a reduction in PCSK9 levels is the mechanism of action through which inclisiran lowers LDL-C.

Other secondary endpoints of interest include:

- Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510 (see table below).
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from Baseline.
 - At any time during the study, 3.8% (9/239) of placebo-treated subjects had ≥50% LDL-C reduction from baseline compared with 66.0% (159/241) of inclisiran-treated subjects.
 - At Day 510, 0.9% (2/229) of placebo-treated subjects had ≥50% LDL-C reduction from baseline compared with 39.8% (92/231) of inclisiran-treated subjects.
- Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk.

- At any visit, 18.4% (44/239) of placebo-treated subjects achieved their corresponding LDL-C targets compared with 77.2% (186/241) of inclisiran-treated subjects.
- At Day 510, 1.4% (1/71) of placebo-treated subjects with ASCVD achieved their LDL-C target of <70 mg/dL compared to 52.5% (31/59) of inclisiran-treated subjects with ASCVD

Table 15. ORION-9: Individual responsiveness of subjects reaching on-treatment LDL-C levels-ITT Population

LDL-C (mg/dL) levels	Placebo (N= 240) n (%)	Inclisiran (N=242) n (%)
Number of Subjects Reaching LDL-C Level at Day 510*		
< 25 mg/dL	0	2 (0.8)
< 50 mg/dL	2 (0.8)	46 (19.0)
< 70 mg/dL	3 (1.3)	99 (40.9)
< 100 mg/dL	21 (8.8)	158 (65.3)
≥ 100 mg/dL	208 (86.7)	73 (30.2)
Missing	11 (4.6)	11 (4.5)

Source: Applicant's ORION-9 submission, Table 14.2.16.1

* Subjects can be counted in multiple categories.

Abbreviations: ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol

Reviewer comment: The results of these secondary efficacy endpoints are generally supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. (b) (4)

[Redacted text block]

Exploratory Endpoints

Additional endpoints explored by this reviewer include percentage change from Baseline in triglycerides, HDL-C, and lipoprotein (a) [Lp(a)] (ITT population).

- The placebo-adjusted percentage change in TG from baseline to Day 510 was -12% (p<0.003).
- The placebo-adjusted percentage change in HDL-C from baseline to Day 510 was +3% (p<0.05).

- The placebo-adjusted percentage change in Lp(a) from baseline to Day 540 was -20% (p<0.0001).

Inclisiran lowered TG by approximately 12% and Lp(a) by 20%. HDL-C increased slightly with inclisiran exposure. These changes are not considered adverse, but the clinical significance is unclear.

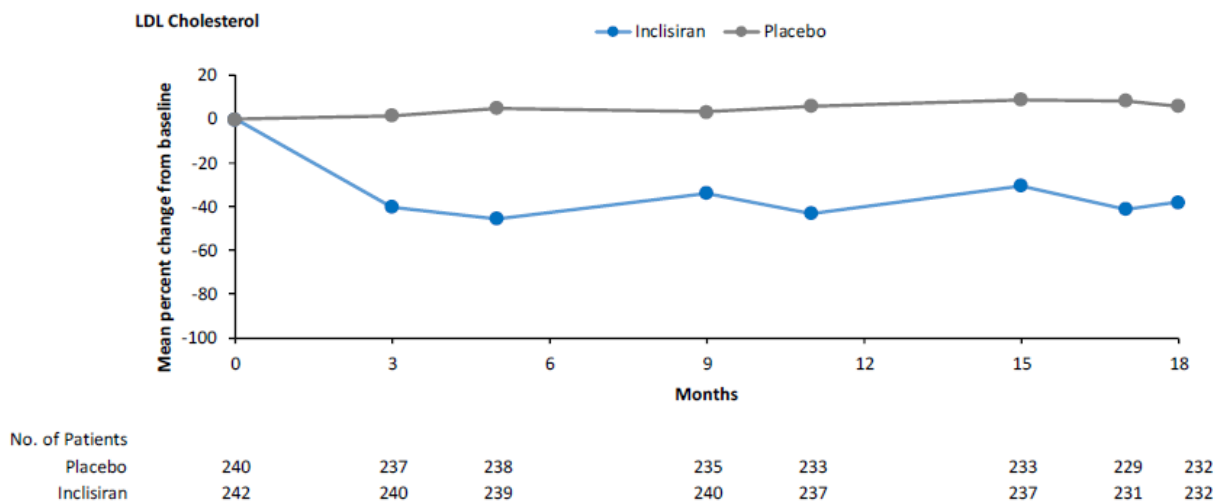
Dose/Dose Response

Not applicable as there is only one dose in this trial.

Durability of Response

As shown in the figure below, inclisiran had a consistent and durable effect on the reduction of LDL-C over time in this study of 18 months duration.

Figure 2. ORION-9: Observed Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with HeFH on Maximally Tolerated Statin Treated with Inclisiran and Placebo-ITT Population



Reflexive LDL-C measurements used as per protocol.
 Source: Applicant's ORION-9 submission, Figures 4 and 14.2.1.3

Persistence of Effect

Not applicable in this trial; refer to Section 7.1.5 for a brief discussion of the persistence of effect.

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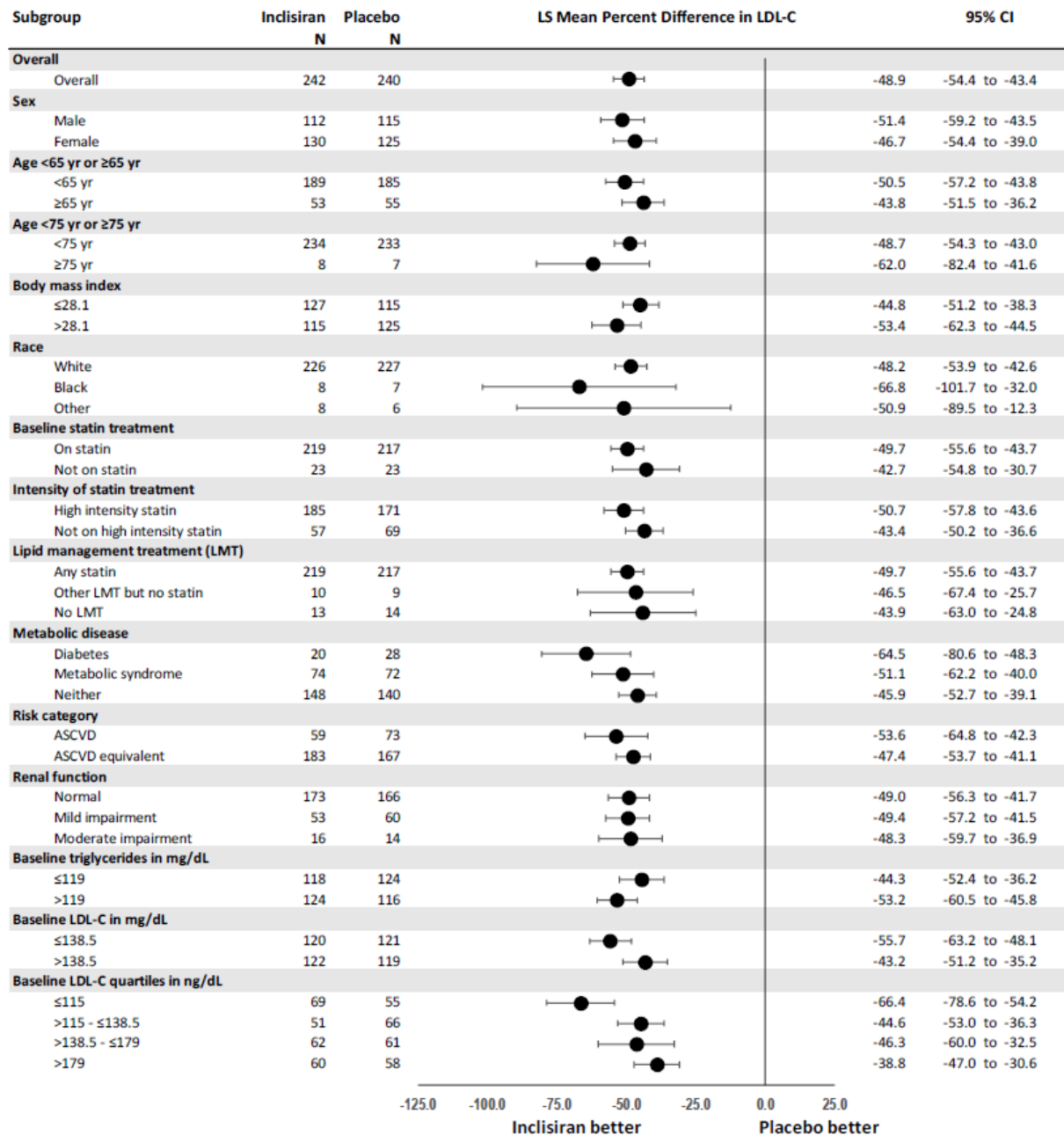
Additional Analyses Conducted on the Individual Trial

Subgroup Analyses of Efficacy

Subgroup analyses for efficacy were performed based on multiple categories using MMRM to account for missing data (see figure below). In all subgroups, inclisiran lowered LDL-C more than placebo ($p < 0.05$). The estimates of the magnitude of the treatment effect were consistent across subgroups.

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Figure 3. ORION-9: Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 - Subgroup Analyses - ITT Population



Source: Applicant's ORION-9 submission, Figures 9 and 14.2.14.1

Reviewer comment: In this trial of HeFH patients, inclisiran demonstrated a clinically meaningful reduction in LDL-C relative to placebo.

6.2. ORION-10 (MDCO-PCS-17-04)

6.2.1. Study Design

Overview and Objective

Title of Study: A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C)

The primary objective was to evaluate the effect of inclisiran treatment on LDL-C levels at Day 510. Other objectives included an assessment of the safety and tolerability profile of inclisiran.

Trial Design

The three pivotal Phase III trials, ORION-9, ORION-10, and ORION-11, evaluated the efficacy and safety of inclisiran sodium 300 mg in subjects with HeFH (ORION-9; 482 subjects), ASCVD (ORION-10; 1561 subjects) and ASCVD and ASCVD Risk Equivalent (ORION-11; 1617 subjects). The design of these 3 trials were nearly identical, the main difference was the study population enrolled into the trial. In this section, only relevant differences in ORION-10 as compared to ORION-9 will be described.

Key Inclusion Criteria that are unique to ORION-10 as compared to ORION-9:

- History of ASCVD (CHD, CVD or PAD)³¹
- Serum LDL-C ≥ 70 mg/dL at screening
- No current or planned renal dialysis or renal transplantation.

³¹ Coronary heart disease (CHD):

- Prior myocardial infarction
- Prior coronary revascularization (PCI or CABG)
- Angiographic or CT-imaging (eg, MDCT/CTA) evidence of coronary atherosclerosis (>70% stenosis in at least one major epicardial coronary artery)

Cerebrovascular disease (CVD):

- Prior ischemic stroke confirmed by a brain imaging study – CT or MRI; thought not to be caused by atrial fibrillation, valvular heart disease or mural thrombus
- Carotid artery stenosis >70% on prior angiography or ultrasound
- History of prior percutaneous or surgical carotid artery revascularization

Peripheral arterial disease (PAD):

- Prior documentation of a resting ankle-brachial index ≤ 0.85
- History of prior percutaneous or surgical revascularization of an iliac, femoral, or popliteal artery
- Prior non-traumatic amputation of a lower extremity due to peripheral artery disease

Statistical Analysis Plan

Sample Size and Power: The sample size calculation was performed with the assumption (which was based on the observed results from a Phase II study) that the difference in change from baseline between the active dose group and the placebo group for LDL-C would be no less than 30 mg/dL, with a standard deviation of 20 mg/dL. Assuming about a 5% drop out rate, the sample size would be approximately 1425 subjects that were evaluable for efficacy across the placebo and inclisiran dose groups. This sample size of at least 1425 evaluable subjects, would provide more than 90% power to detect a 30% reduction of LDL-C levels in the inclisiran group compared to the placebo group at one-sided significance level of 0.025.

Protocol Amendments

Amendment 1, dated 16 Jan 2018:

- The criterion for renally impaired subjects was revised based on a recently completed clinical pharmacology study. Calculated glomerular filtration rate >30 mL/min by eGFR was removed from inclusion criterion #5. Text was added to provide background of the new Phase I clinical data that supported expansion of use in subjects with renal impairment to include severe renal impairment.
- Initiation of protocol-prohibited lipid-lowering therapy (e.g., an approved PCSK9 inhibitor) was added as a possible reason that a subject may have discontinued their participation in the study.
- Clarified standards for vital sign measurements based on FDA comments. When available, an automated blood pressure device was recommended for collection of blood pressure and the result recorded to the nearest mmHg.

Amendment 2, dated 12 Jul 2018:

- Changes were made to the primary endpoint analysis as it related to how missing data were handled for the analyses. Missing data for the primary and key secondary endpoints were imputed according to the algorithm specified in the SAP.
- Changes were made to add the prefilled syringe as a drug product presentation. Blinding of the vials and syringes were described.
- Changes were made to clarify the ADA testing plan.

Amendment 3, dated 10 Sep 2018:

- Changes were made to the Procedures in Case of Emergency section of the protocol to replace [REDACTED] ^{(b) (4)} with The Medicines Company as the contact representative.

- Changes were made to remove the month, year and/or edition associated with the Investigator's Brochure as investigative sites should always refer to the latest edition.

Amendment 4, dated 31 Jan 2019:

- Changes were made to account for refinement in the description of time-adjusted analyses of LDL-C: "After Day 90 and up to Day 540" (versus between Day 90 and Day 540).
- Changes were made to clarify the plan to test for ADA. Serum samples for analysis were collected at every visit but assessment of ADA only occurred for samples collected at the following visits: Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510.
- Changes were made to Schedule of Assessments to align with Health Authority feedback for wider visit windows (± 30 days versus ± 14 days) and to clarify that analysis windows were defined to maximize the amount of data that were included in the analysis models.
- Changes were made to account for the addition of a new analysis set: the FAS included all subjects who were randomized into the study, took any study drug, and had at least 1 post treatment lipid data measured.
- Changes were made regarding the handling of missing data per Health Authority feedback. Additional methods to impute and analyze data were utilized as sensitivity/exploratory analyses for the co-primary endpoints. An MMRM without any imputation (assuming data are MAR) was also performed.
- Changes were made to add analyses for clinically significant (CS) laboratory parameters: Analyses were performed for each laboratory parameter by treatment group for incidence rates of both potentially clinically significant (PCS)/CS values for subjects without PCS/CS value at baseline.

Reviewer comment: The clinical team agreed with the applicant's protocol amendments and do not believe that these modifications had a negative impact on the integrity of the trial or our interpretation of the results.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted in compliance with the protocol, The Medicines Company's standard operating procedures and/or guidelines and any vendor partners where applicable, the US FDA regulations, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and

other local regulations, in operation at the time of the study.

Financial Disclosure

Refer to Section 13.2 Financial Disclosure for additional information.

Patient Disposition

The study was conducted entirely in the United States at 146 sites (81 of these sites enrolled >7 subjects); subjects were randomized at 145 sites. A total of 2329 subjects were screened and 1561 were randomized. In ORION-10, approximately 33% (768/2329) of screened subjects were screen failures. The 3 most common inclusion/exclusion criteria not met was the serum LDL-C ≥ 1.8 mmol/L (70 mg/dL) inclusion criterion in 20% (453/2329), the “any condition that interferes with the study” exclusion criterion in 2.5% (58/2329), and the triglycerides inclusion criterion (fasting triglyceride <400 mg/dL at screening) in 2.4% (56/2329) of screened subjects.

As shown in the table below, at Day 510 approximately 93% (1444/1561) of the ITT Population were still in the study; 92% (715/780) of placebo-treated subjects and 93% (729/781) of inclisiran-treated subjects. At Day 540 (EOS Visit) approximately 91% (1415/1561) completed the study; 89% (694/780) of placebo-treated subjects and 92% (721/781) of inclisiran-treated subjects. A total of 11% (86/780) of placebo-treated subjects discontinued the study. The most common reason for discontinuation from the study was withdrawal of consent (4.4%; 34/780). A total of 8% (60/781) of inclisiran-treated subjects discontinued the study. Similarly, the most common reason for discontinuation from the study was withdrawal of consent (3.1%; 24/781).

The disposition of subjects was reasonably balanced between the treatment groups. All but 2 of the 1561 randomized subjects were treated (778 with placebo and 781 with inclisiran) and included in the Safety Population. The Safety Population excludes 2 subjects assigned to inclisiran who were not dosed and 2 placebo subjects who were dosed instead with inclisiran.

Table 16. ORION-10: Patient Disposition for ITT Population

	Placebo (N=780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Completing the Day 510 visit	715 (91.7)	729 (93.3)	1444 (92.5)
Completing the Day 540 visit	694 (89.0)	721 (92.3)	1415 (90.6)
Discontinued	86 (11.0)	60 (7.7)	146 (9.4)
Death	11 (1.4)	12 (1.5)	23 (1.5)
Adverse event	5 (0.6)	8 (1.0)	13 (0.8)
Withdrew consent	34 (4.4)	24 (3.1)	58 (3.7)

Physician decision	0	1 (0.1)	1 (0.1)
Lost to follow-up	24 (3.1)	10 (1.3)	34 (2.2)
Initiation of PCSK9 inhibitor	9 (1.2)	0	9 (0.6)
Other	3 (0.4)	5 (0.6)	8 (0.5)
Duration on study (days)*			
Mean ± SD	513.4±89.7	516.5±86.3	514.9±88.0
Median	536	536	536
Q1, Q3	29, 576	1, 589	1, 589

Abbreviations: ITT=intent-to-treat; PCSK9= proprotein convertase subtilisin/kexin type 9

* Duration on study is defined as the number of days from the first date of treatment to the date of last recorded visit in the database.

Source: Applicant's ORION-10 submission, Tables 14.1.2.1 and 14.1.7.1. and FDA OCS Analysis Studio, Custom Table Builder. Columns - Dataset: Demographics; Filter: ITTFL = 'Y'. Table Section 1 - Dataset: Disposition; Filter: None.A

Protocol Violations/Deviations

Protocol deviations were similar between the treatment groups (see table below). The most common protocol deviations were prohibited concomitant medication/change in baseline statin or other lipid-lowering therapy dose and mis-dosing for any reason other than subject safety or withdrawal. Changes in lipid-modifying therapy (LMT) during the trial is discussed in more detail in a subsequent section of the review.

Table 17. ORION-10: Protocol Deviations – ITT Population

	Placebo (N=780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Subjects with at least 1 protocol deviation	175 (22.4)	170 (21.8)	345 (22.1)
Inclusion and/or exclusion criteria violation	20 (2.6)	34 (4.4)	54 (3.5)
Laboratory assessments not drawn at Days 1, 510 or 540 (EOS) Visits	25 (3.2)	16 (2.0)	41 (2.6)
Mis-Dosing for any reason other than subject safety or withdrawal*	42 (5.4)	24 (3.1)	66 (4.2)
Prohibited concomitant medication/change in baseline statin or other lipid-lowering therapy dose	95 (12.2)	93 (11.9)	188 (12.0)
SAE form not reported to applicant within 24 hours	12 (1.5)	24 (3.1)	36 (2.3)
Informed consent not signed prior to study entry	0	0	0

Abbreviations: ITT=intent-to-treat; EOS=end of study; SAE=serious adverse event

* Defined as missing dose or a dose delayed by more than 30 days

Source: Applicant's ORION-10 submission, Tables 14.1.5.1

Table of Demographic Characteristics

Table 18. ORION-10: Demographic and Baseline Characteristics of the ITT Population

Demographic Parameters	Placebo Control Group (N= 780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Sex			
Male	548 (70.3)	535 (68.5)	1083 (69.4)
Female	232 (29.7)	246 (31.5)	478 (30.6)
Age			
Mean years (SD)	65.7 (8.9)	66.4 (8.9)	66.0 (8.9)
Median (years)	66.0	67.0	67.0
Min, max (years)	39, 89	35, 90	35, 90
Age Group			
18 - < 65 years	333 (42.7)	297 (38.0)	630 (40.4)
≥ 65 years	447 (57.3)	484 (62.0)	931 (59.6)
18 - < 75 years	649 (83.2)	638 (81.7)	1287 (82.4)
≥ 75 years	131 (16.8)	143 (18.3)	274 (17.6)
Weight			
Mean, kg (SD)	93.6 (21.6)	92.2 (19.6)	92.9 (20.6)
BMI (kg/m ²)			
Mean, kg (SD)	31.8 (6.4)	31.5 (6.3)	31.7 (6.4)
Race			
White	685 (87.8)	653 (83.6)	1338 (85.7)
Black or African American	87 (11.2)	110 (14.1)	197 (12.6)
Asian	1 (0.1)	9 (1.2)	10 (0.6)
American Indian or Alaska Native	4 (0.5)	2 (0.3)	6 (0.4)
Native Hawaiian or other Pacific Islander	3 (0.4)	7 (0.9)	10 (0.6)
Ethnicity			
Hispanic or Latino	104 (13.3)	108 (13.8)	212 (13.6)
Not Hispanic or Latino	676 (86.7)	673 (86.2)	1349 (86.4)
Region			
United States	780 (100)	781 (100)	1561 (100)
Baseline GFR Category (mL/min/1.73 m ²)			
≥15 to <30	7 (0.9)	10 (1.3)	17 (1.1)
≥30 to <60	169 (21.7)	170 (21.8)	339 (21.7)
≥60 to <90	414 (53.1)	422 (54.0)	836 (53.6)
≥90	190 (24.4)	179 (22.9)	369 (23.6)
ASCVD	780 (100)	781 (100)	1561 (100)
Hx of CHD	719 (92.2)	703 (90.0)	1422 (91.1)
Hx of CVD	114 (14.6)	146 (18.7)	260 (16.7)

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Demographic Parameters	Placebo Control Group (N= 780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Hx of PAD	84 (10.8)	90 (11.5)	174 (11.1)
Diabetes Mellitus	331 (42.2)	371 (47.5)	702 (45.0)
Smoking (current, within past 30 days)	111 (14.2)	123 (15.7)	234 (15.0)
Hypertension	701 (89.9)	714 (91.4)	1415 (90.6)
Baseline LDL-C (mg/dL)			
Mean (SD)	104.8 (37.0)	104.5 (39.6)	104.6 (38.3)
Median (mg/dL)	95.0	94.0	95.0
Min, max (mg/dL)	40, 329	33, 466	33, 466
Baseline HDL-C (mg/dL)			
Mean (SD)	45.9 (14.4)	46.6 (14.3)	46.2 (14.3)
Median (mg/dL)	43.0	44.0	44.0
Min, max (mg/dL)	18, 116	20, 116	18, 116
Baseline Total Cholesterol (mg/dL)			
Mean (SD)	180.6 (43.6)	180.6 (46.1)	180.6 (44.8)
Median (mg/dL)	171.5	170.0	171.0
Min, max (mg/dL)	108, 461	70, 552	70, 552
Baseline Triglycerides (mg/dL)			
Mean (SD)	151.5 (88.6)	148.6 (79.1)	150.1 (84.0)
Median (mg/dL)	129.0	127.0	128.0
Min, max (mg/dL)	29, 956	43, 559	29, 956
Baseline non-HDL-C (mg/dL)			
Mean (SD)	134.7 (43.5)	134.0 (44.5)	134.4 (44.0)
Median (mg/dL)	124.0	122.0	124.0
Min, max (mg/dL)	68, 431	49, 496	49, 496
Baseline Apolipoprotein B (mg/dL)			
Mean (SD)	94.6 (25.1)	94.1 (25.6)	94.3 (25.3)
Median (mg/dL)	90.0	89.0	89.0
Min, max (mg/dL)	48, 234	39, 287	39, 287
Baseline PCSK9 (µg/L)			
Mean (SD)	414.9 (145.7)	422.1 (176.9)	418.5 (162.0)
Median (mg/dL)	394.9	405.2	400.9
Min, max (mg/dL)	106, 2416	154, 3814	106, 3814
Baseline Lipoprotein-a (nmol/L)			
Mean (SD)	123.0 (144.0)	120.1 (137.4)	121.6 (140.7)
Median (mg/dL)	56.0	57.0	56.0
Min, max (mg/dL)	2, 996	2, 919	2, 996
Baseline C Reactive Protein (mg/L)			
Mean (SD)	5.1 (8.5)	4.2 (6.9)	4.7 (7.7)

Demographic Parameters	Placebo Control Group (N= 780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Median (mg/dL)	2.3	2.1	2.2
Min, max (mg/dL)	0.1, 101.0	0.1, 76.2	0.1, 101.0

Abbreviations: GFR=glomerular filtration rate; SD=standard deviation; ASCVD=Atherosclerotic Cardiovascular Disease; CHD=Coronary Heart Disease; CVD= Cerebrovascular Disease; PAD= Peripheral Artery Disease
 Source: Applicant’s ORION-10 submission, Tables 14.1.8.1, 14.1.9.1, 14.2.15.1 and 14.3.3.1.1; response to FDA IR (3/12/2020)

Reviewer comment: The demographic and baseline characteristics are largely balanced between the two treatment groups. The study enrolled 86% of subjects who are White and 13% who are Black or African American. There is very limited representation of Asian, American Indian or other groups. Fourteen percent of subjects identified as Hispanic or Latino. Two-thirds (69%) of the study population is male and the mean age is 66 years old. The study population included relevant comorbidities such as ASCVD (100%, primarily CHD), renal impairment (23% [356/1561] had a GFR between 15 and 60 mL/min/1.73m), hypertension (91%) and diabetes (45%).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

At baseline, use of lipid modifying therapy (LMT) was reasonably balanced between the treatment groups (see table below). Overall, 95% (1478/1561) of subjects received LMT, 89% (1393/1561) of subjects received statin therapy, 31% (489/1561) received other LMT and 5% (85/1561) received other LMT and no statin. Approximately 5% (83/1561) were not taking any LMT at baseline.

Overall, 69% (1084/1561) were on a high intensity statin, 19% (292/1561) were on a moderate intensity statin and 1% (12/1561) were on a low intensity statin at baseline. Approximately 10% (153/1561) of subjects were treated with ezetimibe.

Table 19. ORION-10: Baseline Concomitant Medications of the ITT Population

Baseline Medications	Placebo Control Group (N= 780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Baseline Lipid Modifying therapy			
None	50 (6.4)	33 (4.2)	83 (5.3)
Non-statin (other LMT) only	38 (4.9)	47 (6.0)	85 (5.4)
Statins only	481 (61.7)	508 (65.0)	989 (63.4)
Other LMT used (± statin)	249 (31.9)	240 (30.7)	489 (31.3)

Baseline Medications	Placebo Control Group (N= 780) n (%)	Inclisiran (N=781) n (%)	Total (N=1561) n (%)
Baseline Lipid Modifying therapy			
Statins used (± other LMT)	692 (88.7)	701 (89.8)	1393 (89.2)
High Intensity*	546 (70.0)	538 (68.9)	1084 (69.4)
Moderate Intensity**	140 (17.9)	152 (19.5)	292 (18.7)
Low Intensity	6 (0.8)	6 (0.8)	12 (0.8)

Source: Applicant's ORION-10 submission, Table 14.1.16.2.1

Abbreviations: LMT= lipid modifying therapy

* High-Intensity: Atorvastatin 40-80mg; simvastatin 80mg; rosuvastatin 20-60 mg;

** Moderate Intensity: Atorvastatin 10-20mg or 40 mg 3x /week; lovastatin 40-80mg; simvastatin 20-40mg; rosuvastatin <=10 mg QD; pitavastatin 1-4mg; pravastatin 40-80 mg

Reviewer comment: The majority (~70%) of participants were on background high-intensity statin therapy, which is appropriate, as inclisiran, if approved, would be most clinically relevant in patients with HeFH or at higher CV risk not adequately controlled by maximally tolerated statin therapy. The enrolled population adequately reflects the intended clinical population.

Treatment Compliance and Concomitant Medications

Treatment Compliance

All study drugs were administered subcutaneously by clinical study site staff, primarily in the abdominal region (doses on Day 1, Day 90, Day 270, and Day 450). Overall, 86.9% (676/778) of placebo-treated subjects and 89.1% (696/781) of inclisiran-treated subjects received all 4 planned SC doses.

Reviewer comment: Approximately, 87% of placebo-treated subjects and 89% of inclisiran-treated subjects received all 4 planned SC doses. This level of treatment compliance is adequate to allow for a good assessment of steady-state and durable LDL-C reduction.

Changes in Lipid-Modifying Therapy (LMT) During Trial

Approximately 90% (1407/1561) of subjects had no new LMT added or changes to LMT usage during the study. Ten percent (81/780) of subjects in the placebo group and 9% (73/781) in the inclisiran group had changes in LMT use during the trial. Nine subjects (1%) in the placebo group began therapy with a PCSK9 monoclonal antibody and were discontinued; no subject in the inclisiran group began therapy with a PCSK9 monoclonal antibody.

Shifts from baseline in statin intensity were minimal in both treatment groups. Most subjects remained on their statin intensity category (high, moderate, low or none) throughout the trial.

New or changed concomitant medications during the study were similar between the placebo and inclisiran treatment groups.

Efficacy Results – Primary Endpoint

The applicant’s co-primary endpoints for this trial are:

- Percentage change in LDL-C from Baseline to Day 510.
- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

Percentage change in LDL-C from Baseline to Day 510:

The placebo-adjusted change in LDL-C from baseline to Day 510 using observed values was -57.6% (p<0.0001). The primary analysis used the same prespecified washout model as described in ORION-9 to account for missing data. The placebo-adjusted change in LDL-C from baseline to Day 510 using the imputed values was -52.2% (p<0.0001).

Table 20. ORION-10: Primary Efficacy Endpoint – ITT Population

Primary Endpoint	Placebo (N= 780)	Inclisiran (N=781)	p-value
Percentage Change in LDL-C from Baseline to Day 510 (Observed values)			
LS Mean (95% CI)	1.3 (-1.2,3.8)	-56.3 (-58.4, -54.3)	
LS Mean Difference (95% CI) from Placebo		-57.6 (-60.9, -54.4)	<.0001
Percentage Change in LDL-C from Baseline to Day 510 (Washout – Imputed values)			
LS Mean (95% CI)	1.0 (-1.5, 3.4)	-51.3 (-53.8, -48.8)	
LS Mean Difference (95% CI) from Placebo		-52.2 (-55.7, -48.8)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant’s ORION-10 submission, Tables 14, 14.2.1.1, 14.2.2.1.1 and 14.2.15.1

Three additional, prespecified sensitivity analyses (PMM, MMRM, ANCOVA with current use of statins or other LMTs as fixed effects) for handling missing values were used to analyze the percentage change from baseline at Day 510 co-primary endpoints. Similar (-54.5%, -57.2% and -52.3%) and statistically significant (p<0.0001), placebo-adjusted differences were demonstrated for this primary endpoint, regardless of sensitivity analysis used to handle missing values.

Reviewer comment: In a population with ASCVD, inclisiran lowers LDL-C to a clinically meaningful degree: -51% from the inclisiran group's baseline and -52% from baseline as compared to the placebo group.

Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540
 Compared to placebo, the time-adjusted percentage change from baseline after Day 90 and up to Day 540 was -53.8% (p<0.0001) (see table below).

Table 21. ORION-10: Co-Primary Efficacy Endpoint – Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540 ITT Population

Primary Endpoint	Placebo (N= 780)	Inclisiran (N=781)	p-value
Time-Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540*			
LS Mean (95% CI)	2.5 (0.8,4.3)	-51.3 (-53.0, -49.5)	
LS Mean Difference (95% CI) from Placebo		-53.8 (-56.2, -51.3)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant's ORION-10 submission, Tables 15 and 14.2.1.1

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.

Sensitivity analyses (PMM, MMRM, ANCOVA with current use of statins or other LMTs as fixed effects) for the co-primary endpoint of time-adjusted percentage change from baseline after Day 90 and up to Day 540, demonstrated similar (-54.5%, -57.2% and -52.3%) and statistically significant (p<0.0001), placebo-adjusted differences, regardless of sensitivity analysis used to handle missing values.

Data Quality and Integrity

The study was well executed and largely adhered to the protocol. The protocol amendments were reasonable and unlikely to have had a negative impact on the integrity of the trial or our interpretation of the results. Protocol deviations were similar between the treatment groups and were not believed to have a negative impact on study results. Subject retention was very good (91%). The applicant made reasonable efforts to blind study medication from subjects and investigators. There were no notable financial conflicts of interest. Datasets were complete,

generally straightforward to navigate, and of high quality. There were no potential issues concerning the submitted data quality or integrity that raise questions about the purported efficacy results. Thus, the study has generated data that are robust, interpretable, and persuasive in supporting the proposed indication.

Efficacy Results – Secondary and other relevant endpoints

Three key secondary endpoints were defined in the protocol and statistical analysis plan:

- Absolute change in LDL-C from Baseline to Day 510.
 - The placebo-adjusted absolute change from baseline to Day 510 in LDL-C levels was -54.1 mg/dL ($p < 0.0001$) for inclisiran-treated subjects.
- Time-adjusted absolute change in LDL-C from Baseline after Day 90 and up to Day 540.
 - Compared to placebo, the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was -53.3 mg/dL ($p < 0.0001$).
- Percentage change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C.
 - The placebo-adjusted percentage change in PCSK9 from baseline to Day 510 was -83.3% ($p < 0.0001$).
 - The placebo-adjusted percentage change in TC from baseline to Day 510 was -33.1% ($p < 0.0001$).
 - The placebo-adjusted percentage change in Apo-B from baseline to Day 510 was -43.1% ($p < 0.0001$).
 - The placebo-adjusted percentage change in non-HDL-C from baseline to Day 510 was -47.4% ($p < 0.0001$).

Table 22. ORION-10: Key Secondary Efficacy Endpoints-ITT Population

Key Secondary Efficacy Endpoints	Placebo (N= 780)	Inclisiran (N=781)	p-value
Absolute Change in LDL-C (mg/dL) from Baseline to Day 510; Control-Based Pattern-Mixture Model (PMM)*			
LS Mean (95% CI)	-2.1 (-4.4,0.2)	-56.2 (-58.5, -53.9)	
LS Mean Difference (95% CI) from Placebo		-54.1 (-57.4, -50.9)	<.0001
Time-Adjusted Absolute Change in LDL-C (mg/dL) from Baseline After Day 90 and up to Day 540; PMM*			
LS Mean (95% CI)	-0.4 (-2.1, 1.4)	-53.7 (-55.4, -51.9)	
LS Mean Difference (95% CI) from Placebo		-53.3	<.0001

		(-55.8, -50.8)	
Percentage Change from Baseline to Day 510 in PCSK9; PMM*			
LS Mean (95% CI)	13.5 (9.3, 17.8)	-69.8 (-73.9, -65.7)	
LS Mean Difference (95% CI) from Placebo		-83.3 (-89.3, -77.3)	<.0001
Percentage Change in TC from Baseline to Day 510; PMM*			
LS Mean (95% CI)	-0.4 (-2.0, 1.1)	-33.6 (-35.1, -32.0)	
LS Mean Difference (95% CI) from Placebo		-33.1 (-35.3, -31.0)	<.0001
Percentage Change in Apo-B from Baseline to Day 510; PMM*			
LS Mean (95% CI)	-1.7 (-3.5, 0.0)	-44.8 (-46.5, -43.1)	
LS Mean Difference (95% CI) from Placebo		-43.1 (-45.5, -40.7)	<.0001
Percentage Change in non-HDL-C from Baseline to Day 510; PMM*			
LS Mean (95% CI)	-0.1 (-2.1, 2.0)	-47.4 (-49.4, -45.4)	
LS Mean Difference (95% CI) from Placebo		-47.4 (-50.3, -44.5)	<.0001

Source: Applicant's ORION-10 submission, Tables 14.2.3.1, 14.2.4.1, 14.2.5.1, 14.2.6.1, 14.2.7.1, and 14.2.8.1
Abbreviations: Apo-B=apolipoprotein B; CI=confidence interval; HDL-C = high density lipoprotein cholesterol; ITT=intent-to-treat; LDL-C = low density lipoprotein cholesterol; LS=least squares; MAR=missing at random
* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's Method.

Reviewer comment: The results of the key secondary efficacy endpoints are consistent and supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. This is expected as LDL-C is a major component of TC and non-HDL-C, and apolipoprotein B is the primary apolipoprotein of LDL-C. In addition, a reduction in PCSK9 levels is the mechanism of action through which inclisiran lowers LDL-C.

Other secondary endpoints of interest include:

- Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510 (see table below).

- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from Baseline.
 - At any time during the study, 6.5% (50/767) of placebo-treated subjects had ≥50% LDL-C reduction from baseline compared with 91.4% (701/767) of inclisiran-treated subjects.
 - At Day 510, 2.6% (17/666) of placebo-treated subjects had ≥50% LDL-C reduction from baseline compared with 72.8% (503/691) of inclisiran-treated subjects.
- Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk.
 - At any visit, 36.1% (277/767) of placebo-treated subjects achieved their corresponding LDL-C targets compared with 94.1% (722/767) of inclisiran-treated subjects.
 - At Day 510, 17.9% (119/666) of placebo-treated subjects with ASCVD achieved their LDL-C target of <70 mg/dL compared to 84.1% (581/691) of inclisiran-treated subjects with ASCVD

Table 23. ORION-10: Individual responsiveness of subjects reaching on-treatment LDL-C levels-ITT Population

LDL-C (mg/dL) levels	Placebo (N= 780) n (%)	Inclisiran (N=781) n (%)
Number of Subjects Reaching LDL-C Level at Day 510*		
< 25 mg/dL	4 (0.5)	160 (20.5)
< 50 mg/dL	19 (2.4)	483 (61.8)
< 70 mg/dL	119 (15.3)	581 (74.4)
< 100 mg/dL	387 (49.6)	651 (83.4)
≥ 100 mg/dL	279 (35.8)	40 (5.1)
Missing	114 (14.6)	90 (11.5)

Source: Applicant's ORION-10 submission, Table 14.2.16.1

* Subjects can be counted in multiple categories.

Abbreviations: ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol

Reviewer comment: The results of these secondary efficacy endpoints are generally supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. (b) (4)

[Redacted]

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Exploratory Endpoints

Additional endpoints explored by this reviewer include percentage change from Baseline in triglycerides, HDL-C, and lipoprotein (a) [Lp(a)] (ITT population).

- The placebo-adjusted percentage change in TG from baseline to Day 510 was -10% ($p < 0.0001$).
- The placebo-adjusted percentage change in HDL-C from baseline to Day 510 was +5% ($p < 0.0001$).
- The placebo-adjusted percentage change in Lp(a) from baseline to Day 540 was -32% ($p < 0.0001$).

Reviewer comment: Inclisiran lowered TG by approximately 10% and Lp(a) by 30%. HDL-C increased slightly with inclisiran exposure. These changes are not considered adverse and, particularly the Lp(a) reduction, trend in a potentially beneficial direction; however, the true clinical significance of these changes is unclear.

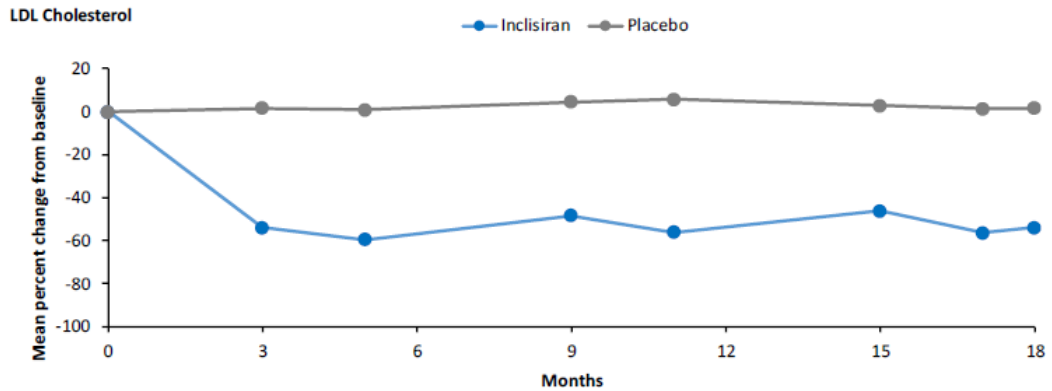
Dose/Dose Response

Not applicable as there is only one dose in this trial.

Durability of Response

As shown in the figure below, inclisiran had a consistent and durable effect on the reduction of LDL-C over time in this study of 18 months duration.

Figure 4. ORION-10: Observed Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with ASCVD on Maximally Tolerated Statin Treated with Inclisiran and Placebo-ITT Population



No. of Patients								
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

Reflexive LDL-C measurements used as per protocol.
 Source: Applicant's ORION-10 submission, Figures 4 and 14.2.1.3

Persistence of Effect

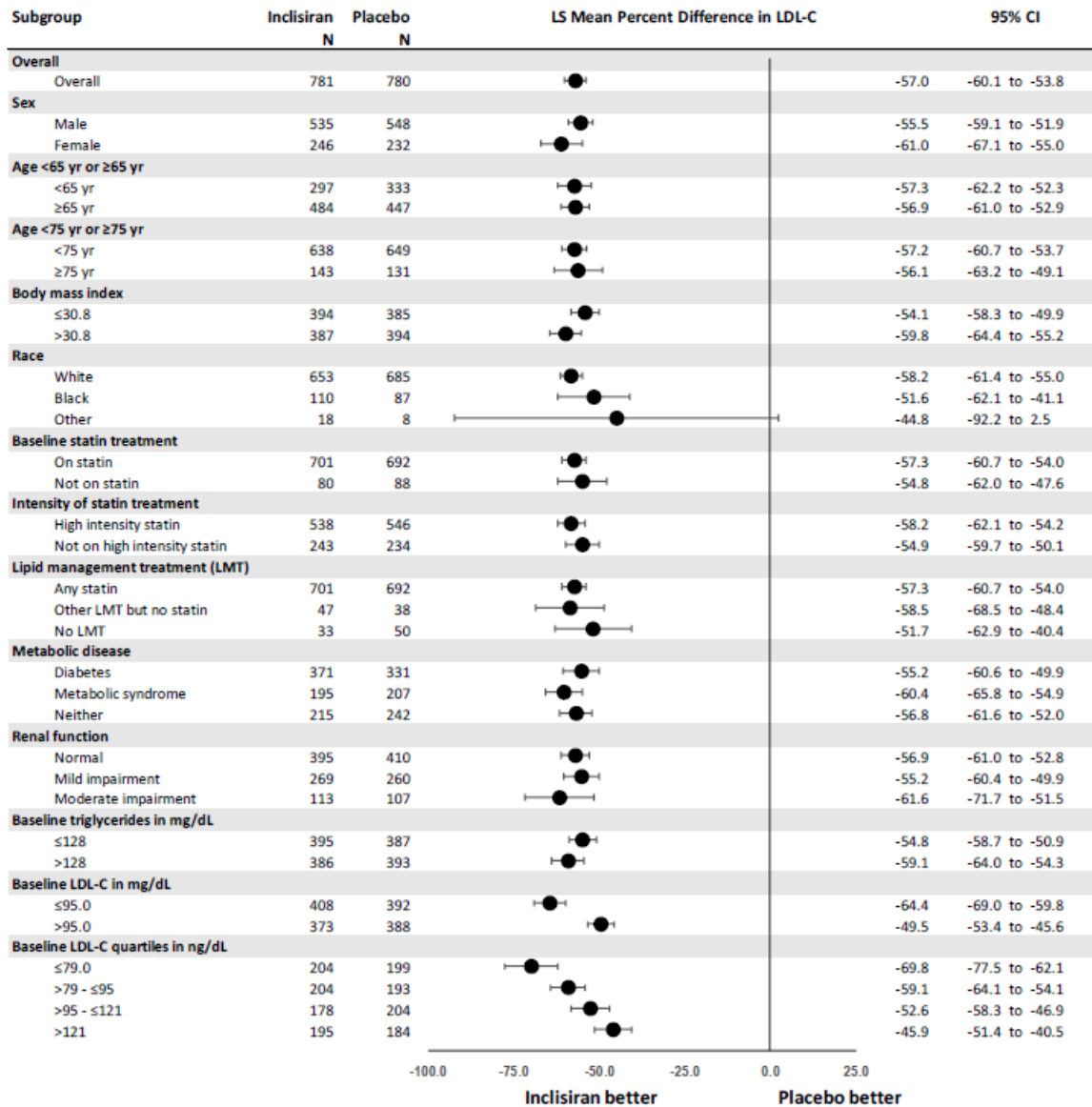
Not applicable in this trial; refer to Section 7.1.5 for a brief discussion of the persistence of effect.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses of Efficacy

Subgroup analyses for efficacy were performed based on multiple categories using MMRM to account for missing data (see figure below). In all subgroups, inclisiran lowered LDL-C more than placebo. The estimate of the treatment effect was generally similar across subgroups, although there was a trend toward increased magnitude of treatment effect with lower baseline LDL-C.

Figure 5. ORION-10: Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 - Subgroup Analyses - ITT Population



Source: Applicant's ORION-10 submission, Figures 7 and 14.2.14.1

Reviewer comment: In this trial of patients with ASCVD, inclisiran demonstrated a clinically meaningful reduction in LDL-C relative to placebo.

6.3. ORION-11 (MDCO-PCS-17-08)

6.3.1. Study Design

Overview and Objective

Title of Study: A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C)

ORION-11 was an international (non-US), multi-center study conducted (i.e., screened potential study subjects) in 72 centers in 8 countries: Czech Republic, Germany, Hungary, Netherlands, Poland, South Africa, Ukraine, and United Kingdom. The primary objective was to evaluate the effect of inclisiran treatment on LDL-C levels at Day 510. Other objectives included an assessment of the safety and tolerability profile of inclisiran.

Trial Design

The three pivotal Phase III trials, ORION-9, ORION-10, and ORION-11, tested the efficacy and safety of inclisiran sodium 300 mg in subjects with HeFH (ORION-9; 482 subjects), ASCVD (ORION-10; 1561 subjects) and ASCVD and ASCVD Risk Equivalent (ORION-11; 1617 subjects). The design of these 3 trials were nearly identical, the main difference was the study population enrolled into the trial. In this section, only relevant differences in ORION-11 as compared to ORION-9 and ORION-10 will be described.

Key Inclusion Criteria that are unique to ORION-11 as compared to ORION-10:

- History of ASCVD (CHD, CVD or PAD) or ASCVD-risk equivalent³²
- Serum LDL-C ≥ 70 mg/dL at screening for ASCVD subjects or ≥ 100 mg/dL for ASCVD-risk equivalent subjects at screening.
- Calculated glomerular filtration rate >30 mL/min by estimated glomerular filtration rate (eGFR) using standardized clinical methodology.

Reviewer comment: As was discussed at the End-of-Phase 2 meeting on April 6, 2017 and in the FDA letter to the applicant on 9/13/2019, our current regulatory approach to LDL-C-lowering drugs is that the (b) (4) indication would likely be similar to that granted for evolocumab and alirocumab (i.e., as an adjunct to diet and maximally tolerated statin therapy

³² ASCVD risk equivalent is defined as those subjects with type 2 diabetes mellitus, FH, or 10-year risk of 20% or greater of having a CV event assessed by Framingham Risk Score or equivalent (target LDL-C of <100 mg/dL).

for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C unless the applicant can provide positive results from a CVOT. The applicant was informed that they could include patients with ASCVD-risk equivalents in their phase 3 trials, (b) (4)

[Redacted]

[Redacted] (b) (4)

The safety data should represent the entire trial population (both with ASCVD and those with only ASCVD-risk equivalents) so changes would not need to be made in reporting adverse event statistics.

Thus, in ORION-11, the presentation of the efficacy data will be slightly different than in ORION-10 (all ASCVD patients) and ORION-9 (all HeFH patients) in that the ASCVD-risk equivalent patients will be removed from the final efficacy findings (b) (4).

Protocol Amendments

Amendment 1 (05 Jan 2018) included both clinical and administrative amendments. Clarifications were made to the protocol synopsis and main body to address comments received from an FDA review of the study protocol and correct typographical errors noted since finalization of the original version of the protocol. In this amendment, a U.S. IND No. (127589) was added to the title page, as all sites were conducted under the US IND. Exclusion criteria were modified to allow NYHA class III heart failure subjects and last known left ventricular ejection fraction was changed from <30% to <25% based on FDA feedback. Additional details were provided within the Efficacy Analysis section to clarify that the secondary efficacy endpoints would not be tested if 1 of the co-primary efficacy endpoints null hypothesis failed to be rejected. Withdrawal criteria were updated to clarify training requirements and the data collected for subjects that terminated the study early. Also, initiation of protocol-prohibited lipid-lowering therapy (e.g., an approved PCSK9 inhibitor) was added to the eCRF as one of the pre-identified reasons for a subject to discontinue from participating in the study.

Text was updated in footnote 1 and 7 in the Schedule of Assessments table to clarify standards for vital sign measurements. The Screening Period (Day -14 to -1) section was updated to clarify the laboratory results required for Randomization, a reference was added, and duplicated text was removed. The Chemistry section was updated to clarify that HbA1C would not be performed on Days 150 and 330. Based on FDA request, updates and clarifications were made to the SAP sections of the protocol: The ITT population would be the primary population for the efficacy analysis. Efficacy analysis would also be performed for the mITT population as supportive analysis. Sensitivity analyses would be performed on the primary and key secondary efficacy endpoints to assess the impact of missing values. Sensitivity analyses to explore the dropout pattern and its possible impact on treatment comparisons would be performed. Pattern-Mixture Model (PMM) would be used to explore the possibility of data missing not at random (MNAR) for subjects who discontinued study treatment. A control-based pattern-mixture model would be utilized. Multiple imputation would be used to account for uncertainty in the imputation process and results from the imputed datasets would be combined using Rubin's method. Furthermore, a tipping point analysis would be performed to search for the tipping point that reverses the study conclusion.

Amendment 2 (31 Jan 2019) included only clinical amendments. In this amendment, the description of the co-primary endpoint was clarified to be "time adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540". Monitoring of ADA serum samples were updated to clarify the distinction between timing of sampling for ADA and which samples were to be assessed for ADA. Based on health authority feedback, a wider visit window (± 30) was added to the Schedule of Assessment table to give subjects greater flexibility to make visit windows and ensure more data captured. The modified windows were also aligned with the rules of protocol deviation. Based on FDA, updates and clarifications were made to the SAP sections of the protocol.

Reviewer comment: The clinical team agreed with the applicant's protocol amendments and do not believe that these modifications had a negative impact on the integrity of the trial or our interpretation of the results.

Statistical Analysis Plan (SAP) Changes

An addendum to the SAP (dated 26 Sept 2019) incorporated changes to align the statistical analyses of this study to the SAPs of subsequent Phase III studies and integrated analyses. Key changes in the statistical analyses are listed below.

- Statin/LMT Use at Baseline

Most subjects (94.7%) were currently using statins or other LMT at baseline. The applicant states that due to the default method of equal weighting the effects in the models, the small number of subjects who were not currently using statins or other LMT at baseline were skewing the least squares means estimates of the treatment groups. Therefore, additional analyses

were performed excluding this effect from the efficacy models. All statistical models that included the statin or other LMT use at baseline effect were rerun with that effect removed (“a” tables in applicant’s document).

- Modified Multiple Imputation Washout Model (“b” tables in applicant’s document)

The multiple imputation washout model was modified such that subjects in the inclisiran group who received all 4 doses of study drug, had the Day 510 value missing, and had evaluable data at Day 540, had their intermittent missing Day 510 values imputed assuming the missing data were MAR. This washout model was pre-specified in the SAPs of subsequent Phase III studies and integrated analyses as the primary method of analysis for the primary endpoint of percentage change in LDL-C from baseline at Day 510. The applicant believes that this method is the most appropriate method for imputation of missing data as it provides the best estimate of what the values of missing data points would have been, had they been measured. All statistical models that used the multiple imputation washout model were rerun for the primary efficacy endpoint (percentage change in LDL-C from baseline to Day 510) using the modified multiple imputation washout model imputed data.

6.3.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that the study was conducted in compliance with the protocol, The Medicines Company’s standard operating procedures and/or guidelines and any vendor partners where applicable, the US FDA regulations, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki, and other local regulations, in operation at the time of the study.

Financial Disclosure

Refer to Section 13.2 Financial Disclosure for additional information.

Patient Disposition

The study was conducted in 72 centers in 8 countries: Czech Republic (2 centers), Germany (5 centers), Hungary (4 centers), Netherlands (1 center), Poland (19 centers), South Africa (8 centers), Ukraine (9 centers), and United Kingdom (24 centers).

A total of 2381 subjects were screened and 1617 were randomized. In ORION-11, approximately 32% of screened subjects were screen failures. The most common inclusion/exclusion criterion not met was the subject not meeting appropriate serum LDL-C

inclusion criterion of LDL-C $\geq$ 70 mg/dL (19.5%; 465/2381 subjects). The second most common criterion not met was the exclusion criterion of any condition that interfered with the study in 3% (68/2381) of subjects.

The 1617 randomized subjects were enrolled in 71 sites from 7 countries (no subjects were enrolled from 1 site in Netherlands). Forty-seven of 71 sites had more than 10 subjects enrolled. Poland enrolled the most subjects (649, 44%), followed by United Kingdom (419, 29%), Ukraine (102, 7%) and Hungary (97, 7%).

As shown in the table below, at Day 510 approximately 97% (1561/1617) of the ITT Population were still in the study; 97% (779/807) of placebo-treated subjects and 97% (782/810) of inclisiran-treated subjects. At Day 540 (EOS Visit) approximately 95% (1542/1617) completed the study; 95% (770/807) of placebo-treated subjects and 95% (772/810) of inclisiran-treated subjects. A total of 5% (37/807) of placebo-treated subjects discontinued the study. The most common reason for discontinuation from the study was withdrawal of consent (2%; 17/807), followed by death (2%; 15/807). Similarly, a total of 5% (38/810) of inclisiran-treated subjects discontinued the study. The most common reason for discontinuation from the study was death (2%; 14/810) followed by withdrawal of consent (2%; 13/810).

The disposition of subjects was reasonably balanced between the treatment groups. All 1617 randomized subjects were included in the ITT Population (the primary efficacy analysis Population). All but 2 of the 1617 randomized subjects were treated (805 with placebo and 810 with inclisiran) and included in the Safety Population. Two subjects (both randomized to placebo) were excluded from the Safety Population because they did not receive any study drug. Another subject (Subject (b) (6)) was incorrectly administered inclisiran instead of placebo on Day 450. This subject is included in the inclisiran Safety Population but included in the placebo ITT Population.

Table 24. ORION-11: Patient Disposition for ITT Population

	Placebo (N=807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
Completing the Day 510 visit	779 (96.5)	782 (96.5)	1561 (96.5)
Completing the Day 540 visit	770 (95.4)	772 (95.3)	1542 (95.4)
Discontinued	37 (4.6)	38 (4.7)	75 (4.6)
Death	15 (1.9)	14 (1.7)	29 (1.8)
Adverse event	0	4 (0.5)	4 (0.2)
Withdrew consent	17 (2.1)	13 (1.6)	30 (1.9)
Physician decision	1 (0.1)	1 (0.1)	2 (0.1)

Lost to follow-up	3 (0.4)	6 (0.7)	9 (0.6)
Initiation of PCSK9 inhibitor	0	0	0
Other	1 (0.1)	0	1 (0.1)
Duration on study (days)*			
Mean ± SD	527.9±58.6	528.8±55.5	528.4±57.1
Median	536	535	535
Q1, Q3	3, 614	43, 614	3, 614

Abbreviations: ITT=intent-to-treat; PCSK9= proprotein convertase subtilisin/kexin type 9

* Duration on study is defined as the number of days from the first date of treatment to the date of last recorded visit in the database.

Source: Applicant's ORION-11 submission, Tables 14.1.2.1 and 14.1.7.1. and FDA OCS Analysis Studio, Custom Table Builder. Columns - Dataset: Demographics; Filter: ITTFL = 'Y'. Table Section 1 - Dataset: Disposition; Filter: None.A

ASCVD Only Patients

In ORION-11, 87.4% (1414/1617) of subjects in the study had ASCVD; 87.0% (702/807) placebo-treated subjects and 87.9% (712/810) inclisiran-treated subjects.

At Day 540 (EOS Visit) approximately 95% (669/702) of placebo-treated subjects and 96% (682/712) of inclisiran-treated subjects with ASCVD completed the study. A total of 5% (33/702) of placebo-treated subjects discontinued the study. The most common reason for discontinuation from the study was withdrawal of consent (2%; 16/702), followed by death (2%; 14/702). A total of 4% (30/712) of inclisiran-treated subjects discontinued the study. The most common reason for discontinuation from the study was death (2%; 13/712) followed by withdrawal of consent (1%; 9/712). The median duration on study was 536 days for the placebo group and 535 days for the inclisiran group.

Protocol Violations/Deviations

Protocol deviations were similar between the treatment groups (see table below). The most common protocol deviations were prohibited concomitant medication/change in baseline statin or other lipid-lowering therapy dose and mis-dosing for any reason other than subject safety or withdrawal. Changes in lipid-modifying therapy during the trial is discussed in more detail in a subsequent section of the review.

Table 25. ORION-11: Protocol Deviations – ITT Population

	Placebo (N=807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
Subjects with at least 1 protocol deviation	130 (16.1)	115 (14.2)	245 (15.2)
Inclusion and/or exclusion criteria violation	15 (1.9)	11 (1.4)	26 (1.6)

Laboratory assessments not drawn at Days 1, 510 or 540 (EOS) Visits	16 (2.0)	18 (2.2)	34 (2.1)
Mis-Dosing for any reason other than subject safety or withdrawal*	22 (2.7)	27 (3.3)	49 (3.0)
Prohibited concomitant medication/change in baseline statin or other lipid-lowering therapy dose	81 (10.0)	65 (8.0)	146 (9.0)
SAE form not reported to applicant within 24 hours	13 (1.6)	9 (1.1)	22 (1.4)
Informed consent not signed prior to study entry	0	0	0

Abbreviations: ITT=intent-to-treat; EOS=end of study; SAE=serious adverse event

* Defined as missing dose or a dose delayed by more than 30 days

Source: Applicant's ORION-11 submission, Tables 14.1.5.1

Table of Demographic Characteristics

Table 26. ORION-11: Demographic and Baseline Characteristics of the ITT Population

Demographic Parameters	Placebo Control Group (N= 807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
Sex			
Male	581 (72.0)	579 (71.5)	1160 (71.7)
<i>Male (ASCVD only patients)</i>	531/702 (75.6)	534/712 (75.0)	
Female	226 (28.0)	231 (28.5)	457 (28.3)
<i>Female (ASCVD only patients)</i>	171/702 (24.4)	178/712 (25.0)	
Age			
Mean years (SD)	64.8 (8.7)	64.8 (8.3)	64.8 (8.5)
Median (years)	65.0	66.0	65.0
Min, max (years)	34, 87	20, 88	20, 88
<i>Age (ASCVD only patients)</i>			
<i>Mean years (SD)</i>	65.0 (8.6)	65.1 (7.9)	
<i>Median (years)</i>	65.0	66.0	
<i>Min, max (years)</i>	35, 87	38, 88	
Age Group			
18 - < 65 years	366 (45.4)	367 (45.3)	733 (45.3)
≥ 65 years	441 (54.6)	443 (54.7)	884 (54.7)
18 - < 75 years	693 (85.9)	721 (89.0)	1414 (87.4)
≥ 75 years	114 (14.1)	89 (11.0)	203 (12.6)
<i>Age Group (ASCVD only patients)</i>			
<i>18 - < 65 years</i>	313/702 (44.6)	317/712 (44.5)	
<i>≥ 65 years</i>	389/702 (55.4)	395/712 (55.5)	
<i>18 - < 75 years</i>	599/702 (85.3)	631/712 (88.6)	
<i>≥ 75 years</i>	103/702 (14.7)	81/712 (11.4)	

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Demographic Parameters	Placebo Control Group (N= 807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
Weight			
Mean, kg (SD)	87.6 (18.2)	85.8 (16.2)	86.7 (17.3)
BMI (kg/m ²)			
Mean, kg (SD)	30.2 (5.2)	29.7 (4.8)	30.0 (5.0)
Race			
White	796 (98.6)	791 (97.7)	1587 (98.1)
Black or African American	8 (1.0)	12 (1.5)	20 (1.2)
Asian	2 (0.2)	6 (0.7)	8 (0.5)
American Indian or Alaska Native	0	1 (0.1)	1 (0.1)
Native Hawaiian or other Pacific Islander	1 (0.1)	0	1 (0.1)
<i>Race (ASCVD only patients)</i>			
<i>White</i>	695/702 (99.0)	697/712 (97.9)	
<i>Black or African American</i>	5/702 (0.7)	11/712 (1.5)	
<i>Asian</i>	2/702 (0.3)	4/712 (0.6)	
Ethnicity			
Hispanic or Latino	4 (0.5)	5 (0.6)	9 (0.6)
Not Hispanic or Latino	803 (99.5)	805 (99.4)	1608 (99.4)
<i>Ethnicity (ASCVD only patients)</i>			
<i>Hispanic or Latino</i>	3/702 (0.4)	5/712 (0.7)	
<i>Not Hispanic or Latino</i>	699/702 (99.6)	707/712 (99.3)	
Region			
Czech Republic	11 (1.4)	10 (1.2)	21 (1.3)
Germany	41 (1.5)	42 (5.2)	83 (5.1)
United Kingdom	231 (28.6)	231 (28.5)	462 (28.6)
Hungary	52 (6.4)	52 (6.4)	104 (6.4)
Poland	357 (44.2)	360 (44.4)	717 (44.3)
Ukraine	54 (6.7)	55 (6.8)	109 (6.7)
South Africa	61 (7.6)	60 (7.4)	121 (7.5)
Netherlands	0	0	0
Baseline GFR Category (mL/min/1.73 m ²)			
≥15 to <30	2 (0.2)	1 (0.1)	3 (0.2)
≥30 to <60	98 (12.1)	108 (13.3)	206 (12.7)
≥60 to <90	482 (59.7)	459 (56.7)	941 (58.2)
≥90	225 (27.9)	242 (29.9)	467 (28.9)
ASCVD	702 (87.0)	712 (87.9)	1414 (87.4)
Hx of CHD	623/702 (88.7)	614/712 (86.2)	1237/1414 (87.5)
Hx of CVD	119/702 (17.0)	114/712 (16.0)	233/1414 (16.5)
Hx of PAD	72/702 (10.3)	75/712 (10.5)	147/1414 (10.4)

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Demographic Parameters	Placebo Control Group (N= 807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
ASCVD Risk Equivalent	105 (13.0)	98 (12.1)	203 (12.6)
Diabetes Mellitus	272 (33.7)	296 (36.5)	568 (35.1)
<i>DM in ASCVD patients</i>	206/702 (29.3)	230/712 (32.3)	
Smoking (current, within past 30 days)	132 (16.4)	160 (19.8)	292 (18.1)
<i>Smoking in ASCVD patients</i>	116/702 (16.5)	141/712 (19.8)	
Hypertension	661 (81.9)	640 (79.0)	1301 (80.5)
<i>Hypertension in ASCVD patients</i>	582/702 (82.9)	573/712 (80.5)	
Baseline LDL-C (mg/dL)			
Mean (SD)	103.7 (36.4)	107.2 (41.8)	105.4 (39.2)
Median (mg/dL)	96.0	97.0	97.0
Min, max (mg/dL)	41, 335	32, 556	32, 556
Baseline TC (mg/dL)			
Mean (SD)	183.3 (42.8)	187.3 (48.2)	185.3 (45.6)
Median (mg/dL)	175.0	177.0	176.0
Min, max (mg/dL)	95, 425	100, 659	95, 659
Baseline Triglycerides (mg/dL)			
Mean (SD)	151.8 (77.9)	152.0 (78.3)	151.9 (78.1)
Median (mg/dL)	135.0	127.0	135.0
Min, max (mg/dL)	38, 1253	42, 722	38, 1253
Baseline non-HDL-C (mg/dL)			
Mean (SD)	133.9 (41.0)	137.6 (46.9)	135.8 (44.1)
Median (mg/dL)	126.0	126.0	126.0
Min, max (mg/dL)	63, 375	50, 570	50, 570
Baseline Apolipoprotein B (mg/dL)			
Mean (SD)	95.1 (25.2)	97.1 (28.0)	96.1 (26.6)
Median (mg/dL)	91.0	92.0	91.0
Min, max (mg/dL)	48, 231	50, 335	48, 335
Baseline PCSK9 (µg/L)			
Mean (SD)	352.7 (97.4)	354.9 (98.9)	353.8 (98.2)
Median (mg/dL)	340.5	345.9	342.0
Min, max (mg/dL)	127, 712	134, 737	127, 737
Baseline Lipoprotein-a (nmol/L)			
Mean (SD)	106.4 (123.2)	107.8 (122.8)	107.1 (123.0)
Median (mg/dL)	35.0	42.0	39.0
Min, max (mg/dL)	2, 713	2, 686	2, 713
Baseline C Reactive Protein (mg/L)			
Mean (SD)	3.7 (12.1)	3.5 (6.8)	3.6 (9.8)
Median (mg/dL)	1.6	1.5	1.6

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Demographic Parameters	Placebo Control Group (N= 807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
Min, max (mg/dL)	0.1, 303.0	0.1, 82.4	0.1, 303.0
<i>ASCVD Patients Only</i>	n=702	n=712	n=1414
<i>Baseline LDL-C (mg/dL)</i>			
Mean (SD)	98.9 (31.6)	102.2 (34.3)	100.6 (33.0)
Median (mg/dL)	92.0	95.0	93.5
Min, max (mg/dL)	41, 307	32, 469	32,469
<i>Baseline TC (mg/dL)</i>			
Mean (SD)	177.3 (37.0)	181.3 (40.7)	179.3 (38.9)
Median (mg/dL)	171.0	174.0	172.0
Min, max (mg/dL)	95, 395	100, 567	95,567
<i>Baseline Triglycerides (mg/dL)</i>			
Mean (SD)	147.6 (66.5)	147.6 (71.3)	147.6 (68.9)
Median (mg/dL)	132.0	133.0	133.0
Min, max (mg/dL)	38, 502	42, 551	38, 551
<i>Baseline non-HDL-C (mg/dL)</i>			
Mean (SD)	128.3 (35.4)	131.8 (39.3)	130.1 (37.5)
Median (mg/dL)	122.0	123.0	122.0
Min, max (mg/dL)	63, 324	50, 514	50, 514
<i>Baseline Apolipoprotein B (mg/dL)</i>			
Mean (SD)	91.8 (22.6)	93.6 (23.9)	92.7 (23.3)
Median (mg/dL)	88.0	89.0	89.0
Min, max (mg/dL)	48, 211	50, 293	48, 293
<i>Baseline PCSK9 (µg/L)</i>			
Mean (SD)	352.2 (97.0)	353.9 (98.9)	353.1 (97.9)
Median (mg/dL)	339.1	343.3	341.1
Min, max (mg/dL)	127, 712	134, 737	127, 737
<i>Baseline Lipoprotein-a (nmol/L)</i>			
Mean (SD)	108.5 (123.6)	110.2 (124.9)	109.3 (124.2)
Median (mg/dL)	37.0	43.0	40.0
Min, max (mg/dL)	2, 713	2, 686	2, 713
<i>Baseline C Reactive Protein (mg/L)</i>			
Mean (SD)	3.7 (12.7)	3.3 (6.2)	3.5 (10.0)
Median (mg/dL)	1.6	1.4	1.5
Min, max (mg/dL)	0.1, 303.0	0.1, 82.4	0.1, 303.0

Abbreviations: GFR=glomerular filtration rate; SD=standard deviation; ASCVD=Atherosclerotic Cardiovascular Disease; CHD=Coronary Heart Disease; CVD= Cerebrovascular Disease; PAD= Peripheral Artery Disease
Source: Applicant's ORION-11 submission, Tables 14.1.8.1, 14.1.9.1, 14.2.15.1, 14.1.8.1.13, 14.1.9.1.13 and 14.3.3.1.1; response to FDA IRs

Reviewer comment: The demographic and baseline characteristics are largely balanced between the two treatment groups. The study enrolled 98% of subjects who are White; there is minimal representation of non-white and Hispanic or Latino patients. Seventy-two percent of the study population is male and the mean age is 65 years old. The study population included relevant comorbidities such as ASCVD (87%, primarily CHD), renal impairment (13% had a GFR between 30 and 60 and 58% had a GFR between 60 and 90 mL/min/1.73m²), hypertension (81%) and diabetes (35%).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

At baseline, use of lipid modifying therapy (LMT) was reasonably balanced between the treatment groups (see table below). Overall, 97% (1565/1617) of subjects received LMT, 95% (1532/1617) of subjects received statin therapy, 12% (191/1617) received other LMT and 2% (33/1617) received other LMT and no statin. Approximately 3% (52/1617) were not taking any LMT at baseline.

Overall, 78% (1261/1617) were on a high intensity statin, 16% (251/1617) were on a moderate intensity statin and 0.4% (6/1617) were on a low intensity statin at baseline. Approximately 7% (114/1617) of subjects were treated with ezetimibe.

Table 27. ORION-11: Baseline Concomitant Medications of the ITT Population

Baseline Medications	Placebo Control Group (N= 807) n (%)	Inclisiran (N=810) n (%)	Total (N=1617) n (%)
Baseline Lipid Modifying therapy			
None	26 (3.2)	26 (3.2)	52 (3.2)
Non-statin (other LMT) only	15 (1.9)	18 (2.2)	33 (2.0)
Statins only	686 (85.0)	688 (84.9)	1374 (85.0)
Other LMT used (± statin)	95 (11.8)	96 (11.9)	191 (11.8)
Statins used (± other LMT)	766 (94.9)	766 (94.6)	1532 (94.7)
High Intensity*	628 (77.8)	633 (78.1)	1261 (78.0)
Moderate Intensity**	128 (15.9)	123 (15.2)	251 (15.5)
Low Intensity	3 (0.4)	3 (0.4)	6 (0.4)

Abbreviations: LMT= lipid modifying therapy

* High-Intensity: Atorvastatin 40-80mg; ezetimibe/rosuvastatin zinc 30mg; rosuvastatin 20-80 mg; simvastatin 60-80 mg

** Moderate Intensity: Atorvastatin 10-20mg; rosuvastatin 5mgQOD- <20 mg QD; simvastatin 20-40 mg; fluvastatin 80mg; pravastatin 40 mg

Source: Applicant's ORION-11 submission, Table 14.1.16.2.1.c

ASCVD Only Patients

At baseline, 80.2% (563/702) of placebo-treated subjects with ASCVD were on a high intensity

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statin at baseline and 80.5% (573/712) of inclisiran-treated subjects with ASCVD were on a high intensity statin at baseline. At baseline, 15% (106/702) of placebo-treated subjects and 15% (105/712) of inclisiran-treated subjects with ASCVD were on a moderate intensity statin at baseline. At baseline, 4% in each group were not on a statin and 2% in each group were on no lipid-modifying therapy.

Reviewer comment: The majority (~78%) of participants in ORION-11 were on background high-intensity statin therapy, which is appropriate, as inclisiran, if approved, would be most clinically relevant in patients with HeFH or at higher CV risk not adequately controlled by maximally tolerated statin therapy. In terms of background lipid-lowering therapy, especially high-intensity statin use, the enrolled population adequately reflects the intended clinical population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

All study drugs were administered subcutaneously by clinical study site staff, primarily in the abdominal region (doses on Day 1, Day 90, Day 270, and Day 450). Overall, 92% (748/804) of placebo-treated subjects and 91% (747/811) of inclisiran-treated subjects received all 4 planned SC doses.

Reviewer comment: Over 91% of study subjects received all 4 doses of study drug. This level of treatment compliance is acceptable and will allow for a good assessment of steady-state and durable LDL-C reduction.

Changes in Lipid-Modifying Therapy (LMT) During Trial

Nine percent (73/807) of subjects in the placebo group and 7% (54/810) in the inclisiran group had changes in LMT use during the trial. No subjects in either group began therapy with a PCSK9 monoclonal antibody.

Shifts from baseline in statin intensity were minimal in both treatment groups. Most subjects remained on their statin intensity category (high, moderate, low or none) throughout the trial.

New or changed concomitant medications during the study were similar between the placebo and inclisiran treatment groups.

Efficacy Results – Primary Endpoint

Reviewer comment: The following sections of the efficacy evaluation focuses on the ITT Population of 1617 subjects but will also include a separate evaluation of efficacy in ASCVD subjects only; this evaluation excludes the 203 ASCVD-risk-equivalent subjects.

The applicant’s co-primary endpoints for this trial are:

- Percentage change in LDL-C from Baseline to Day 510.
- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540.

Percentage change in LDL-C from Baseline to Day 510:

The primary analysis used the same prespecified washout model as described in ORION-10 to account for missing data. The placebo-adjusted change in LDL-C from baseline to Day 510 using the imputed values was -47.8% (p<0.0001).

Table 28. ORION-11: Primary Efficacy Endpoint – ITT Population

Primary Endpoint	Placebo (N= 807)	Inclisiran (N=810)	p-value
Percentage Change in LDL-C from Baseline to Day 510 (Washout – Imputed values)*			
LS Mean (95% CI)	4.0 (1.7, 6.4)	-43.8 (-46.2, -41.4)	
LS Mean Difference (95% CI) from Placebo		-47.8 (-51.1, -44.5)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant’s ORION-11 submission, Table 14.2.1.1.a

* A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. Analysis of covariance (ANCOVA) on each of the 100 datasets was performed by including fixed effects for treatment and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin’s Method.

Three additional, prespecified sensitivity analyses (PMM, MMRM, ANCOVA with country as a covariate) for handling missing values were used to analyze the percentage change from baseline at Day 510 primary endpoint. Similar (-51.8%, -52.7% and -49.9%) and statistically significant (p<0.0001), placebo-adjusted differences were demonstrated for this primary endpoint, regardless of sensitivity analysis used to handle missing values.

Reviewer comment: In a population with ASCVD and ASCVD-risk-equivalents, inclisiran lowers LDL-C to a clinically meaningful degree: -44% from the inclisiran group’s baseline and -48% from baseline as compared to the placebo group.

Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540

Compared to placebo, the time-adjusted percentage change from baseline after Day 90 and up to Day 540 was -49.2% (p<0.0001) (see table below).

Table 29. ORION-11: Co-Primary Efficacy Endpoint – Time-adjusted Percentage Change from Baseline after Day 90 and up to Day 540 ITT Population

Primary Endpoint	Placebo (N= 807)	Inclisiran (N=810)	p-value
Time-Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540*			
LS Mean (95% CI)	3.4 (1.7,5.1)	-45.8 (-47.5, -44.1)	
LS Mean Difference (95% CI) from Placebo		-49.2 (-51.6, -46.8)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant’s ORION-11 submission, Tables 15 and 14.2.1.1 .b

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin’s method.

Sensitivity analyses (PMM, MMRM, ANCOVA with country as a covariate) for the co-primary endpoint of time-adjusted percentage change from baseline after Day 90 and up to Day 540, demonstrated similar (-51.4%, -49.9% and -49.5%) and statistically significant (p<0.0001), placebo-adjusted differences, regardless of sensitivity analysis used to handle missing values.

ASCVD Only Patients

Percentage change in LDL-C from Baseline to Day 510:

Using a washout model to impute for missing data, the placebo-adjusted change in LDL-C from baseline to Day 510 for subjects with ASCVD was -50.6% (p<0.0001).

The time-adjusted LDL-C percentage change from baseline after Day 90 and up to Day 540 in subjects with ASCVD was -50.2% (p<0.0001) in inclisiran treated subjects compared to placebo treated subjects.

Table 30. ORION-11: Primary Efficacy Endpoints – ASCVD Only Population

Primary Endpoint	Placebo (N= 702)	Inclisiran (N=712)	p-value
Percentage Change in LDL-C from Baseline to Day 510 (Washout – Imputed values)*			
LS Mean (95% CI)	4.3 (1.9, 6.7)	-46.3 (-48.8, -43.8)	
LS Mean Difference (95% CI) from Placebo		-50.6 (-54.0, -47.2)	<.0001
Time-Adjusted Percentage Change in LDL-C from Baseline after Day 90 and up to Day 540**			
LS Mean (95% CI)	3.7 (1.9, 5.5)	-46.5	

Primary Endpoint	Placebo (N= 702)	Inclisiran (N=712)	p-value
		(-48.3, -44.7)	
LS Mean Difference (95% CI) from Placebo		-50.2 (-52.8, -47.7)	<.0001

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol; LS=least squares

Source: Applicant's ORION-11 submission, Table 14.2.1.1.13.b

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

** A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear combination of the estimated means after Day 90 and up to Day 540 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's method.

Data Quality and Integrity

The study was well executed and largely adhered to the protocol. The protocol amendments were reasonable and unlikely to have had a negative impact on the integrity of the trial or our interpretation of the results. Protocol deviations were similar between the treatment groups and were not believed to have a negative impact on study results. Subject retention was excellent (95% over 18 months). The applicant made reasonable efforts to blind study medication from subjects and investigators. There were no notable financial conflicts of interest. Datasets were complete, generally straightforward to navigate, and of high quality. There were no potential issues concerning the submitted data quality or integrity that raise questions about the purported efficacy results. Thus, the study has generated data that are robust, interpretable, and persuasive in supporting the proposed indication.

Efficacy Results – Secondary and other relevant endpoints

Three key secondary endpoints were defined in the protocol and statistical analysis plan (PMM):

- Absolute change in LDL-C from Baseline to Day 510:
 - The placebo-adjusted absolute change from baseline to Day 510 in LDL-C levels was -51.9 mg/dL (p<0.0001) for inclisiran-treated subjects.
 - *For ASCVD only patients:* The placebo-adjusted absolute change from baseline to Day 510 in LDL-C levels was -50.8 mg/dL (p<0.0001) for inclisiran-treated subjects.
- Time-adjusted absolute change in LDL-C from Baseline after Day 90 and up to Day 540:
 - Compared to placebo, the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was -48.9 mg/dL (p<0.0001).

- *For ASCVD only patients:* Compared to placebo, the time-adjusted absolute change from baseline after Day 90 and up to Day 540 was -48.3 mg/dL (p<0.0001).
- Percentage change from Baseline to Day 510 in PCSK9, TC, Apo-B, and non-HDL-C.
 - The placebo-adjusted percentage change in PCSK9 from baseline to Day 510 was -79.3% (p<0.0001).
 - *For ASCVD only patients:* The placebo-adjusted percentage change in PCSK9 from baseline to Day 510 was -79.9% (p<0.0001).
 - The placebo-adjusted percentage change in TC from baseline to Day 510 was -29.8% (p<0.0001).
 - *For ASCVD only patients:* The placebo-adjusted percentage change in TC from baseline to Day 510 was -30.0% (p<0.0001).
 - The placebo-adjusted percentage change in Apo-B from baseline to Day 510 was -38.9% (p<0.0001).
 - *For ASCVD only patients:* The placebo-adjusted percentage change in Apo-B from baseline to Day 510 was -39.5% (p<0.0001).
 - The placebo-adjusted percentage change in non-HDL-C from baseline to Day 510 was -43.3% (p<0.0001).
 - *For ASCVD only patients:* The placebo-adjusted percentage change in non-HDL-C from baseline to Day 510 was -43.9% (p<0.0001).

Table 31. ORION-11: Key Secondary Efficacy Endpoints-ITT Population

Key Secondary Efficacy Endpoints	Placebo (N= 807)	Inclisiran (N=810)	p-value
Absolute Change in LDL-C (mg/dL) from Baseline to Day 510; Control-Based Pattern-Mixture Model (PMM)*			
LS Mean (95% CI)	1.0 (-1.3,3.2)	-50.9 (-53.1, -48.7)	
LS Mean Difference (95% CI) from Placebo		-51.9 (-55.0, -48.7)	<.0001
Time-Adjusted Absolute Change in LDL-C (mg/dL) from Baseline After Day 90 and up to Day 540; PMM*			
LS Mean (95% CI)	0.3 (-1.4, 2.0)	-48.6 (-50.4, -46.9)	
LS Mean Difference (95% CI) from Placebo		-48.9 (-51.4, -46.5)	<.0001
Percentage Change from Baseline to Day 510 in PCSK9; PMM*			

LS Mean (95% CI)	15.6 (13.7, 17.5)	-63.6 (-65.6, -61.7)	
LS Mean Difference (95% CI) from Placebo		-79.3 (-82.0, -76.6)	<.0001
Percentage Change in TC from Baseline to Day 510; PMM*			
LS Mean (95% CI)	1.8 (0.4,3.2)	-28.0 (-29.4, -26.6)	
LS Mean Difference (95% CI) from Placebo		-29.8 (-31.8, -27.8)	<.0001
Percentage Change in Apo-B from Baseline to Day 510; PMM*			
LS Mean (95% CI)	0.8 (-0.8, 2.4)	-38.2 (-39.8, -36.5)	
LS Mean Difference (95% CI) from Placebo		-38.9 (-41.2, -36.7)	<.0001
Percentage Change in non-HDL-C from Baseline to Day 510; PMM*			
LS Mean (95% CI)	2.2 (0.2, 4.1)	-41.2 (-43.1, -39.2)	
LS Mean Difference (95% CI) from Placebo		-43.3 (-46.0, -40.6)	<.0001

Source: Applicant's ORION-11 submission, Tables 14.2.3.1.a, 14.2.4.1.a, 14.2.5.1.a, 14.2.6.1.a, 14.2.7.1.a, and 14.2.8.1.a

Abbreviations: Apo-B=apolipoprotein B; CI=confidence interval; HDL-C = high density lipoprotein cholesterol; ITT=intent-to-treat; LDL-C = low density lipoprotein cholesterol; LS=least squares; MAR=missing at random

* A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's Method.

Reviewer comment: The results of the key secondary efficacy endpoints are consistent and supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. This is expected as LDL-C is a major component of TC and non-HDLC, and apolipoprotein B is the primary apolipoprotein of LDL-C. In addition, a reduction in PCSK9 levels is the mechanism of action through which inclisiran lowers LDL-C.

Other secondary endpoints of interest include:

- Individual responsiveness defined as the number of subjects reaching on-treatment LDL-C levels of <25 mg/dL, <50 mg/dL, <70 mg/dL, and <100 mg/dL at Day 510 (see table below).
- Proportion of subjects in each group with greater or equal to 50% LDL-C reduction from Baseline.

- At any time during the study, 6% (47/800) of placebo-treated subjects had ≥50% LDL-C reduction from baseline compared with 82% (658/803) of inclisiran-treated subjects.
- At Day 510, 2.3% (17/739) of placebo-treated subjects had ≥50% LDL-C reduction from baseline compared with 58% (418/724) of inclisiran-treated subjects.
- Proportion of subjects in each group who attain global lipid targets for their level of ASCVD risk.
 - At any visit, 42% (335/800) of placebo-treated subjects achieved their corresponding LDL-C targets compared with 92% (741/802) of inclisiran-treated subjects.
 - At Day 510, 16% (103/644) of placebo-treated subjects with ASCVD achieved their LDL-C target of <70 mg/dL compared to 82% (522/639) of inclisiran-treated subjects with ASCVD.

Table 32. ORION-11: Individual responsiveness of subjects reaching on-treatment LDL-C levels-ITT Population

LDL-C (mg/dL) levels	Placebo (N= 807) n (%)	Inclisiran (N=810) n (%)
Number of Subjects Reaching LDL-C Level at Day 510*		
< 25 mg/dL	1 (0.1)	95 (11.7)
< 50 mg/dL	19 (2.4)	420 (51.9)
< 70 mg/dL	104 (12.9)	564 (69.6)
< 100 mg/dL	425 (52.7)	661 (81.6)
≥ 100 mg/dL	314 (38.9)	63 (7.8)
Missing	68 (8.4)	86 (10.6)

Source: Applicant's ORION-11 submission, Table 14.2.16.1

* Subjects can be counted in multiple categories.

Abbreviations: ITT=intent-to-treat; LDL-C=low density lipoprotein cholesterol

Reviewer comment: The results of these secondary efficacy endpoints are generally supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. (b) (4)

[Redacted text block]

Exploratory Endpoints

Additional endpoints explored by this reviewer include percentage change from Baseline in triglycerides, HDL-C, and lipoprotein (a) [Lp(a)] (ITT population).

- The placebo-adjusted percentage change in TG from baseline to Day 510 was -9% ($p < 0.0001$).
- The placebo-adjusted percentage change in HDL-C from baseline to Day 510 was 6% ($p < 0.0001$).
- The placebo-adjusted percentage change in Lp(a) from baseline to Day 540 was -19% ($p < 0.0001$).

Reviewer comment: Inclisiran lowered TG by approximately 9% and Lp(a) by 19%. HDL-C increased 6% with inclisiran exposure. These changes are not considered adverse and trend in a potentially beneficial direction; however, the true clinical significance of these changes is unclear.

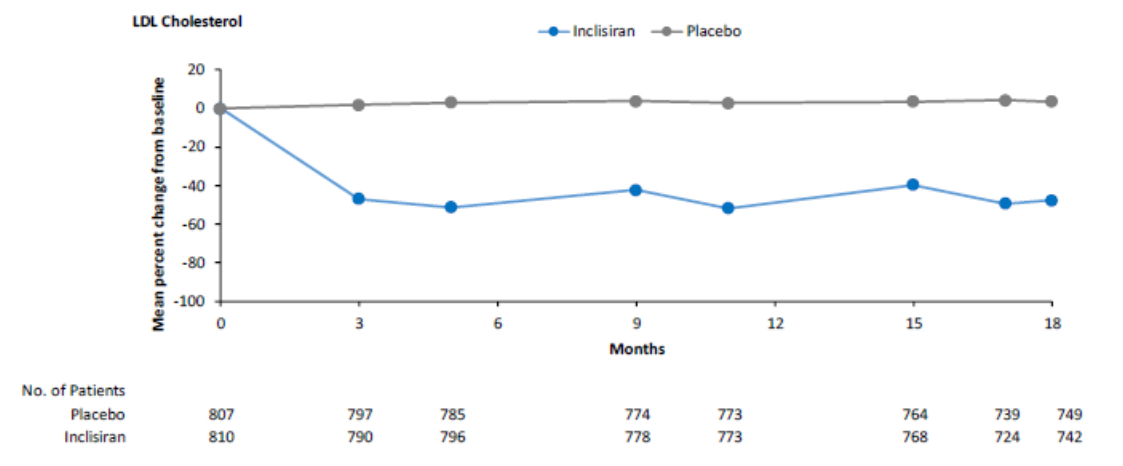
Dose/Dose Response

Not applicable as there is only one dose in this trial.

Durability of Response

As shown in the figure below, inclisiran had a consistent and durable effect on the reduction of LDL-C over time in this study of 18 months duration.

Figure 6. ORION-11: Observed Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with ASCVD and ASCVD-risk-equivalents on Maximally Tolerated Statin Treated with Inclisiran and Placebo-ITT Population



Reflexive LDL-C measurements used as per protocol.

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Source: Applicant's ORION-11 submission, Figures 4 and 14.2.1.3

Persistence of Effect

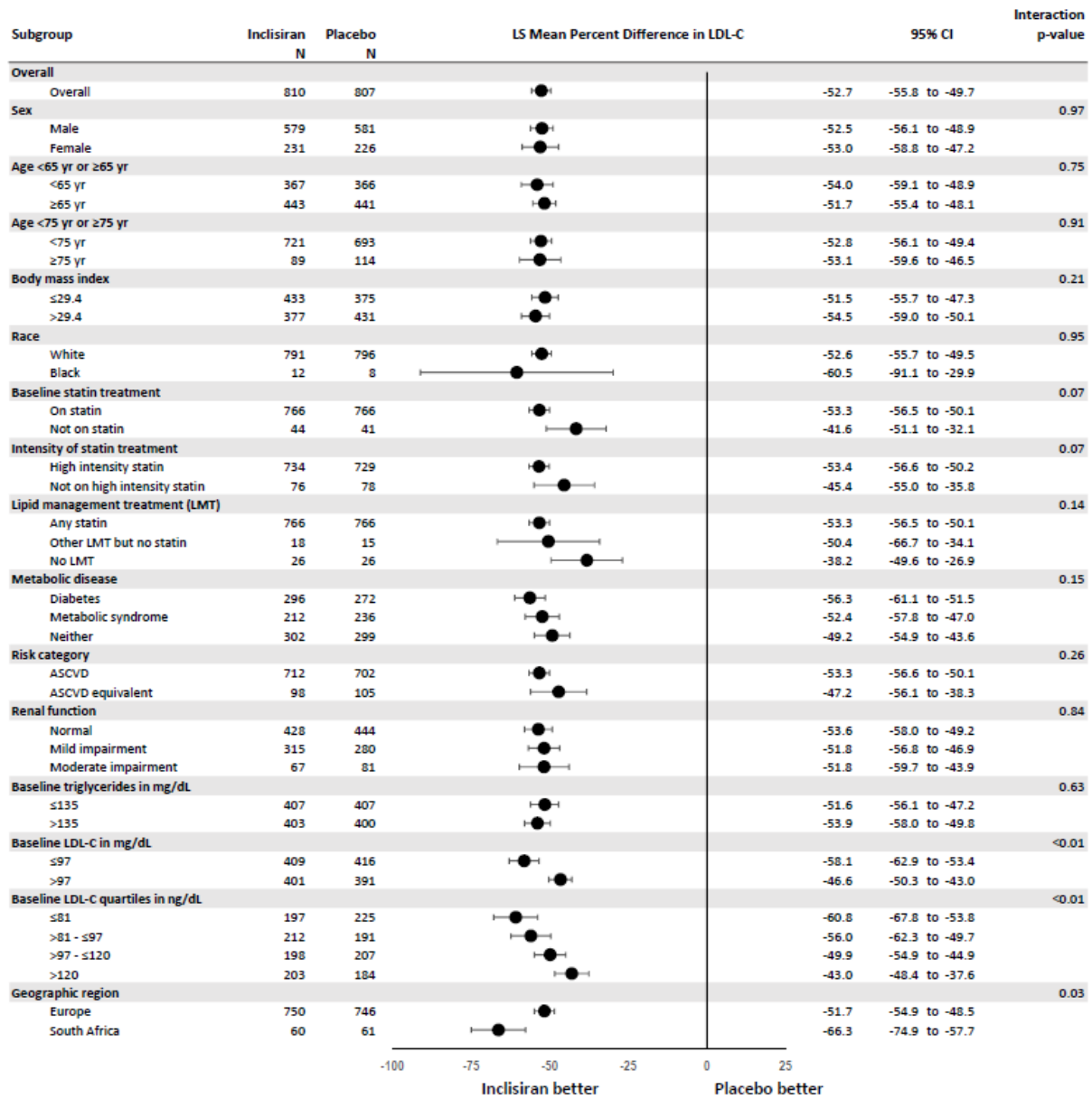
Not applicable in this trial; refer to Section 7.1.5 for a brief discussion of the persistence of effect.

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses of Efficacy

Subgroup analyses for efficacy were performed based on multiple categories using MMRM to account for missing data (see figure below). In all subgroups, inclisiran lowered LDL-C more than placebo. The estimate of the treatment effect was generally similar across subgroups, although there was a trend toward increased magnitude of treatment effect with lower baseline LDL-C, similar to that observed in ORION-10. In this trial, there was also a possible trend towards greater treatment effect in patients on statin compared to patients not on statin, and in patients on higher-intensity statin compared to lower intensity statin. These trends related to background lipid management were not apparent in subgroup analyses of ORION-10.

Figure 7. ORION-11: Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 - Subgroup Analyses - ITT Population



Source: FDA Information Request to Applicant dated 5/26/20, ORION-11 FP Day 510 CSR v2.1 (corrected)

Reviewer comment: In this trial of patients with ASCVD and ASCVD-risk-equivalents, inclisiran demonstrated a clinically meaningful reduction in LDL-C relative to placebo.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The focus of Section 7 will be pooled analyses or comparisons for the three phase 3 trials, ORION-9, ORION-10, and ORION-11.

- ORION-9: 482 subjects with HeFH
- ORION-10: 1561 subjects with ASCVD, and
- ORION-11: 1617 subjects with ASCVD or ASCVD risk equivalents.

All 3 trials were placebo-controlled, double-blind, randomized, multicenter, 18-month trials of nearly identical design which provided data from a total of 3,660 subjects at CV risk (3457 with HeFH or ASCVD) with elevated LDL-C levels, despite receiving the maximally tolerated dose of LDL-C lowering therapies. The trials used the same study endpoints, the same inclisiran dose (300 mg) and dosing regimen, and the same visit schedule; details of this are described in Section 6.

The applicant's co-primary efficacy endpoints were:

- Percentage change in LDL-C from baseline to Day 510
- Time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540

As discussed in Section 6 in more detail, the family-wise type I error rate was controlled at a 2-sided significance level of $\alpha=0.05$ by using a nested testing procedure. The percentage change in LDL-C from baseline to Day 510 was tested first. If the null hypothesis was rejected at a 2-sided significance level of $\alpha=0.05$ and superiority of inclisiran over placebo was claimed, then the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 was to be tested, also at a 2-sided significance level of $\alpha=0.05$. The primary endpoints used a reflexive LDL-C approach: either calculated LDL-C (based on the Friedewald formula) was used, or if the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, or calculated LDL-C was missing, directly measured (using ultracentrifugation) LDL-C was used if it was available. For percentage change in LDL-C, missing values were imputed for LDL-C after a reflexive approach using the multiple imputation (100 total imputed datasets) washout model. For time-adjusted percentage change in LDL-C, a control-based PMM was used to explore the possibility of missing data being missing not at random (MNAR) for subjects who discontinued

the study.

The difference between investigational study drug and placebo in mean percent change in LDL-C from baseline to study endpoint is the regulatory standard to support approval of LDL-C lowering therapies. The strong evidence that has established LDL-C as a causal factor in the development of ASCVD and that robust and sustained lowering of LDL-C can improve CV outcomes is discussed in Section 2.1.

The second co-primary endpoint of time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 provides an estimate of LDL-C changes over time. The data demonstrate a consistency with the Day 510 results and confirms how we expect the treatment to work over time. (b) (4)

as it is important to demonstrate that LDL-C lowering is consistently maintained over time, FDA labels of recently approved LDL-C lowering therapies do contain figures that show the mean percent change from baseline in LDL-C over the duration of the trial (usually ~ 1 year) in patients treated with placebo and patients treated with study drug.

Reviewer comment: (b) (4)

I do recommend including figures that show the mean percent change from baseline in LDL-C over the duration of the 18-month trial in patients in the Phase 3 trials.

Patient Disposition in Phase 3 Trials: Overall, 93.5% (3422/3660) of subjects completed the Phase III trials (92.8% [1695/1827] of placebo-treated subjects and 94.3% [1728/1833] of inclisiran-treated subjects). The most common reasons for discontinuing the study were withdrew consent (placebo-treated subjects 55 [3%], inclisiran-treated subjects 37 [2%]); death (placebo-treated subjects 27 [1.5%], inclisiran-treated subjects 27 [1.5%]); and lost to follow-up (placebo-treated subjects 29 [1.6%], inclisiran-treated subjects 17 [0.9%]).

Lipid-Modifying Therapies (LMT)

LMT usage at baseline was similar in the inclisiran and placebo groups in the individual trials and the pooled population. Looking at all 3 trials together, almost all subjects (94% [3441/3660]) were on statins at study entry. High-intensity statins were prescribed to 74% (2701/3660), moderate-intensity statins were prescribed to 17% (613/3660) and 14% (513/3660) were taking ezetimibe. Nine placebo-treated subjects and no inclisiran-treated subjects started a PCSK9 monoclonal antibody during the Phase III trials.

The placebo-adjusted change in LDL-C from baseline to Day 510 in the individual Phase III

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trials and the pooled group are shown in the table below and demonstrate the efficacy of inclisiran.

Table 33. Percentage Change in LDL-C from Baseline to Day 510 in ORION-9, -10, -11 and Pooled Study-ITT Population

Primary Endpoint	ORION-9			ORION-10			ORION-11			Pooled		
	Placebo (N=240)	Inclisiran (N=242)	p-value	Placebo (N=780)	Inclisiran (N=781)	p-value	Placebo (N=807)	Inclisiran (N=810)	p-value	Placebo (N=1827)	Inclisiran (N=1833)	p-value
Percentage Change in LDL-C from Baseline to Day 510 (Washout – Imputed values) *												
LS Mean (95% CI)	8.2 (4.3, 12.2)	-39.7 (-43.7, -35.6)		1.0 (-1.5, 3.4)	-51.3 (-53.8, -48.8)		4.0 (1.8,6.3)	-45.8 (-48.2, -43.5)		5.6 (3.9,7.3)	-45.1 (-46.9, -43.3)	
LS Mean Difference (95% CI) from Placebo		-47.9 (-53.5, -42.3)	<.0001		-52.2 (-55.7, -48.8)	<.0001		-49.9 (-53.1, -46.6)	<.0001		-50.7 (-52.9, -48.4)	<.0001

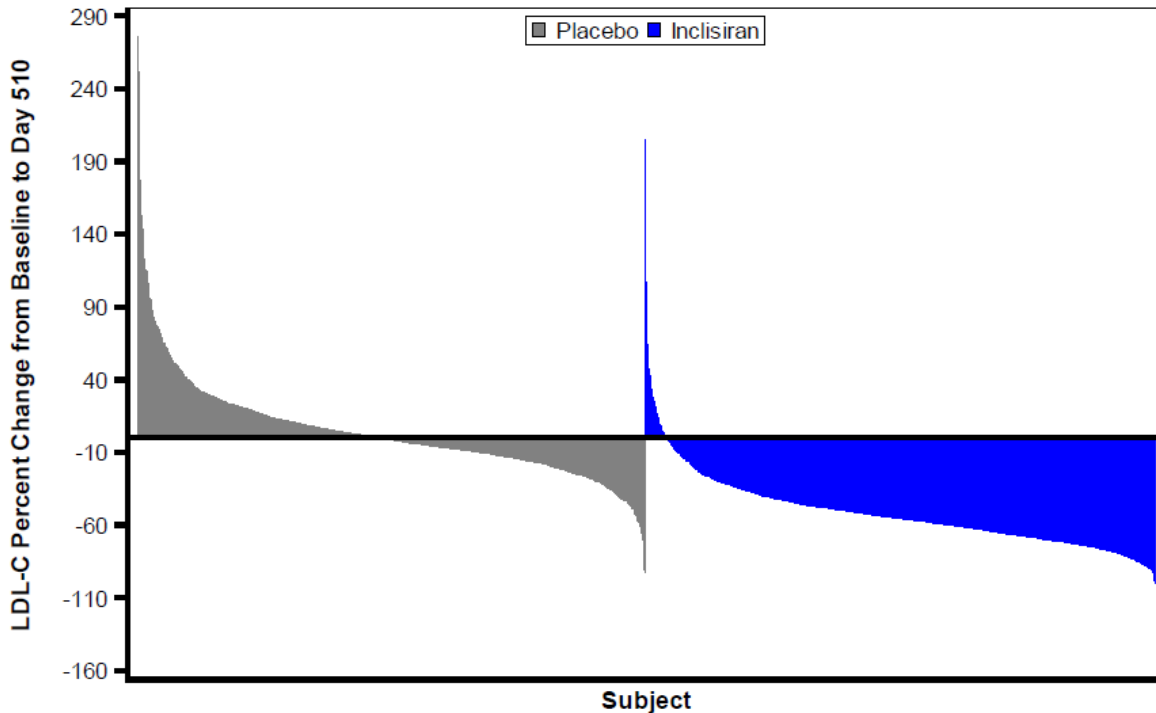
*A multiple imputation washout model was used for missing data imputation with 100 total imputed datasets. This modified model assumed missing Day 510 MAR for Inclisiran subjects if they received all 4 doses and had data observed at Day 540. Analysis of covariance (ANCOVA) on each of the 100 datasets was performed by including fixed effects for treatment and study, and baseline LDL-C as a covariate. Treatment effects from the 100 analyses were combined using Rubin’s Method.

Abbreviations: CI=confidence interval; ITT=Intent-to-Treat; LDL-C=low-density lipoprotein cholesterol; LS=least squares

Source: modified by reviewer from Applicant’s ISE Table 12

The waterfall plot below illustrates how the majority of subjects in the inclisiran group experienced a sizable LDL-C reduction at Day 510 compared to the placebo group.

Figure 8. Waterfall Plot of Percent Change in LDL-C from Baseline to Day 510 – Pool of ORION-9, -10 and -11 (Subjects with LDL-C data in ITT Population)



Source: Applicant's CSR for ISE, Figure 14.2.3.1.1.1.

ADAs analysis

Assessment of ADA occurred at Randomization (prior to injection), Day 30, Day 150, Day 330, and Day 510. At other study visits, samples were collected and stored. If a subject had a positive sample in the screening assay, all stored samples for that subject were also analyzed in the screening assay in order to provide a complete time course of the ADA profile for that subject. Each positive sample in the screening assay was subsequently analyzed in the confirmatory assay and if positive in the confirmatory assay then the sample was analyzed in the titration assay to determine the ADA titer.

The three phase 3 trials of 18-months duration included approximately 9,100 ADA assays from 1830 subjects treated with inclisiran sodium 300mg. There were 1740 subjects with no confirmed positive ADA, 49 subjects with confirmed post-baseline positive ADA with a maximum titer level of 50 and 100, and 41 subjects with a confirmed post-baseline positive ADA with a maximum titer level of 200, 400, and 800.

In response to an FDA information request, the applicant provided figures of observed LDL-C and PCSK9 level over time according to ADA maximum titer levels in patients in the inclisiran treatment arm for the Safety Pool. The figures show that ADA confirmed positive samples by titer level were not associated with a loss of effect for either LDL-C or PCSK9 levels over time.

In response to an FDA information request, the applicant provided waterfall plots of percent change from Baseline in LDL-C at Last Value during the treatment period according to ADA status³³ in patients on inclisiran in the Safety Pool. The pattern of the individual subject responses in these 3 groups is similar and does not show that a positive ADA response was associated with a reduction in LDL-C lowering with inclisiran.

Reviewer comment: Across the phase 3 trials, the LDL-C reduction ranges from -48 to -52%. The majority of subjects in the inclisiran group experienced a sizable LDL-C reduction at Day 510 compared to the placebo group. These results are consistent, statistically significant and clinically meaningful across trials. The limitation to this evidence of effectiveness in LDL-C reduction is that the effect of inclisiran on cardiovascular morbidity and mortality has not been determined.

7.1.2. Secondary and Other Endpoints

The key secondary efficacy endpoints included:

- Absolute change in LDL-C from baseline to Day 510
- Time adjusted absolute change in LDL-C from baseline after Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C

The Hochberg procedure was applied to control the family-wise type I error rate at a 2-sided significance level of $\alpha=0.05$ for the key secondary endpoints.

Reviewer comment: Key secondary endpoints that are relevant to clinical practice include percent change in non-HDL-C, TC and Apo-B from baseline to Day 510. The applicant is seeking labeling claims based on these pre-specified secondary endpoints and I agree that they should be presented in the product labeling.

The placebo-adjusted change in TC, Apo-B and non-HDL-C from baseline to Day 510 in the

³³No confirmed positive ADA post baseline (n=1740), transient confirmed ADA (n=66) or persistent confirmed ADA (n=24): 'Persistent' ADA was defined as any confirmed positive ADA at the subject's last sample obtained up to Day 510; 'Transient' ADA was defined as a negative post treatment ADA sample occurring after a positive ADA sample and the subject's last sample analyzed was also negative.

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individual Phase III trials and the pooled group are shown in the table below.

Table 34. Percentage Change in Total Cholesterol, Apo-B and non-HDL-C from Baseline to Day 510 in ORION-9, -10, -11 and Pooled Trials-ITT Population

Primary Endpoint	ORION-9			ORION-10			ORION-11			Pooled		
	Placebo (N=240)	Inclisiran (N=242)	p-value	Placebo (N=780)	Inclisiran (N=781)	p-value	Placebo (N=807)	Inclisiran (N=810)	p-value	Placebo (N=1827)	Inclisiran (N=1833)	p-value
Percentage Change in TC from Baseline to Day 510 (PMM*)												
LS Mean (95% CI)	6.7 (4.0,9.4)	-25.1 (-27.8, -22.4)		-0.4 (-2.0, 1.1)	-33.6 (-35.1, -32.0)		1.8 (0.4,3.2)	-28.0 (-29.4, -26.6)		2.9 (1.9,4.0)	-28.6 (-29.6, -27.6)	
LS Mean Difference (95% CI) from Placebo		-31.8 (-35.6, -28.0)	<.0001		-33.1 (-35.3, -31.0)	<.0001		-29.8 (-31.8, -27.8)	<.0001		-31.5 (-32.9, -30.1)	<.0001
Percentage Change in Apo-B from Baseline to Day 510 (PMM*)												
LS Mean (95% CI)	2.9 (0.1, 5.7)	-33.1 (-35.9, -30.4)		-1.7 (-3.5, 0.0)	-44.8 (-46.5, -43.1)		0.8 (-0.8, 2.4)	-38.2 (-39.8, -36.5)		1.6 (0.4,2.7)	-38.8 (-39.9, -37.6)	
LS Mean Difference (95% CI) from Placebo		-36.1 (-40.0, -32.1)	<.0001		-43.1 (-45.5, -40.7)	<.0001		-38.9 (-41.2, -36.7)	<.0001		-40.3 (-41.9, -38.8)	<.0001
Percentage Change in non-HDL-C from Baseline to Day 510 (PMM*)												
LS Mean (95% CI)	7.4 (3.9, 10.9)	-34.9 (-38.5, -31.4)		-0.1 (-2.1, 2.0)	-47.4 (-49.4, -45.4)		2.2 (0.2, 4.1)	-41.2 (-43.1, -39.2)		3.6 (2.2,5.0)	-41.3 (-42.7, -40.0)	

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Primary Endpoint	ORION-9			ORION-10			ORION-11			Pooled		
	Placebo (N=240)	Inclisiran (N=242)	p-value	Placebo (N=780)	Inclisiran (N=781)	p-value	Placebo (N=807)	Inclisiran (N=810)	p-value	Placebo (N=1827)	Inclisiran (N=1833)	p-value
LS Mean Difference (95% CI) from Placebo		-42.4 (-47.3, -37.4)	<.0001		-47.4 (-50.3, -44.5)	<.0001		-43.3 (-46.0, -40.6)	<.0001		-44.9 (-46.8, -43.1)	<.0001
Abbreviations: Apo-B=apolipoprotein B; CI=confidence interval; HDL-C = high density lipoprotein cholesterol; ITT=intent-to-treat; LDL-C = low density lipoprotein cholesterol; LS=least squares; MAR=missing at random * A control-based pattern mixture model (PMM) was used for missing data imputation with 100 total imputed datasets. A mixed-effects model for repeated measures (MMRM) on each of the 100 datasets was performed by including fixed effects for treatment, visit, interaction between treatment and visit, and baseline LDL-C as a covariate. A linear contrast at Day 510 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's Method. Source: modified by reviewer from Applicant's ISE Table 21												

Reviewer comment:

Across the phase 3 trials, the TC reduction ranges from -30 to -33%; the Apo-B reduction ranges from -36 to -43%; and the non-HDL-C reduction ranges from -42 to -47%, compared to placebo. The results of the key secondary efficacy endpoints are consistent, statistically significant, clinically meaningful and supportive of the LDL-C reduction that was shown in the primary efficacy endpoint. This is expected as LDL-C is a major component of TC and non-HDL-C; in addition, apolipoprotein B is the primary apolipoprotein of LDL-C.

Across the phase 3 trials, the TG reduction ranges from -9 to -12%; the HDL-C increase ranges from +3 to +6%; and the Lp(a) reduction ranges from -19 to -32%, compared with placebo. Although epidemiological studies suggest that Lp(a) levels are independently associated with atherosclerotic disease, it is unclear if modifying Lp(a), per se, with inclisiran would reduce cardiovascular risk among patients with well-controlled LDL-C but elevated Lp(a). In addition, it is unclear whether the modest changes in TG and HDL-C observed are clinically meaningful.

7.1.3. Subpopulations

The baseline demographics of the pooled group of ORION-9, -10, and -11 are shown in the table below.

Table 35. Demographic and Baseline Characteristics for the ITT/Efficacy Population for ORION-9, -10 and -11

Demographic Parameters	Placebo Control Group (N= 1827) n (%)	Inclisiran (N=1833) n (%)	Total (N=3660*) n (%)
Sex			
Male	1244 (68.1)	1226 (66.9)	2470 (67.5)
Female	583 (31.9)	607 (33.1)	1190 (32.5)
Age			
Mean years (SD)	63.9 (9.9)	64.1 (9.9)	64.0 (9.9)
Median (years)	65.0	65.0	65.0
Min, max (years)	21, 89	20, 90	20, 90
Age Group			
18 - < 65 years	884 (48.4)	853 (46.5)	1737 (47.5)
≥ 65 years	943 (51.6)	980 (53.5)	1923 (52.5)
18 - < 75 years	1575 (86.2)	1593 (86.9)	3168 (86.6)
≥ 75 years	252 (13.8)	240 (13.1)	492 (13.4)
Weight			
Mean, kg (SD)	89.7 (20.0)	88.3 (18.4)	89.0 (19.2)
BMI (kg/m ²)			
Mean, kg (SD)	30.7 (5.8)	30.4 (5.7)	30.6 (5.7)

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Demographic Parameters	Placebo Control Group (N= 1827) n (%)	Inclisiran (N=1833) n (%)	Total (N=3660*) n (%)
Race			
White	1708 (93.5)	1670 (91.1)	3378 (92.3)
Black or African American	102 (5.6)	130 (7.1)	232 (6.3)
Asian	8 (0.4)	22 (1.2)	30 (0.8)
American Indian or Alaska Native	4 (0.2)	4 (0.2)	8 (0.2)
Native Hawaiian or other Pacific Islander	5 (0.3)	7 (0.4)	12 (0.3)
Ethnicity			
Hispanic or Latino	116 (6.3)	120 (6.5)	236 (6.4)
Not Hispanic or Latino	1711 (93.7)	1713 (93.5)	3424 (93.6)
Region			
Canada	11 (0.6)	12 (0.7)	23 (0.6)
Czech Republic	16 (0.9)	17 (0.9)	33 (0.9)
Germany	41 (2.2)	42 (2.3)	83 (2.3)
Denmark	26 (1.4)	23 (1.3)	49 (1.3)
Spain	42 (2.3)	42 (2.3)	84 (2.3)
United Kingdom	231 (12.6)	231 (12.6)	462 (12.6)
Hungary	52 (2.8)	52 (2.8)	104 (2.8)
Netherlands	19 (1.0)	19 (1.0)	38 (1.0)
Poland	357 (19.5)	360 (19.6)	717 (19.6)
Sweden	16 (0.9)	18 (1.0)	34 (0.9)
Ukraine	54 (3.0)	55 (3.0)	109 (3.0)
United States	812 (44.4)	814 (44.4)	1626 (44.4)
South Africa	150 (8.2)	148 (8.1)	298 (8.1)
Baseline GFR Category (mL/min/1.73 m ²)			
≥15 to <30	9 (0.5)	11 (0.6)	20 (0.5)
≥30 to <60	287 (15.7)	295 (16.1)	582 (15.9)
≥60 to <90	1034 (56.6)	1012 (55.2)	2046 (55.9)
≥90	497 (27.2)	515 (28.1)	1012 (27.7)
ASCVD	1555 (85.1)	1552 (84.7)	3107 (84.9)
Hx of CHD	1412/1555 (90.8)	1370/1552 (88.3)	2782/3107 (89.5)
Hx of CVD	244/1555 (15.7)	267/1552 (17.2)	511/3107 (16.4)
Hx of PAD	157/1555 (10.1)	168/1552 (10.8)	325/3107 (10.5)
ASCVD Risk Equivalent	272 (14.9)	281 (15.3)	553 (15.1)
Diabetes Mellitus	631 (34.5)	687 (37.5)	1318 (36.0)
Smoking (current, within past 30 days)	271 (14.8)	311 (17.0)	582 (15.9)
Hypertension	1463 (80.1)	1456 (79.4)	2919 (79.8)
Baseline LDL-C (mg/dL)			

Demographic Parameters	Placebo Control Group (N= 1827) n (%)	Inclisiran (N=1833) n (%)	Total (N=3660*) n (%)
Mean (SD)	110.8 (43.6)	111.9 (44.9)	
Median (mg/dL)	100.0	100.0	
Min, max (mg/dL)	40, 460	32, 556	

* 3655 subjects (481, 1559, and 1615 subjects in ORION-9, ORION-10, and ORION-11, respectively), were included in the Safety Population. In ORION-10, the Safety Population excludes 2 subjects assigned to inclisiran who were not dosed and 2 placebo subjects who were dosed instead with inclisiran. In ORION-11, two subjects (both randomized to placebo) were excluded from the Safety Population because they did not receive any study drug. Another subject was incorrectly administered inclisiran instead of placebo on Day 450. This subject is included in the inclisiran Safety Population but included in the placebo ITT Population.

Abbreviations: GFR=glomerular filtration rate; SD=standard deviation; ASCVD=Atherosclerotic Cardiovascular Disease; CHD=Coronary Heart Disease; CVD= Cerebrovascular Disease; PAD= Peripheral Artery Disease

Source: Applicant's ISS-ISE, Tables 14.1.8.1.1 and 14.1.9.1.1, 14.2.15.1.1 and FDA JMP Clinical 7.1 demographics analysis

Reviewer comment: The demographic and baseline characteristics are largely balanced between the two treatment groups. The study enrolled 92% of subjects who are White, 6% who are Black or African American and <1% from other racial groups. Thus, there is limited representation of Black groups and inadequate representation of Asian, American Indian or other groups. Six percent of subjects identified as Hispanic or Latino. Two-thirds (68%) of the study population is male and the mean age is 64 years old. Of the 1833 patients treated with inclisiran in the Phase 3 trials, approximately 980 (54%) patients were ≥ 65 years and 240 (13%) patients were ≥ 75 years. The study population included relevant comorbidities such as ASCVD (85%, primarily CHD), renal impairment (mild [56%, 2,046/3660], moderate [16%, 582/3660], or severe [0.5%, 20/3660]) as assessed by the central laboratory at screening using eGFR, hypertension (80%) and diabetes (36%). Thus, with the limitations of underrepresentation of non-white groups and only 32% women, participants studied in the Phase III program adequately represent the intended target population for inclisiran treatment for patients with ASCVD and/or HeFH as an adjunct to maximally tolerated statin therapy.

Placebo-adjusted LDL-C percentage changes from baseline to Day 510 for subgroups

Treatment differences in percentage change from baseline in LDL-C at Day 510 in the pooled ORION-9, -10 and -11 trials by subgroup – ITT Population is shown in Figure 9 and described in more detail below.

Sex: There was no meaningful difference in the estimate of the treatment effect by sex. In the 3 Phase III trials, 67% (2470/3660) of subjects were male and 33% (1190/3660) were female. In the pooled group, as in the individual trials, similar and statistically significant placebo-adjusted

LDL-C percentage changes from baseline to Day 510 were observed (males: -54%; females: -55%).

Age: There was no difference or trend in the estimate of the treatment effect by age. In the 3 Phase III trials, 47% (1737/3660) of subjects were <65 years and 53% (1923/3660) were ≥65 years; 87% (3168/3660) of subjects were <75 years and 13% (492/3660) were ≥75 years. In the pooled group, as in the individual trials, similar and statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed: <65 years: -54%; ≥65 years: -54%; <75 years: -54%; ≥75 years: -55%.

Body Mass Index

Overall, 50% (1830/3660) of subjects in the Phase 3 trials had a baseline BMI less than the median value (29.7 kg/m²) and 50% (1828/3660) had a baseline BMI greater than the median value. In the pooled group, statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed in both subgroups. As was seen in the individual trials, a slightly larger percentage change was noted in subjects with a BMI higher than the median (>29.74 kg/m²: -57%) compared with subjects with a BMI lower than the median (≤29.74 kg/m²: -52%).

Race

There was no meaningful difference in the estimated treatment effect by race. In the 3 Phase III trials, 92% (3378/3660) of subjects were White and 6% (232/3660) of subjects were Black/African-American and <2% (50/3660) were of other races. In the pooled group, similar and statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were seen in Whites (-54%), Blacks/African Americans (-54%), and subjects of other races (-50%).

Ethnicity

In the 3 Phase III trials, 94% (3424/3660) of subjects were not Hispanic or Latino and 6% (236/3660) were Hispanic or Latino. In the pooled group, statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed in both subgroups. A larger percentage change was noted for subjects who were not Hispanic or Latino (-55%) compared with subjects with the ethnicity of Hispanic or Latino (-44%).

Reviewer comment: Whether this is due to the smaller sample size and increased variability of the result or inter-individual differences or is a true reflection of ethnic differences is not known; further investigation with a larger sample size of Hispanic/Latino individuals would be needed to clarify this.

Study Center Region

Overall, 45% (1649/3660) of subjects in the Phase III trials were from North America, 47%

(1713/3660) from Europe, and 8% (298/3660) from South Africa. In the pooled group, statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed in all subgroups. A larger percentage change was noted for subjects from North America (-56%) and South Africa (-58%) compared with subjects from Europe (-51%).

Baseline Statin Use

In the Phase III trials, 92% (3361/3660) were receiving a statin at baseline and 8% (299/3660) were not receiving statins at baseline. In the pooled group, as in the individual trials, statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed in subjects on or off statins; however, a larger percentage change was noted for subjects on statins (-55%) compared with subjects off statins (-49%). As the group not receiving a statin was small compared to the group taking a statin, the difference could be due to chance. It is also possible that patients not taking statins at baseline were somehow different than on-statin patients, accounting for the difference.

Baseline Statin Intensity

In the Phase III trials, 74% (2701/3660) of subjects were on high-intensity statins and 26% (959/3660) of subjects were not. In the pooled group, similar and statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were seen in subjects on a high-intensity statin (-55%) and subjects not on a high-intensity statin (-53%).

Baseline Triglyceride Level

Overall, 50% (1832/3660) of subjects in the Phase 3 trials had baseline triglycerides less than or equal to the median value (130 mg/dL) and 50% (1828/3660) had values greater than the median value. Similar and statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed in subjects with baseline triglycerides ≤ 130 mg/dL (-52%) and > 130 mg/dL (-56%).

Metabolic Disease

Overall, 36% (1318/3660) of subjects in the Phase III trials had diabetes, 28% (1025/3660) had metabolic syndrome, and 36% (1317/3660) had neither. In the pooled group, statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were observed for these 3 subgroups. A larger percentage change was noted for subjects with diabetes (-56%) and subjects with metabolic syndrome without diabetes (-56%) compared with subjects with neither diabetes or metabolic syndrome (-51%). In ORION-9, which enrolled patients with HeFH, 10% of patients had diabetes at baseline compared to 45% in ORION-10 and 35% in ORION-11. In the overall pool, 3.6% (48/1318) of patients had HeFH along with DM compared to 18.5% (434/2342) in the group without DM (this group included patients with metabolic syndrome). This imbalance in the proportion of patients with HeFH may have contributed to the finding that patients with diabetes experienced a slightly greater decrease in LDL-C.

Renal Function

In the Phase 3 studies, severe renal impairment was seen in 0.5% (20/3660) of subjects; 16% (582/3660) had moderate impairment; 56% (2046/3660) had mild impairment; and 28% (1012/3660) had normal renal function as assessed by the central laboratory at screening for study eligibility using eGFR. In the pooled group, similar and statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 were seen across the eGFR subgroups (normal renal function: -54%; mild renal impairment: -53%; moderate renal impairment: -57%).

Baseline LDL-C

Overall, 50.6% (1852/3660) of subjects in the Phase 3 studies had a baseline LDL-C less than or equal to the median value (100 mg/dL) and 49.4% (1808/3660) of subjects had a value greater than the median value. In the pooled group, statistically significant placebo-adjusted LDL-C percentage changes from baseline to Day 510 was observed in both subgroups. Similar to what was seen in the individual trials, a larger percentage change was noted for subjects with baseline LDL-C ≤ 100 mg/dL (-61%) compared with subjects with baseline LDL-C > 100 mg/dL (-47%).

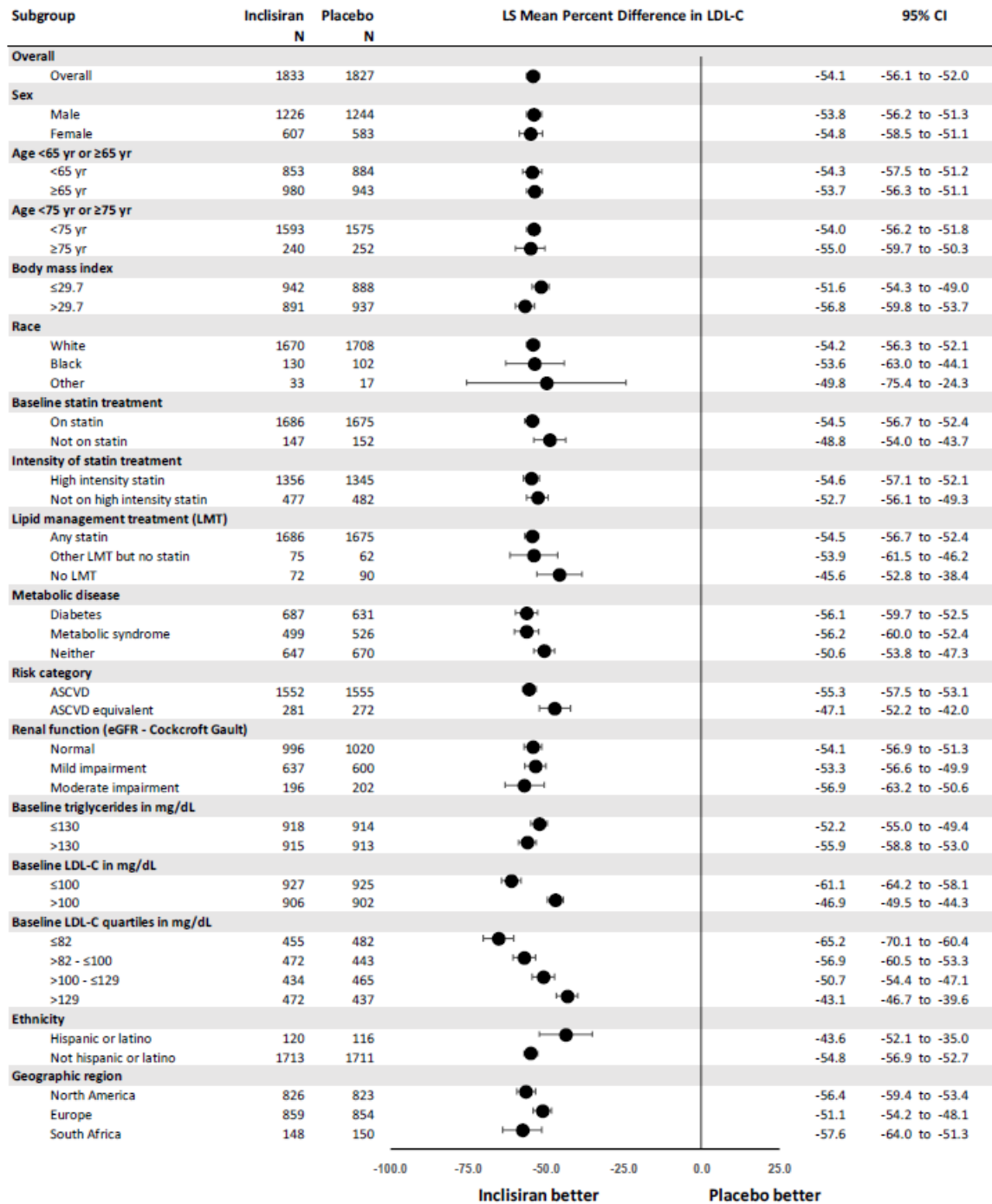
Looking at baseline LDL-C by quartiles, particularly for ORION-10, ORION-11 and the pooled group, a decreasing percentage change in LDL-C was seen as baseline LDL-C values increased from the lowest to the highest quartile. However, an increasing absolute change in LDL-C was seen as baseline LDL-C values increased from the lowest to the highest quartile, showing that the higher the baseline LDL-C, the more absolute reduction of LDL-C was demonstrated, particularly in the inclisiran group.

The absolute change, and [percent change], in LDL-C from baseline to Day 510 by baseline LDL-C quartile [LS mean difference (95% CI) from placebo] was as follows:

1. Baseline LDL-C quartile ≤ 82 mg/dl: -45.4 mg/dL (-48.7, -42.1) [percent change was -65.2%]
2. Baseline LDL-C quartile > 82 and ≤ 100 mg/dl: -50.2 mg/dL (-53.7, -46.7) [percent change was -56.9%]
3. Baseline LDL-C quartile > 100 and ≤ 129 mg/dl: -55.0 mg/dL (-59.2, -50.7) [percent change was -50.7%]
4. Baseline LDL-C quartile > 129 mg/dl: -70.1 mg/dL (-76.2, -64.0) [percent change was -43.1%]

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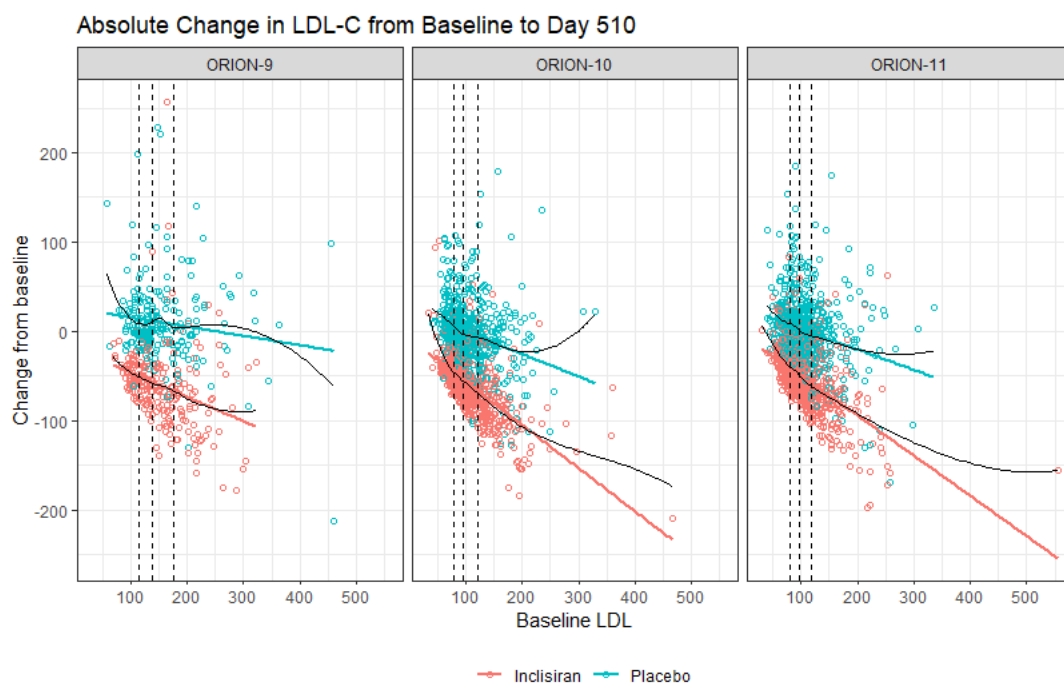
Figure 9. Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 in ORION-9, -10, and -11 Pool by Subgroup – ITT Population



Source: ISE report, Figure 6

The FDA statistical reviewer looked at these trends with baseline LDL-C by quartiles in more detail. The figure below looks at the absolute change in LDL-C from Baseline to Day 510 in ORION-9, -10 and -11. This shows the trend across the 3 trials of an increased absolute reduction in LDL-C with increased baseline LDL-C. This trend appears in both groups but is more obvious in the inclisiran group.

Figure 10. Absolute Change In LDL-C from Baseline to Day 510 in ORION-9, -10 and -11

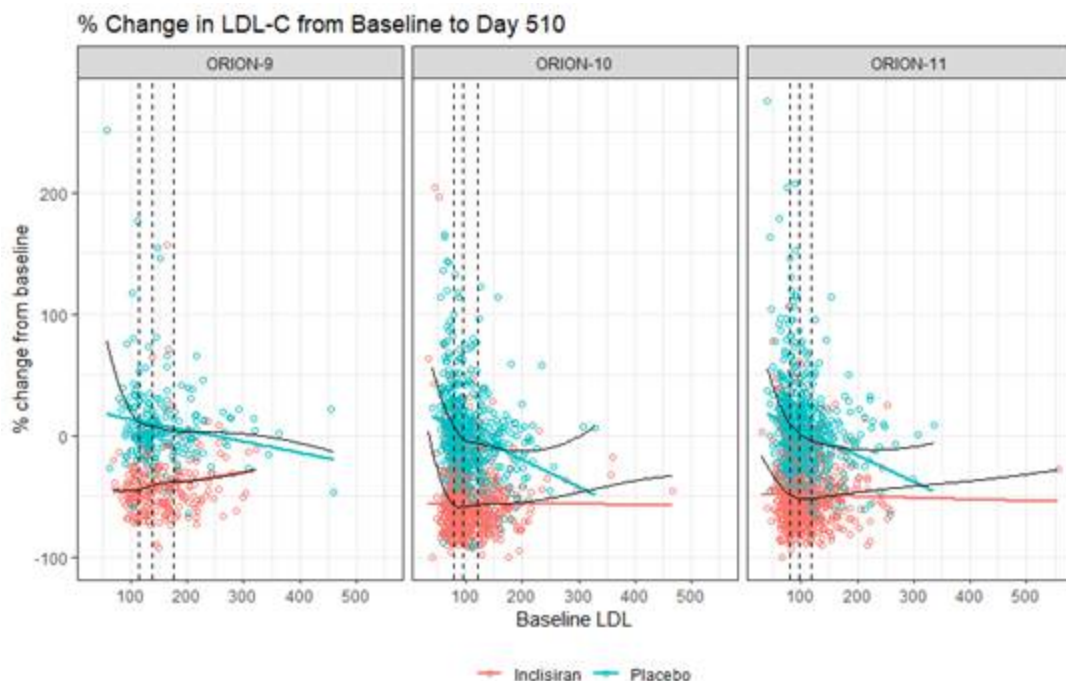


Source: FDA Statistical Reviewer, Dr. Jennifer Clark.

Plots use local regression fitting to accommodate for differences in trend seen between different levels of baseline LDL. The linearity assumption is relaxed, and a nonparametric regression is used to fit the curve (black lines). Linear regression lines are seen for comparative purposes. Vertical lines are drawn at the quartiles for each of the datasets, 25% of baseline LDL measurements fall between each of these lines.

The figure below looks at the percentage change in LDL-C from Baseline to Day 510 in ORION-9, -10 and -11. In the inclisiran group, the trend for percentage change is fairly flat, particularly in the 2nd and 3rd quartile. In ORION-10 and -11, the 2nd and 3rd quartile represents a narrow range of LDL values and may represent a more homogenous population than the 1st and 4th quartile, which includes patients in the extreme portions of the baseline LDL distribution. Across the quartiles in ORION-10 and -11, there is a slight trend showing a decreasing percentage change in LDL-C as baseline LDL-C values increased from the lowest to the highest quartile.

Figure 11. Percentage Change In LDL-C from Baseline to Day 510 in ORION-9, -10 and -11



Source: FDA Statistical Reviewer, Dr. Jennifer Clark.

Plots use local regression fitting to accommodate for differences in trend seen between different levels of baseline LDL. The linearity assumption is relaxed, and a nonparametric regression is used to fit the curve (black lines). Linear regression lines are seen for comparative purposes. Vertical lines are drawn at the quartiles for each of the datasets, 25% of baseline LDL measurements fall between each of these lines.

Reviewer comment: Consistent, statistically significant placebo-adjusted LDL-C percent changes from baseline to Day 510 were seen across various subpopulations defined by baseline demographic characteristics and disease comorbidities. The efficacy results are generally similar in various subpopulations. In the inclisiran group from ORION-10 and ORION-11, a trend towards decreasing percentage change in LDL-C, as compared to placebo, was seen as baseline LDL-C values increased from the lowest to the highest quartile. However, the regression analysis indicated that the effect is fairly flat across baseline LDL levels.

7.1.4. Dose and Dose-Response

Inclisiran was administered via single use prefilled syringe or a vial and syringe (300 mg inclisiran sodium in 1.5 mL aqueous solution containing 284 mg of inclisiran) for injection by a healthcare professional.

In each of the three Phase 3 trials (ORION-9, -10 and -11), inclisiran sodium 300 mg or placebo was administered as a subcutaneous (SC) injection on Day 1 with a second dose on Day 90,

followed by 6-month dosing intervals at Days 270 and 450 and follow-up until Day 540. The Phase III dose and dosage regimen for inclisiran was selected based on data from the ALNPCSSC-001 Phase I, ORION-1 Phase II studies and population PD modeling, since a limited number of doses and dose regimens were tested clinically. There were no clinically meaningful safety events at higher doses; therefore, dose selection was not limited or determined by safety findings.

ALN-PCSSC-001 Phase I study

ALN-PCSSC-001 was a placebo-controlled, Phase I, single-ascending-dose (SAD) and multiple-dose (MD) study that evaluated single subcutaneous (SC) doses of inclisiran sodium ranging from 25 mg to 800 mg and repeat doses of 125 mg to 500 mg administered either monthly (QM), every 2 weeks (Q2W), or weekly (QW). Inclisiran doses of 25 mg, 100 mg, 300 mg, 500 mg, and 800 mg were evaluated in the SAD phase of Study ALN-PCSSC-001 (see Table below). A dose-dependent reduction in LDL-C was seen up to 300 mg inclisiran, after which there was a plateauing of dose effect. Thus, doses > 300 mg do not appear to result in greater LDL-C reduction.

Table 36. Study ALN-PCSSC-001: Observed Mean Percent Change in LDL-C (**β-Quantification Method**) in Single-dose Groups

Parameter	Placebo	Inclisiran 25 mg Single dose	Inclisiran 100 mg Single dose	Inclisiran 300 mg Single dose	Inclisiran 500 mg Single dose	Inclisiran 800 mg Single dose
Mean % change at Day 84 (n)	-7.5 (5)	-27.9 (2)	-36.6 (3)	-48.4 (3)	-47.6 (3)	-41.9 (5)
Mean % change at Day 140 (n)	NA	-15.1 (1)	-38.7 (2)	-43.9 (3)	-38.7 (2)	-45.5 (4)
Mean % change at Day 180 (n)	NA	NA	-26.3 (2)	-47.8 (3)	-37.9 (2)	-35.2 (4)

Abbreviations: NA=not applicable

Source: ALN-PCSSC-001 Applicant's CSR Table 14.2-1.1.1

In the MD groups, doses of 125 mg weekly for 4 weeks, 250 mg twice given 2 weeks apart, 300 mg twice given 1 month apart (with or without statin) and 500 mg twice given 1 month apart (with or without statin) were evaluated. The most commonly used statins in the group with statin concomitant medication were atorvastatin (7 subjects [15.6%]) and simvastatin (5 subjects [11.1%]).

Table 37. Study ALN-PCSSC-001: Observed Mean Percent Change in LDL-C (**β-Quantification Method**) in Multiple-dose Groups

Group	Mean % change at Day 84 (n)	Mean % change at Day 140 (n)	Mean % change at > Day 180 (n)

Placebo without statin	-17.7 (6)	NA	NA
Placebo with statin	-1.7 (3)	NA	NA
300 mg inclisiran QW4 without statin	-57.4 (6)	-49.0 (6)	Day 196 -45.6 (6)
300 mg inclisiran QW4 with statin	-42.6 (3)	-36.7 (3)	Day 196 -38.2 (2)
500 mg inclisiran QW4 without statin	-50.7 (6)	-51.9 (6)	Day 196 -44.4 (6)
500 mg inclisiran QW4 with statin	-49.9 (5)	-48.9 (3)	Day 196 -45.9 (4)
125 mg inclisiran qwx4	-39.6 (6) ^a	-41.0 (6) ^b	Day 189 -37.6 (6)
250 mg inclisiran q2wx2	-51.3 (6)	-45.5 (6) ^c	Day 182 -43.6 (6)

a Day 77; data for Day 84 is not available.

b Day 133; data for Day 140 is not available.

c Day 154; data for Day 140 is not available.

Abbreviations: NA=not available; Q4W=once every 4 weeks; qwx4=once weekly for 4 weeks; q2wx2=twice given 2 weeks apart.

Source: ALN-PCSSC-001 Applicant's CSR Table 14.2-1.1.2

ORION-1 Phase II study

ORION-1 (MDCO-PCS-15-01) was a Phase II, placebo-controlled, double-blind, randomized, dose-finding study conducted in subjects with ASCVD or ASCVD risk equivalents and elevated LDL-C despite maximum tolerated dose of lipid modifying therapies. In ORION-1, subjects received a single-dose of inclisiran or matching placebo on Day 1. The single-dose groups (inclisiran 200 mg, 300 mg, 500 mg and 3 matching placebo groups) received no further study drug. The double-dose groups (placebo, inclisiran 100 mg, 200 mg, 300 mg and 3 matching placebo groups) received a second dose of study drug on Day 90.

In the single-dose groups, percentage change from baseline to Day 180, is shown in the table below. Doses > 300 mg do not appear to result in clinically meaningful greater LDL-C reduction.

Table 38. ORION 1: Percentage Change in LDL-C from Baseline to Day 180 – mITT Population; Single Dose

Parameter	Placebo (N= 64)	Inclisiran 200 mg Single dose (N=60)	Inclisiran 300 mg Single dose (N=60)	Inclisiran 500 mg Single dose (N=60)
LS Mean (95% CI)	2.1 (-2.9, 7.2)	-27.9 (-33.1, -22.7)	-38.4 (-43.6, -33.2)	-41.9 (-47.2, -36.7)
LS Mean Difference (95%)		-30.1	-40.5	-44.1

Parameter	Placebo (N= 64)	Inclisiran 200 mg Single dose (N=60)	Inclisiran 300 mg Single dose (N=60)	Inclisiran 500 mg Single dose (N=60)
CI) from Placebo		(-38.8, -21.3)	(-49.3, -31.8)	(-52.8, -35.3)
Dunnett-adjusted p value		<0.0001	<0.0001	<0.0001

Source: CSR ORION-1, Table 5.2.2.1

Abbreviations; CI=confidence interval; LDL-C=low-density lipoprotein cholesterol; LS=least squares; mITT=modified intent-to-treat; SD=standard deviation

In the double-dose groups (dosed on Day 1 and 90), percentage change from baseline to Day 180, is shown in the table below.

Table 39. ORION 1: Percentage Change in LDL-C from Baseline to Day 180 – mITT Population; Double Dose

Parameter	Placebo (N= 61)	Inclisiran 100 mg Double dose (N=59)	Inclisiran 200 mg Double dose (N=60)	Inclisiran 300 mg Double dose (N=59)
LS Mean (95% CI)	1.8 (-2.6, 6.3)	-35.5 (-40.0, -31.0)	-44.9 (-49.3, -40.4)	-52.6 (-57.1, -48.1)
LS Mean Difference (95% CI) from Placebo		-37.3 (-44.9, -29.7)	-46.7 (-54.3, -39.1)	-54.5 (-62.1, -46.8)
Dunnett-adjusted p value		<0.0001	<0.0001	<0.0001

Source: CSR ORION-1, Table 5.2.2.2

Abbreviations; CI=confidence interval; LDL-C=low-density lipoprotein cholesterol; LS=least squares; mITT=modified intent-to-treat; SD=standard deviation

Reviewer comment: Based on the evidence summarized above, the dose selection of inclisiran sodium 300 mg administered as a SC injection on Day 1 with a second dose on Day 90, followed by 6-month dosing intervals, is supported by the data and is appropriate.

ORION-3 is the ongoing long-term extension study for subjects who completed ORION-1. Subjects who received inclisiran in ORION-1 are receiving inclisiran throughout ORION-3. Subjects who received placebo in ORION-1 received evolocumab for 1 year and were then transitioned to inclisiran for the remainder of the study. Subjects in this group either received their final dose of evolocumab on Day 336, approximately 24 days before their first dose of inclisiran or received their final dose of evolocumab on Day 360, the same study visit as their first dose of inclisiran.

There were 436 subjects from the ORION-1 study who were eligible to participate in ORION-3; 382 (88%) subjects continued into ORION-3. Of the 382 subjects participating in ORION-3, 290 had received inclisiran in ORION-1 and received inclisiran only in ORION-3; 92 subjects had received placebo in ORION-1 and received evolocumab followed by inclisiran in ORION-3.

In the placebo/evolocumab/inclisiran group, at Day 360 the percentage change in LDL-C from ORION-3 baseline was -47%. Thirty days after switching to the first administration of inclisiran, mean changes from baseline LDL-C were -56% (final dose of evolocumab on Day 336 group) and -64% (final dose of evolocumab on Day 360 group). The latter group likely had a greater change in LDL-C from the combined effect of evolocumab and inclisiran administered on the same day. By Day 450, LDL-C percentage change was similar for both groups: -42% and -44%.

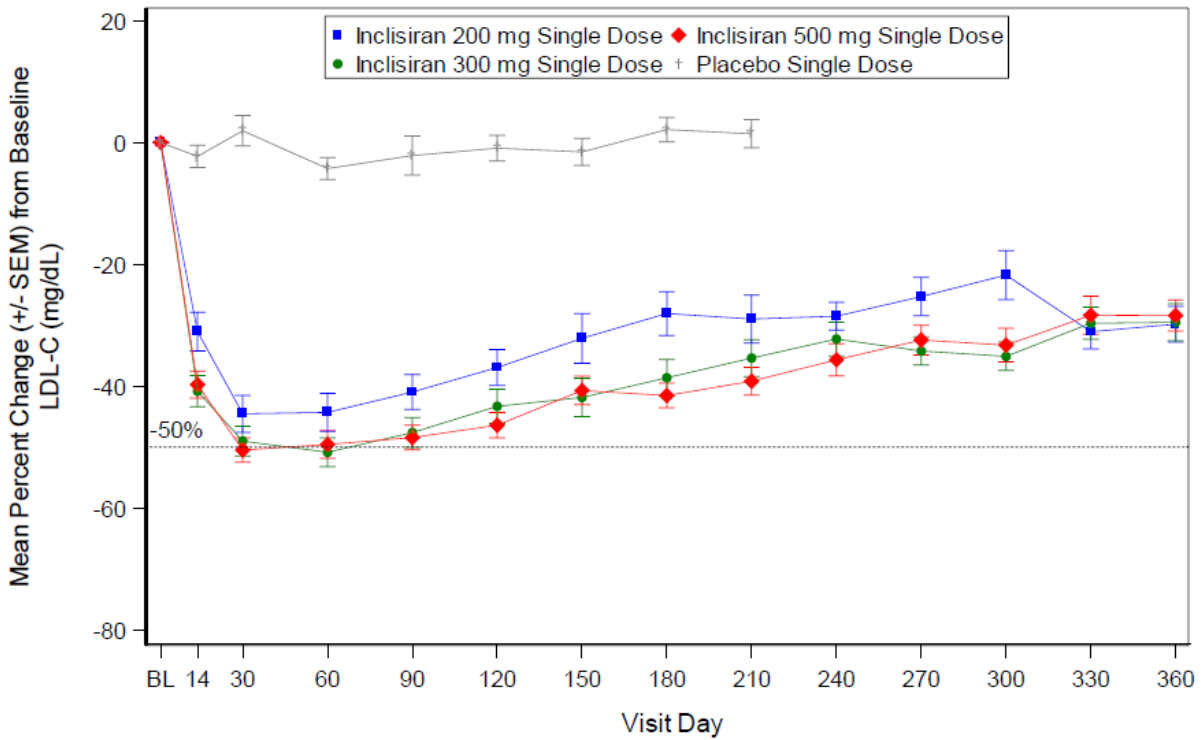
(b) (4)

Refer to 4.5 Clinical Pharmacology for details on dose-disease interactions.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The onset of LDL-C lowering appears to occur by Week 2 with maximal response seen between Days 30 to 60 for most subjects in ORION-1. Inclisiran has a prolonged pharmacodynamic effect on LDL-C and PCSK9 levels after the treatment is stopped. As shown in the following figure from ORION-1, at Day 360, after a single dose, the mean percentage change in LDL-C from Baseline was -30% for 200 mg, -30% for 300 mg, and -28% for 500 mg. At Day 210, in the placebo group, the mean percent change from Baseline at Day 210 was 1%; in the inclisiran 300 mg group, the mean percent change from Baseline at Day 210 was -35%.

Figure 12. ORION-1: Percentage Change from Baseline LDL-C (mg/dL) by Dose Group over Time– Single-Dose Groups (mITT Population)



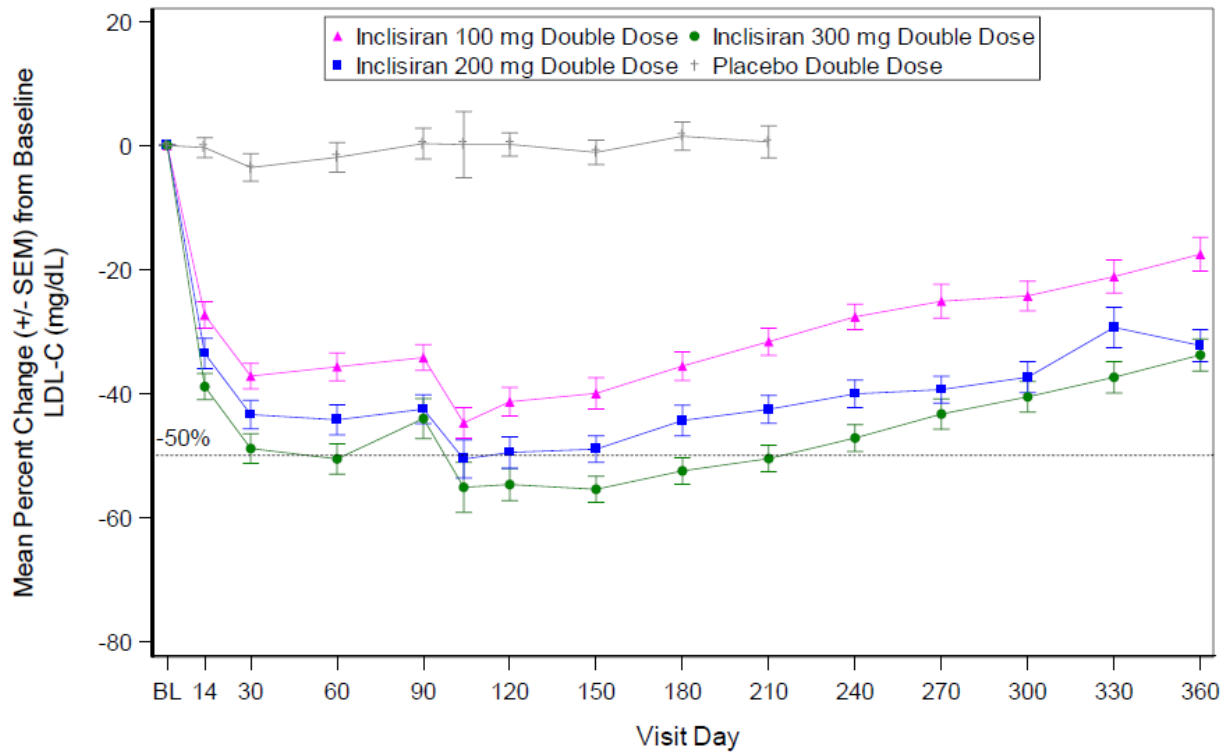
Source: ORION-1 Day 360 CSR, Figure 5.3.2.1

Note: Data for placebo-treated subjects are not presented beyond Day 210 since the majority of placebo-treated subjects did not have data collected beyond this timepoint.

Abbreviations: LDL-C=low-density lipoprotein cholesterol; mITT=modified intent-to-treat; SEM=standard error of the mean.

As shown in the following figure for the double-dose groups (dosed on Day 1 and 90), at Day 360, the mean percentage change in LDL-C from Baseline was -18% for 100 mg, -32% for 200 mg, and -34% for 300 mg.

Figure 13. ORION-1: Percentage Change from Baseline LDL-C (mg/dL) by Dose Group over Time– Double-Dose Groups (mITT Population)



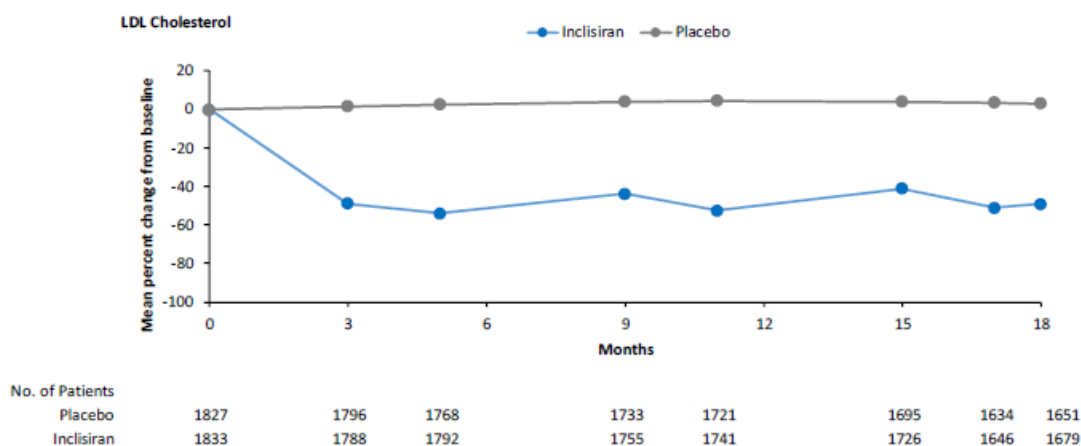
Source: ORION-1 Day 360 CSR, Figure 5.3.2.2

Note: Data for placebo-treated subjects are not presented beyond Day 210 since the majority of placebo-treated subjects did not have data collected beyond this timepoint.

Abbreviations: LDL-C=low-density lipoprotein cholesterol; mITT=modified intent-to-treat; SEM=standard error of the mean.

The persistence of efficacy was shown previously in Figure 2, Figure 4, and Figure 6 for ORION-9, ORION-10 and ORION-11, respectively. The pooled data, representing 1679 patients in the inclisiran group and 1651 patients in the placebo group at 18 months, is shown in the figure below.

Figure 14. Percentage Change from Baseline LDL-C (mg/dL) by Visit in Pooled Data from ORION-9, ORION-10 and ORION-11: ITT Population



Source: ISE, Figure 3

Inclisiran had a consistent and durable effect on the reduction of LDL-C over time in these three trials of 18 months duration.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Inclisiran is administered by a health care provider via subcutaneous injection at Day 1, Day 90 and then every 6 months during the clinical trials and in the postmarketing setting. Thus, other than patients being non-compliant with clinic appointments to receive the injection, there should not be significant potential differences in how the drug was administered and used in the clinical trial and its expected use in the postmarket setting that could affect whether the benefit demonstrated in the clinical trials can reasonably be expected to be achieved in the postmarket setting.

In these phase 3 trials, the entry criteria and exclusions were appropriate for the population that might receive the drug. Of the 1833 patients treated with inclisiran in the Phase 3 trials, approximately 980 (54%) patients were ≥ 65 years and 240 (13%) patients were 75 years of age and older. Non-white individuals and, to a lesser degree, women, were underrepresented in the enrolled population. Overall, participants studied in the Phase III program adequately represent the intended target population for inclisiran treatment for patients with ASCVD and/or HeFH as an adjunct to maximally tolerated statin therapy.

7.2.2. Other Relevant Benefits

Some patients may prefer daily oral agents over injectable medications. Some patients may prefer an injection every 6 months to injections every 2 or 4 weeks, which is the dosing regimen for PCSK9 inhibitor monoclonal antibodies. It is possible, but not proven, that less frequent dosing with inclisiran may improve a patient's adherence. This may be a relevant benefit which factors in a small way into the overall assessment of the drug's benefit.

Inclisiran has a prolonged and robust pharmacodynamic effect on LDL-C levels which allows for infrequent dosing. However, unlike alirocumab, evolocumab and statins, we do not have CV outcome data with inclisiran that confirms a reduction in CV morbidity and mortality, nor do we have the long-term safety data assessment that is possible from a CVOT that is several years in duration and enrolls thousands of patients.

7.3. Integrated Assessment of Effectiveness

LDL-C is a valid surrogate endpoint for evaluating risk reduction of CVD and/or CHD. LDL-C lowering has been proven to consistently reduce the risk of atherosclerotic cardiovascular disease in large randomized controlled trials of LDL-C-lowering therapies, namely statins and PCSK9 inhibitors. In the absence of cardiovascular outcomes data, contemporary decisions to approve novel LDL-lowering therapies are influenced by the direction and magnitude of drug-induced changes in LDL-C, the mechanism of action of the novel agent, as well as the effects of the drug on other lipid parameters, markers of cardiometabolic risk, and any evidence for off-target toxicity.

Inclisiran's mechanism of action involves the reduction of intrahepatic PCSK9 levels which leads to an increase in LDL-C receptor recycling and expression on the hepatocyte cell surface, thereby increasing LDL-C uptake and lowering LDL-C. Patients that have defective LDL-C receptors and consequent diminution in LDL receptor activity, particularly patients with homozygous familial hypercholesterolemia who are LDL receptor-negative, have a decreased LDL-C lowering response to drugs like statins and PCSK9 inhibitors that work through the LDL-C receptor. Inclisiran is therefore unlikely to show a sizable effect in these patients who have failed to show a meaningful LDL-C response to statins and PCSK9 inhibitor monoclonal antibodies.

As detailed in Section 6, ORION-9, ORION-10 and ORION-11 included a population of approximately 3500 patients with HeFH or ASCVD with elevated LDL-C despite maximally tolerated statin therapy who were treated with inclisiran sodium 300 mg administered subcutaneously at Day 1, Day 90 and every 6 months afterward for a duration of 18 months. The study population included relevant comorbidities such as increased age, renal impairment, hepatic impairment, hypertension and diabetes.

The data from these 3 trials demonstrated a robust, durable LDL-C reduction with supportive results in total cholesterol, non-HDL-C and apo-B endpoints. The LDL-C reduction of 48-52% is

clinically meaningful. The majority of subjects in the inclisiran group experienced a sizable LDL-C reduction at Day 510 compared to the placebo group. Consistent, statistically significant placebo-adjusted LDL-C percent changes from baseline to Day 510 were seen across various subpopulations defined by baseline demographic characteristics and disease comorbidities.

The applicant has submitted evidence of effectiveness that meets the statutory evidentiary standard. It is important to note that the cardiovascular outcome trial with inclisiran is ongoing so the effect of inclisiran on cardiovascular morbidity and mortality has not been determined. The lack of this data will limit the scope of the indication and thus supports a narrower indication than the applicant's proposed indication of:

- INCLISIRAN is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) to reduce low-density lipoprotein cholesterol (LDL-C).

Based on data showing robust LDL-C reductions and an acceptable safety profile, this reviewer recommends approval for the following indication:

- INCLISIRAN is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).

8. Review of Safety

8.1. Safety Review Approach

This safety review focuses on the pooled data (Safety Pool) from the three controlled Phase 3 studies: ORION-9, ORION-10, and ORION-11 which were also the focus of the efficacy review. These three studies were similar in design---all were placebo-controlled, double-blind, randomized and were 18 months in duration. Additionally, the studies had the same endpoints, used the same 300 mg inclisiran dose and dosing regimen, and had the same visit schedule.

The three studies investigated the effects of inclisiran on the spectrum of patients with primary hyperlipidemia. ORION-9 enrolled patients with heterozygous familial hypercholesterolemia, while ORION-10 comprised patients with atherosclerotic cardiovascular disease and ORION-11 included patients with atherosclerotic cardiovascular disease and atherosclerotic risk

equivalents.

In the Phase 3 studies, patients were randomized 1:1 to either inclisiran or placebo and were required to be on a background of maximally tolerated statin therapy with or without other LDL-C lowering agents such as ezetimibe before randomization. The Safety population was defined as all patients who received at least one dose of investigational product.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In the Safety population, which included all patients in clinical studies (Phase 1, 2, and 3), there were a total of 4332 patients, of which 2452 patients were exposed to any dose of inclisiran. Approximately 2118 patients were exposed to inclisiran 300 mg dose.

Table 40. Exposure in Safety Population (All Clinical Studies)

Study	Number of Subjects		
	Inclisiran		Inclisiran plus Control
	300 mg	Other Dose	
ORION-9	241	–	481
ORION-10	781	–	1559
ORION-11	811	–	1615
ORION-1	122	248	497
ORION-3	87 ^a	–	–
ORION-2	4	–	4
ORION-6	28	–	28
ORION-7	31	–	31
ALN-PCSSC-001	13	38	69
ORION-12	–	48	48
Totals	2118	334	4332
Total subjects treated with Inclisiran	2452		–

Source: Table 7, ISS.

a- Includes only those subjects who had previously received placebo in ORION-1 and were transitioned to inclisiran in ORION-3

The following table shows the exposure to inclisiran in the Safety Pool, which included patients in the three Phase 3 studies, ORION-9, -10, and -11. The main safety review focuses on the patients in the Safety Pool.

Table 41. Exposure in Safety Pool (ORION-9, -10, and -11)

Study	Number of Patients

	Inclisiran	Inclisiran plus Control
ORION-11	811	1615
ORION-10	781	1559
ORION-9	241	481
Total	1833	3655

Source: Table 7, ISS.

Reviewer Comment: ORION-11 contributed the greatest number of patients to the Safety Pool with 1615 patients, followed by 1559 patients in ORION-10 and 481 patients in ORION-9.

8.2.2. Relevant characteristics of the safety population:

See the efficacy section for a complete discussion of the randomized population of the Safety Pool as the Safety Pool was very similar (less 5 patients) to the ITT population from the three Phase 3 trials. The following table summarizes some of the Baseline demographics of the Safety pool.

Table 42. Summary of Baseline Characteristics by Treatment Arm, Safety Pool

Baseline Characteristic	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Sex		
Male	1240 (68%)	1228 (67%)
Female	582 (32%)	605 (33%)
Race		
White	1704 (93.5%)	1669 (91.1%)
Black or African American	101 (5.5%)	131 (7.1%)
Asian	8 (0.4%)	22 (1.2%)
American Indian or Alaska Native	4 (0.2%)	4 (0.2%)
Native Hawaiian or other Pacific Islander	5 (0.3%)	7 (0.4%)
Ethnicity		
Latino or Hispanic	116 (6.4%)	120 (6.5%)
Not Latino or Hispanic	1706 (93.6%)	1713 (93.5%)
Diabetes Mellitus		
Yes	630 (34.6%)	687 (37.5%)
No	1192 (65.4%)	1146 (62.5%)
Cardiovascular History/Risk Factor¹		
ASCVD	1550 (85%)	1553 (85%)
ASCVD Risk Equivalent*	272 (15%)	280 (15.3%)

Baseline Characteristic	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Familial versus non-familial dyslipidemia		
HeFH	240	241
Non-familial	1582	1592
Lipid Modifying Therapy		
Statin only	1249 (68.6)	1298 (70.8)
Statin plus other LMT	1671 (91.7)	1686 (92.0)
Other LMT (with or without statin)	484 (26.6)	463 (25.3)
Other LMT Only	62 (3.4)	75 (4.1)
No LMT	89 (4.9)	72 (3.9)

Source: Reviewer created from ADSL dataset and from Table 10, ISS.

Abbreviations: ASCVD=Atherosclerotic Cardiovascular Disease; *ASCVD risk equivalent=no established cardiovascular disease at Baseline; LMT=Lipid Modifying Therapy.

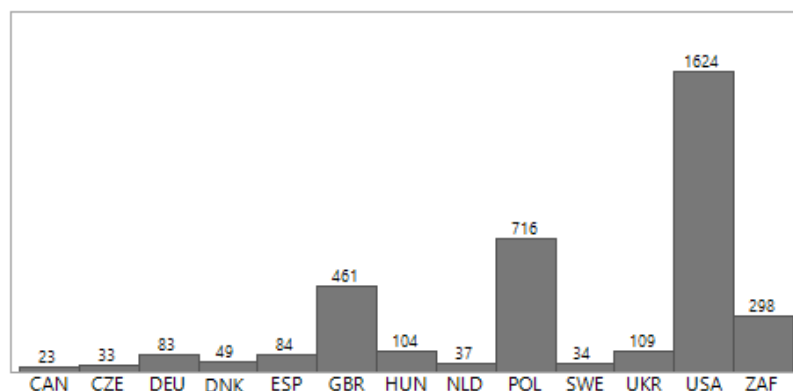
1 – Both categories include patients with HeFH and patients with non-familial hyperlipidemia.

2 – Both categories encompass patients with ASCVD and ASCVD risk equivalents.

Reviewer Comment: In the Safety Pool, mean age of study population was 64 years, 68% of subjects were male, and 92% were white. Cardiovascular risk factors were balanced between the treatment groups, approximately 85% had established cardiovascular disease (ASCVD) and 15% were ASCVD risk equivalents (no established cardiovascular disease at Baseline). Overall, 36% of the study population had diabetes and 80% had hypertension. The majority of the population were on statins.

The following figures shows the number of patients from each participating country.

Figure 15. Number of Patients and Country of Patient Participation, Safety Pool

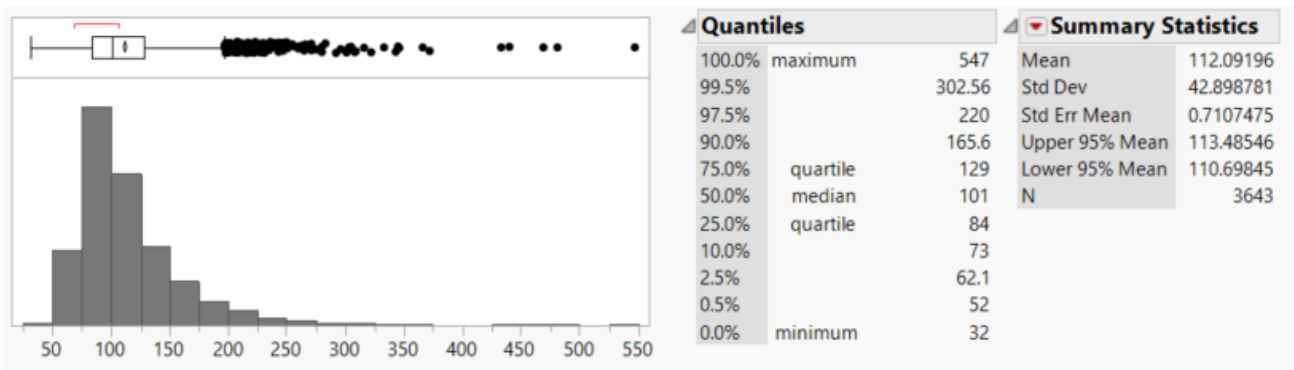


Source: Reviewer created from ADSL dataset. ZAF=South Africa, USA=United States, UKR=Ukraine, SWE=Sweden, POL=Poland, NLD=Netherlands, HUN=Hungary, GBR=Great Britain, ESP=Spain; DNK=Denmark, DEU=Germany, CAN=Canada

Reviewer Comment: Most patients were from the United States, followed by Poland, Great Britain, and South Africa. Despite including a plurality of US patients, the study population under-represents non-white patients relative to the US population.

The following figures shows the distribution of LDL-C, body mass index, and estimated glomerular filtration rate at Baseline for the study population.

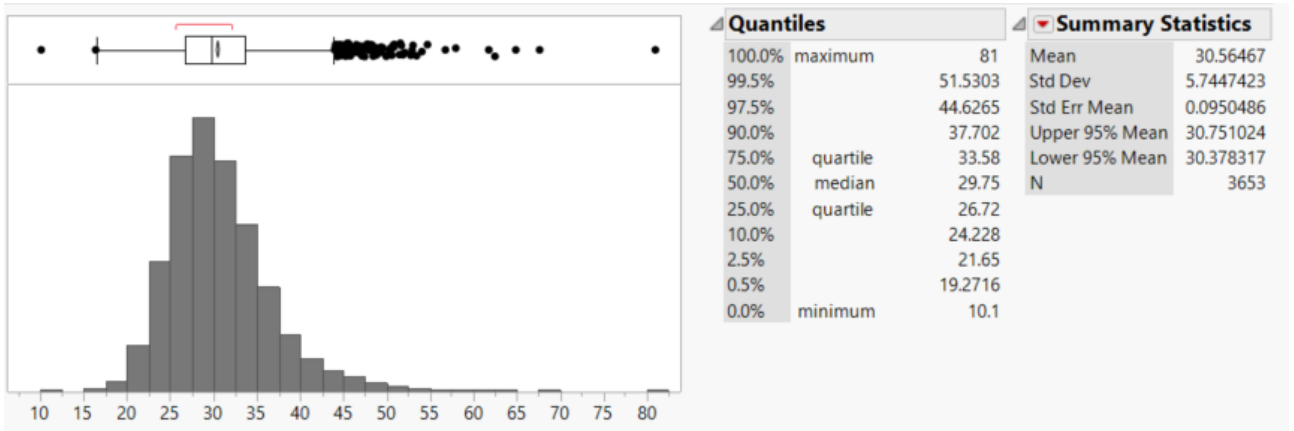
Figure 16. Baseline LDL-C (mg/dL) Distribution, Safety Pool



Source: Reviewer Created from ADSL dataset.

Reviewer Comment: Median LDL-C was 101 mg/dL at Baseline for the overall population.

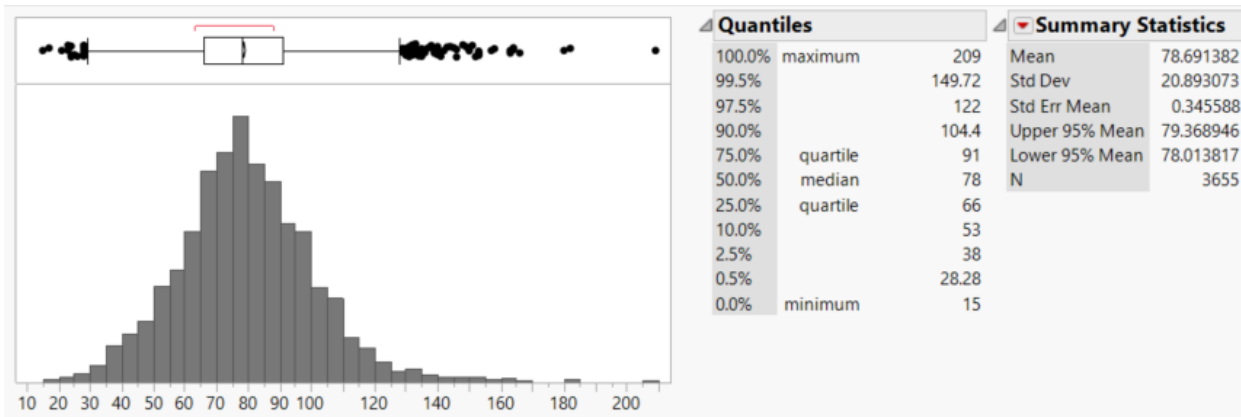
Figure 17. Baseline Body Mass Index (kg/m²) Distribution, Safety Pool



Source: Reviewer Created from ADSL dataset.

Reviewer Comment: For the overall population, the mean body mass index was 30.5 kg/m².

Figure 18. Baseline Glomerular Filtration Rate (eGFR) (mL/min/1.73) Distribution, Safety Pool



Source: Reviewer Created from ADSL dataset.

Reviewer Comment: Mean eGFR for the overall population was 78 mL/min/1.73².

8.2.3. Adequacy of the safety database:

The safety database from the Safety Pool (n=3655) over 18 months was adequate to explore for adverse events in a chronically administered drug.

In the Safety Pool, there were 3655 patients, including both placebo and inclisiran treatment arms. Overall, 94% (3422/3655) of patients completed the Phase 3 studies, 92.8% (1691/1822) of placebo-treated patients and 94.4% (1731/1833) of inclisiran-treated patients.

Table 43. Disposition of Patients for Safety Pool

Category	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Completers	1691 (92.8)	1731 (94.4)
Discontinued	131 (7.2)	102 (5.6)
Withdrew Consent	55 (3.0)	36 (2.0)
Physician Decision	0	2 (0.1)
Lost to Follow-up	29 (1.6)	17 (0.9)
Death	27 (1.5)	27 (1.5)
Adverse Event	5 (0.3)	12 (0.7)
PCSK9 initiation	10 (0.5)	0
Other	5 (0.3)	8 (0.4)
Missing Reason	0	0

Source: ISS, Table 8.

There were 5 patients on placebo and 8 patients on inclisiran who listed “other” as a reason for study discontinuation. This reviewer requested the sponsor for additional clarification. On January 21, 2020, the sponsor submitted the following reasons for discontinuation that was categorized as “other”.

Table 44. Verbatim Reason for Study Discontinuation, Originally Listed as "Other"

Treatment Group	Subject ID	Reason For Discontinuation (verbatim)
ORION-9		
Inclisiran	(b) (6)	MOVED OUT OF STATE, CANNOT ATTEND SITE VISITS.
Inclisiran	(b) (6)	PATIENT REFUSE TO COME BACK AND DRAW HIS BLOODS, HE DOES NOT WANT TO CONTINUE STUDY.
Inclisiran	(b) (6)	PATIENT IS OVERSEAS AND WILL ONLY BE BACK IN 2020, SO SHE IS UNABLE TO COMPLETE THE VISIT
Inclisiran	(b) (6)	THE SUBJECT WILL START STUDYING IN CHICAGO AND CAN THEREFORE NOT CONTINUE WITH THE STUDY IN SWEDEN.
Placebo	(b) (6)	PAT IS ON A LONG VACATION IN ITALY. HE WILL BE BACK (b) (6)
ORION-10		
Placebo	(b) (6)	SPONSOR INDICATED THAT VISIT 9 SHOULD NOT BE COMPLETED OUT OF WINDOW.
Placebo	(b) (6)	SUBJECT WITHDREW FROM THE STUDY DUE TO A RELOCATION TO COLORADO, IN AN AREA WHERE ANOTHER ORION-10 SITE DID NOT EXIST TO PERMIT STUDY CONTINUATION.
Placebo	(b) (6)	SUBJECT WAS WITHDRAWN FROM THE STUDY DUE TO PARTICIPATION IN ANOTHER TRIAL.
Inclisiran	(b) (6)	SUBJECT MOVED TO NEW LOCATION.
Inclisiran	(b) (6)	PATIENT WANTED TO LEAVE THE STUDY DUE TO WANTING TO DONATE PLASMA.
Inclisiran	(b) (6)	PATIENT EARLY TERMED DUE TO MOVING OUT OF STATE.
Inclisiran	(b) (6)	PATIENT MOVED OUT OF STATE AND NEVER RETURNED.
ORION-11		
Placebo	(b) (6)	SUBJECT IS STAYING OUTSIDE OF BYDGOSZCZ AND REFUSED COMING FOR THE VISIT.

Source: Applicant response to Information Request, 1/21/2020.

Reviewer Comment: It is reassuring that none of the verbatim reasons for study discontinuation, originally categorized as “other” appear to be due to an adverse reaction to study drug. Most of the reasons were due to patient relocation.

8.3. Adequacy of Applicant’s Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The datasets were complete and of high quality. This reviewer examined a sample of case report forms and did not have concerns about the process of data gathering.

8.3.2. Categorization of Adverse Events

MedDRA version 20.1 was used to code adverse events. This reviewer assessed the categorization of events by comparing the verbatim terms used by the investigators to the MedDRA Lower Level Term assigned by the applicant. The following picture is a sample of the categorization.

Table 45. Comparison of Reported Term to Mapped MedDRA Lower Level Term

42	Acute blood loss anemia secondary to spontaneous right renal hemorrhage	Hemorrhagic anemia
43	Acute Bronchitis	Acute bronchitis
44	acute bronchitis with bronchospasm	Acute bronchitis
45	Acute Bronchitis, unspecified organism	Acute bronchitis
46	Acute Cardiac Arrest	Cardiac arrest
47	Acute cardiac decompensation	Decompensation cardiac
48	acute carpal tunnel syndrome Left hand	Unilateral carpal tunnel syndrome
49	acute chest infection	Chest infection
50	ACUTE CHEST PAIN NON-CARDIAC	Chest pain (non-cardiac)
51	Acute CHF exacerbation	Congestive cardiac failure aggravated
52	acute cholecystitis	Acute cholecystitis
53	Acute Cholecystitis	Acute cholecystitis
54	ACUTE CHRONIC DIASTOLIA HF	Diastolic heart failure
55	Acute Chronic Obstructive Pulmonary Disease	Chronic obstructive pulmonary disease
56	Acute condition of chronic gastroduodenitis	Gastroduodenitis
57	Acute congestive heart failure episode	Congestive heart failure
58	Acute Congestive Heart Failure Exacerbation	Congestive cardiac failure aggravated
59	acute congstive heart failure exacerbation	Congestive cardiac failure aggravated
50	Acute Conjunctivitis	Acute conjunctivitis
51	Acute COPD exacerbation	COPD exacerbation
52	acute coronary insufficiency	Coronary insufficiency
53	Acute coronary syndrom	Acute coronary syndrome
54	Acute Coronary Syndrome	Acute coronary syndrome
55	Acute Cranial Contusion	Brain contusion
56	Acute CVA	CVA
57	Acute Cystitis	Acute cystitis
58	acute cystitis with hematuria	Acute cystitis
59	Acute Cystitis	Acute cystitis
70	Acute Dehydration	Dehydration

Source: Reviewer generated.

Reviewer Comment: Based on comparing the reported term to the Lower Level Term, this reviewer believes that AEs were generally categorized appropriately.

8.3.3. Routine Clinical Tests

Laboratory assessments were appropriate for the Safety Pool and included hematology, coagulation, chemistry, inflammatory markers, urinalysis, and urine pregnancy test. Anti-drug antibody was collected prior to and 4 hours after the first investigational product injection and then as per the Schedule of Assessments.

8.4. Safety Results

8.4.1. Deaths

The following table summarizes deaths that occurred in the Safety Pool. The incidence of death was 1.5% (27/1822) in placebo-treated patients and 1.5% (27/1833) in inclisiran-treated patients.

Table 46. Summary of Deaths by System Organ Class and Treatment Arm, Safety Pool

System Organ Class	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of Patients with TEAEs Leading to Fatal Outcome*	27 (1.5)	27 (1.5)	54 (1.5)
Cardiac Disorders	9 (0.5)	13 (0.7)	22 (0.6)
Gastrointestinal Disorders	2 (0.1)	0 (0.0)	2 (0.1)
General Disorders and administration site conditions	6 (0.3)	4 (0.2)	10 (0.3)
Infections and infestations	4 (0.2)	1 (0.1)	5 (0.1)
Injury, poisoning and procedural complications	1 (0.1)	0 (0.0)	1 (0.0)
Neoplasms benign, malignant and unspecified	6 (0.3)	4 (0.2)	10 (0.3)
Nervous system disorders	1 (0.1)	1 (0.1)	2 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	4 (0.2)	6 (0.2)

Source: Inclisiran ISS, Table 16. *Please note that a patient may have had more than one AE that contributed to death.

Reviewer Comment: Deaths were balanced between arms at approximately 1.5% of patients. The most common cause of death with inclisiran was within the cardiac disorders SOC at 0.7% and was similar to the placebo treatment arm of 0.5%. This is as expected for the given study population of patients with HeFH and ASCVD. The small number of events limits interpretation of the small numerical imbalance in cardiovascular deaths favoring placebo.

Since Cardiac disorders were the most commonly reported cause of death, this reviewer examined the Preferred terms reported under this SOC.

Table 47. Summary of Deaths-Preferred Terms Under Cardiac Disorders, by Treatment Arm, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
TEAEs Cardiac Disorders (System Organ Class)	9 (0.5)	13 (0.7)	22 (0.6)
Preferred Terms Under Cardiac Disorders			
Acute myocardial infarction	1 (0.1)	1 (0.1)	2 (0.1)
Cardiac arrest	0	1 (0.1)	1 (0.0)
Cardiac failure	1 (0.1)	0	1 (0.0)
Cardiac failure congestive	0	2 (0.1)	2 (0.1)
Cardiomyopathy	0	1 (0.1)	1 (0.0)
Coronary artery disease	1 (0.1)	0	1 (0.0)
Coronary artery insufficiency	0 (0.0)	1 (0.1)	1 (0.0)
Hypertensive heart disease	1 (0.1)	0 (0.0)	1 (0.0)
Left ventricular failure	0	2 (0.1)	2 (0.1)
Myocardial infarction	4 (0.2)	4 (0.2)	8 (0.2)
Myocardial ischaemia	2 (0.1)	1 (0.1)	3 (0.1)
Ventricular fibrillation	1 (0.1)	0 (0.0)	1 (0.0)
Ventricular tachyarrhythmia	0 (0.0)	1 (0.1)	1 (0.0)

Source: Table 14.3.1.16, ISS_ISE Post text Tables.

Reviewer Comment: There was a 4-patient numerical imbalance in cardiovascular deaths between inclisiran and placebo (13 patients with inclisiran and 9 patients on placebo) accounted for by 2 patients with "cardiac failure congestive" and 2 patients "left ventricular failure" versus none on placebo. Trends in the incidence of adverse events in cardiovascular disorders generally and heart failure specifically favoring inclisiran (i.e. higher in placebo) suggest that the numerical imbalance in death may be due to chance.

This reviewer also examined the Preferred Terms under the Neoplasms SOC, the second most commonly reported cause of death. The following table summarizes the PT under the Neoplasms SOC for fatal AEs.

Table 48. Summary of Deaths- Preferred Terms Under Neoplasms Benign, Malignant and Unspecified, by Treatment Arm, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
TEAEs Neoplasms benign, malignant and unspecified (System Organ Class)	6 (0.3)	4 (0.2)	10 (0.3)
Preferred Terms Under Neoplasms benign, malignant and unspecified			
Adenocarcinoma	1 (0.1)	0 (0.0)	1 (0.0)
Bladder cancer	1 (0.1)	0 (0.0)	1 (0.0)
Gastrointestinal lymphoma	0 (0.0)	1 (0.1)	1 (0.0)
Gastroesophageal cancer	1 (0.1)	0 (0.0)	1 (0.0)
Hepatocellular carcinoma	1 (0.1)	0 (0.0)	1 (0.0)
Lung adenocarcinoma	1 (0.1)	0 (0.0)	1 (0.0)
Lung neoplasm malignant	0 (0.0)	2 *0.1)	2 (0.1)
Metastases to liver	1 (0.1)	1 (0.1)	2 (0.1)
Metastatic carcinoma of the bladder	1 (0.1)	0 (0.0)	1 (0.0)
Oesophageal carcinoma	0 (0.0)	1 (0.1)	1 (0.1)

Source: Table 14.3.1.16, ISS_ISE Post text Tables.

Reviewer Comment: The incidence of deaths related to neoplasms was similar in the two treatment arms, 0.3% on placebo and 0.2% on inclisiran. There was no pattern of carcinomas that would point to a specific organ class vulnerable to inclisiran.

This reviewer also examined the Preferred Terms under the General Disorders and Administration Site Conditions SOC, as this category was also commonly reported.

Table 49. Summary of Deaths -Preferred Terms Under General Disorders and Administration Site Conditions, by Treatment Arm, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
TEAEs General disorders and administration site conditions	6 (0.3)	4 (0.2)	10 (0.3)
Preferred Terms Under General			

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
disorders and administration site conditions			
Cardiac death	1 (0.1)	0 (0.0)	1 (0.0)
Death	3 (0.2)	3 (0.2)	6 (0.2)
Multiple organ dysfunction syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Sudden cardiac death	1 (0.1)	1 (0.1)	2 (0.1)

Source: Table 14.3.1.16, ISS_ISE Post text Tables.

Reviewer Comment: Three out of 10 deaths under General disorders and Administrative site conditions were related to cardiac death (“Cardiac Death” and “Sudden Cardiac Death”). Two of the 3 deaths were in the placebo arm and one in the inclisiran arm. Interpretation of the imbalance within this category is limited by the small number of events. The small numerical imbalance in cardiac-related deaths (Cardiac death, Sudden cardiac death) favored inclisiran, in contrast to the trend in the Cardiovascular disorders SOC, again suggesting that these small imbalances may have been due to chance.

8.4.2. Serious Adverse Events

Overall, slightly more patients on placebo (23.0%) reported at least one serious adverse event than on inclisiran (20.4%). The following listing is by either HLGT, HLT or PT depending on which term was considered most informative by the reviewer (see notations within the table next to each SOC for grouping of lower-level term).

Table 50. Serious Adverse Events by System Organ Class and Other Groupings

Serious Adverse Events	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Subject with at least one serious TEAE	419 (23.0)	374 (20.4)
Blood and lymphatic system disorders	5 (0.3)	7 (0.4)
Cardiac disorders	172 (9.4)	146 (8.0)
Cardiac conduction disorders (HLT)	3 (0.2)	4 (0.2)
Rate and rhythm disorder NEC (HLT)	6 (0.3)	2 (0.1)
Supraventricular arrhythmias (HLT)	19 (1.0)	22 (1.2)
Ventricular arrhythmias and cardiac arrest (HLT)	7 (0.4)	11 (0.6)
Cardiac hypertensive complications (HLT)	1 (0.1)	0 (0.0)
Aortic valvular disorders (HLT)	0 (0.0)	3 (0.2)
Mitral valvular disorders (HLT)	3 (0.2)	2 (0.1)

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Serious Adverse Events	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Coronary artery disorders NEC (HLT)	38 (2.1)	28 (1.5)
Ischaemic coronary artery disorders (HLT)	86 (4.7)	72 (3.9)
Heart failures NEC (HLT)	32 (1.8)	19 (1.0)
Myocardial disorders (HLGT)	1 (0.1)	4 (0.2)
Pericardial disorders (HLGT)	3 (0.2)	0 (0.0)
Congenital, familial and genetic disorders	1 (0.1)	0 (0.0)
Ear and labyrinth disorders	1 (0.1)	0 (0.0)
Endocrine disorders	0 (0.0)	2 (0.1)
Eye disorders	2 (0.1)	4 (0.2)
Gastrointestinal disorders	33 (1.8)	26 (1.4)
Abdominal hernias & other wall conditions (HLGT)	3 (0.2)	3 (0.2)
Anal & rectal conditions NEC (HLGT)	0 (0.0)	1 (0.1)
Benign neoplasms gastrointestinal (HLGT)	2 (0.1)	2 (0.1)
Diverticular disorders (HLGT)	4 (0.2)	0 (0.0)
Exocrine pancreas conditions (HLGT)	4 (0.2)	3 (0.2)
Gastrointestinal conditions NEC (HLGT)	1 (0.1)	0 (0.0)
Gastrointestinal haemorrhage NEC (HLGT)	5 (0.3)	4 (0.2)
Gastrointestinal inflammatory conditions (HLGT)	4 (0.2)	3 (0.2)
Gastrointestinal motility & defecation conditions (HLGT)	4 (0.2)	5 (0.3)
Gastrointestinal signs and symptoms (HLGT)	2 (0.1)	3 (0.2)
Gastrointestinal stenosis and obstruction (HLGT)	1 (0.1)	5 (0.3)
Gastrointestinal ulceration and perforation (HLGT)	5 (0.3)	1 (0.1)
Gastrointestinal vascular conditions (HLGT)	2 (0.1)	1 (0.1)
Peritoneal and retroperitoneal conditions (HLGT)	2 (0.1)	0 (0.0)
General disorders and administrative site conditions	37 (2.0)	24 (1.3)
Hepatobiliary disorders	10 (0.5)	9 (0.5)
Immune system disorders	1 (0.1)	1 (0.1)
Infections and infestations	66 (3.6)	71 (3.9)
Bacterial infections NEC (HLT)	5 (0.3)	10 (0.5)
Borrelial infections (HLT)	1 (0.1)	0 (0.0)
Clostridia infections (HLT)	1 (0.1)	1 (0.1)
Esherichia infections (HLT)	1 (0.1)	1 (0.1)
Staphylococcal infections (HLT)	0 (0.0)	2 (0.1)
Streptococcal infections (HLT)	0 (0.0)	2 (0.1)
Abdominal and gastrointestinal infections (HLT)	7 (0.4)	10 (0.5)
Bone and joint infections (HLT)	3 (0.2)	2 (0.1)

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Serious Adverse Events	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
CNS and spinal infections (HLT)	2 (0.1)	0 (0.0)
Dental and oral soft tissue (HLT)	0 (0.0)	1 (0.1)
Hepatobiliary and spleen infections (HLT)	2 (0.1)	2 (0.1)
Infection NEC (HLT)	6 (0.3)	6 (0.3)
Lower respiratory tract and lung infection (HLT)	25 (1.4)	26 (1.4)
Muscle and soft tissue infection (HLT)	1 (0.1)	1 (0.1)
Sepsis, bacteremia, viremia, fungemia NEC (HLT)	8 (0.4)	8 (0.4)
Skin structures and soft tissue infections NEC (HLT)	0	1 (0.1)
Urinary tract infections (HLT)	7 (0.4)	4 (0.2)
Caliciviral infection (HLT)	1 (0.1)	0 (0.0)
Influenza viral infection (HLT)	2 (0.1)	3 (0.2)
Viral infection NEC (HLT)	1 (0.1)	1 (0.1)
Injuries, poisonings and procedural complications	35 (1.9)	24 (1.3)
Investigations	2 (0.1)	0 (0.0)
Metabolism and nutrition disorders	13 (0.7)	15 (0.8)
Musculoskeletal and connective tissue disorders**	31 (1.7)	25 (1.4)
Neoplasms benign, malignant, and unspecified	49 (2.7)	44 (2.4)
Breast and nipple neoplasms malignant (HLT)	3 (0.2)	1 (0.1)
Carcinoid tumors (HLT)	2 (0.1)	1 (0.1)
Colorectal neoplasms malignant (HLT)	3 (0.2)	1 (0.1)
Gastric neoplasms malignant (HLT)	3 (0.2)	1 (0.1)
Gastrointestinal neoplasm malignant NEC (HLT)	1 (0.1)	1 (0.1)
Lip and oral cavity neoplasms malignant (HLT)	0	1 (0.1)
Oesophageal neoplasm malignant (HLT)	0	1 (0.1)
Pancreatic neoplasm malignant (HLT)	1 (0.1)	0 (0.0)
Salivary gland neoplasm malignant (HLT)	0 (0.0)	1 (0.1)
Hepatic neoplasm malignant (HLT)	1 (0.1)	1 (0.1)
Leukaemias (HLGT)	1 (0.1)	2 (0.1)
Lymphomas non-Hodgkin (HLGT)	0 (0.0)	2 (0.1)
Metastases (HLGT)	2 (0.1)	2 (0.1)
Neoplasms malignant site unspecified NEC (HLT)	3 (0.2)	3 (0.2)
Nervous system neoplasm malignant NEC (HLT)	1 (0.1)	0 (0.0)
Nervous system neoplasms unspecified malignancy NEC (HLT)	1 (0.1)	0 (0.0)
Bladder neoplasms malignant (HLT)	5 (0.3)	2 (0.1)
Renal neoplasms malignant (HLT)	3 (0.2)	3 (0.2)
Urinary tract neoplasms unspecified malignancy NEC (HLT)	1 (0.1)	0 (0.0)
Reproductive neoplasms female malignant and unspecified (HLGT)	2 (0.1)	2 (0.1)
Reproductive neoplasms male malignant and unspecified (HLGT)	10 (0.5)	7 (0.4)
Respiratory and mediastinal neoplasms malignant and unspecified (HLGT)	7 (0.4)	6 (0.3)
Skin neoplasms malignant and unspecified (HLGT)	5 (0.3)	9 (0.5)

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Serious Adverse Events	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Soft tissue neoplasms malignant and unspecified (HLGT)	1 (0.1)	0 (0.0)
Nervous system disorders	53 (2.9)	41 (2.2)
Central nervous system vascular disorders (HLGT)	26 (1.4)	28 (1.5)
Cranial nerve disorders (HLGT)	1 (0.1)	1 (0.1)
Encephalopathies (HLGT)	1 (0.1)	0 (0.0)
Headaches (HLGT)	1 (0.1)	3 (0.2)
Increased intracranial pressure and hydrocephalus (HLGT)	2 (0.1)	0 (0.0)
Mental impairment disorders (HLGT)	1 (0.1)	1 (0.1)
Movement disorders (HLGT)	1 (0.1)	0 (0.0)
Loss of consciousness (PT)	0 (0.0)	1 (0.1)
Syncope (PT)	9 (0.5)	5 (0.3)
Dizziness (PT)	0 (0.0)	3 (0.2)
Presyncope (PT)	1 (0.1)	2 (0.1)
Sensory disturbance (PT)	1 (0.1)	0 (0.0)
Peripheral neuropathies (HLGT)	3 (0.2)	0 (0.0)
Seizures (HGLT)	3 (0.2)	0 (0.0)
Spinal cord and nerve root disorders (HLGT)	5 (0.3)	1 (0.1)
Brain injury (PT)	1 (0.1)	1 (0.1)
Product issues	1 (0.1)	2 (0.1)
Psychiatric disorders	5 (0.3)	7 (0.4)
Renal and urinary disorders	17 (0.9)	17 (0.9)
Glomerulonephritis and nephrotic syndrome (HLT)	0 (0.0)	1 (0.1)
Renal disorders NEC (HLT)	0 (0.0)	1 (0.1)
Renal failure and impairment (HLT)	12 (0.7)	12 (0.7)
Renal neoplasms (cyst) (PT)	0 (0.0)	1 (0.1)
Renal obstructive disorders (HLT)	1 (0.1)	0 (0.0)
Renal vascular and ischaemic conditions (HLT)	1 (0.1)	0 (0.0)
Ureteric disorders (HLGT)	1 (0.1)	0 (0.0)
Urethral disorders (HLGT)	0 (0.0)	1 (0.1)
Urinary tract signs and symptoms (HLGT)	1 (0.1)	2 (0.1)
Urolithiasis (HLGT)	3 (0.2)	1 (0.1)
Reproductive system and breast disorders	5 (0.3)	3 (0.2)
Respiratory, thoracic and mediastinal disorders	31 (1.7)	29 (1.6)
Skin and subcutaneous tissue disorders	3 (0.2)	1 (0.1)
Surgical and medical procedures	1 (0.1)	1 (0.1)
Vascular disorders	32 (1.8)	32 (1.7)

Serious Adverse Events	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
*HLTs were well-balanced **PTs were well-balanced		

Source: Table 14.3.1.5.2

Reviewer Comment: Overall, slightly fewer patients on inclisiran (20%) than on placebo (23%) reported at least one serious adverse event than. Most serious adverse events were well balanced between the treatment arms.

The most commonly reported serious adverse events were in the Cardiac disorders SOC (9.4% in Placebo and 8.0% in Inclisiran), followed by Infections (3.6% in Placebo and 3.9% in Inclisiran) and Nervous System disorders (2.7% in Placebo and 2.4% in Inclisiran). Adverse events under Cardiac disorders SOC is expected for the high-risk cardiac population (HeFH and ASCVD). Under Nervous System disorders, the preferred term “central nervous system vascular disorders” (such as strokes) were most frequent (1.4% -placebo and 1.5% -inclisiran) and would also be expected given the study population.

Although serious adverse events most frequently reported for inclisiran was in the Cardiac disorders SOC, the incidence was less than placebo (8.0% on inclisiran vs. 9.4% on placebo). High Level Terms most frequently reported under the Cardiac disorders was “coronary artery disorders NEC” (n=28, 1.5% for inclisiran and n=38, 2.1% for placebo) and “ischaemic coronary artery disorders” (n=72, 3.9% for inclisiran and n=86, 4.7% for placebo). It is not surprising that in the Safety pool population composed of HeFH, ASCVD and patients at risk for ASCVD, coronary artery disorders had such high incidence in both the placebo and inclisiran treatment arms. Although the trend in cardiovascular serious adverse events favoring inclisiran is not definitive, the results are reassuring. There is an ongoing cardiovascular outcomes trial to assess the effect of inclisiran on major adverse cardiovascular events.

Serious adverse events second-most frequently reported for the inclisiran treatment arm were in Infections and infestations SOC (n=71, 3.9%) which was slightly higher than placebo (n=66, 3.6%). High Level Term most frequently reported under this SOC was “Lower respiratory tract and lung infections”, n=26, 1.4% for inclisiran and n=25, 1.4% for placebo. These events are expected for the patient population, and the incidence of events was balanced between arms.

Nervous system disorders SOC were the third most frequently reported serious adverse events. “Central nervous system vascular disorders” most often reported under this SOC, and the incidence was balanced between arms. Other preferred terms were less frequently reported with inclisiran than placebo.

The following table summarizes the most commonly reported Preferred Terms that were

categorized as a serious adverse event within the inclisiran treatment arm.

Table 51. Serious Adverse Events- Preferred Terms Most Commonly Reported, $\geq 0.5\%$ Within Inclisiran Treatment Arm, Safety Pool

System Organ Class	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Subject with at least one Serious Adverse Event	419 (23.0)	374 (20.4)	793 (21.7)
Coronary artery disease	33 (1.8)	24 (1.3)	57 (1.6)
Acute myocardial infarction	31 (1.7)	21 (1.1)	52 (1.4)
Angina pectoris	20 (1.1)	21 (1.1)	41 (1.1)
Angina unstable	25 (1.4)	16 (0.9)	41 (1.1)
Pneumonia	17 (0.9)	21 (1.1)	38 (1.0)
Atrial fibrillation	15 (0.8)	20 (1.1)	35 (1.0)
Cardiac failure congestive	22 (1.2)	12 (0.7)	34 (0.9)
Non-cardiac chest pain	18 (1.0)	14 (0.8)	32 (0.9)
Chronic obstructive pulmonary disease	12 (0.7)	11 (0.6)	23 (0.6)
Myocardial infarction	10 (0.5)	12 (0.7)	22 (0.6)
Peripheral arterial occlusive disease	10 (0.5)	9 (0.5)	19 (0.5)

Source: Table 14.3.1.5.1

Reviewer Comment: Atrial fibrillation (n=20, 1.1%), pneumonia (n=21, 1.1%) and myocardial infarction (n=12, 0.7%) were reported at slightly higher incidence rates for inclisiran than placebo (0.8%, 0.9%, and 0.5%, respectively). The difference from placebo for these adverse events was small (5 patients or less), and therefore no conclusive clinical significance can be drawn. Numerical imbalances in cardiac ischemic events (Coronary artery disease, Acute myocardial infarction, Angina unstable) and heart failure generally favored inclisiran.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Patient discontinuations from the *study* are discussed in the disposition of the Safety Pool in Section 8.2.

The incidence of TEAE leading to withdrawal of *study treatment* was 1.9% (35/1822) in the placebo-treated patients and 2.5% (45/1833) in inclisiran-treated patients.

Table 52. Treatment Emergent Adverse Events Leading to Withdrawal from Treatment, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Subject with at least one TEAE leading to withdrawal from treatment	35 (1.9)	45 (2.5)
Blood and lymphatic system disorders	1 (0.1)	0 (0.0)
Lymphadenopathy mediastinal	1 (0.1)	0 (0.0)
Cardiac disorders	3 (0.2)	3 (0.2)
Acute coronary syndrome	1 (0.1)	0 (0.0)
Angina pectoris	0 (0.0)	1 (0.1)
Angina unstable	1 (0.1)	0 (0.0)
Cardiac arrest	0 (0.0)	1 (0.1)
Cardiac failure congestive	1 (0.1)	0 (0.0)
Tachycardia	0 (0.0)	1 (0.1)
Eye disorders	2 (0.1)	0 (0.0)
Ophthalmic vein thrombosis	1 (0.1)	0 (0.0)
Visual impairment	1 (0.1)	0 (0.0)
Gastrointestinal disorders	3 (0.2)	4 (0.2)
Colitis ischaemic	1 (0.1)	0 (0.0)
Constipation	0 (0.0)	1 (0.1)
Diarrhoea	1 (0.1)	0 (0.0)
Dyspepsia	0 (0.0)	1 (0.1)
Nausea	0 (0.0)	1 (0.1)
Pancreatitis necrotising	0 (0.0)	1 (0.1)
Peptic ulcer	1 (0.1)	0 (0.0)
Vomiting	0 (0.0)	1 (0.1)
General disorders and administration site conditions	3 (0.2)	4 (0.2)
Asthenia	1 (0.1)	0 (0.0)
Exercise tolerance decreased	1 (0.1)	0 (0.0)
Fatigue	2 (0.1)	0 (0.0)
Injection site hypersensitivity	0 (0.0)	1 (0.1)
Injection site reaction	0 (0.0)	3 (0.2)
Hepatobiliary disorders	0 (0.0)	1 (0.1)
Hepatic cirrhosis	0 (0.0)	1 (0.1)
Infections and infestations	3 (0.2)	2 (0.1)
Cavernous sinus thrombosis	1 (0.1)	0 (0.0)
Gastroenteritis	0 (0.0)	1 (0.1)
Gastroenteritis norovirus	1 (0.1)	0 (0.0)
Pneumonia	1 (0.1)	1 (0.1)

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	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Subject with at least one TEAE leading to withdrawal from treatment	35 (1.9)	45 (2.5)
Skin infection	1 (0.1)	0 (0.0)
Injuries, poisonings and procedural complications	2 (0.1)	1 (0.1)
Rib fracture	1 (0.1)	1 (0.1)
Subarachnoid haemorrhage	1 (0.1)	0 (0.0)
Investigations	5 (0.3)	2 (0.1)
Aspartate aminotransferase increased	0 (0.0)	1 (0.1)
Blood pressure increased	0 (0.0)	1 (0.1)
Computerised tomogram thorax abnormal	1 (0.1)	0 (0.0)
Glycosylated haemoglobin increased	1 (0.1)	0 (0.0)
Hepatic enzyme increased	1 (0.1)	0 (0.0)
Liver function test increased	1 (0.1)	0 (0.0)
Weight decreased	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.1)
Hypovolaemia	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders**	4 (0.2)	7 (0.4)
Arthralgia	2 (0.1)	2 (0.1)
Inclusion body myositis	0 (0.0)	1 (0.1)
Muscle spasms	0 (0.0)	1 (0.1)
Myalgia	2 (0.1)	2 (0.1)
Pain in extremity	0 (0.0)	1 (0.1)
Undifferentiated connective tissue disease	0 (0.0)	1 (0.1)
Neoplasms benign, malignant, and unspecified	10 (0.5)	13 (0.7)
Adenocarcinoma gastric	0 (0.0)	1 (0.1)
Bladder transitional cell carcinoma	1 (0.1)	0 (0.0)
Clear cell renal cell carcinoma	1 (0.1)	0 (0.0)
Colon cancer	1 (0.1)	0 (0.0)
Colon cancer metastatic	1 (0.1)	0 (0.0)
Gastroesophageal cancer	1 (0.1)	0 (0.0)
Hepatic cancer	0 (0.0)	1 (0.1)
Intestinal adenocarcinoma	0 (0.0)	1 (0.1)
Lung neoplasm malignant	0 (0.0)	1 (0.1)
Metastases to central nervous system	0 (0.0)	1 (0.1)
Metastases to liver	1 (0.1)	1 (0.1)
Myelodysplastic syndrome	1 (0.1)	0 (0.0)
Non-small cell lung cancer	1 (0.1)	0 (0.0)
Oesophageal carcinoma	0 (0.0)	1 (0.1)
Pancreatic carcinoma metastatic	1 (0.1)	0 (0.0)
Prostate cancer	2 (0.1)	4 (0.2)
Rectal adenocarcinoma	0 (0.0)	1 (0.1)

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	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Subject with at least one TEAE leading to withdrawal from treatment	35 (1.9)	45 (2.5)
Renal cancer	0 (0.0)	1 (0.1)
Renal cancer metastatic	0 (0.0)	1 (0.1)
Squamous cell carcinoma of the cervix	0 (0.0)	1 (0.1)
Nervous system disorders	7 (0.4)	8 (0.4)
Cerebral infarction	1 (0.1)	0 (0.0)
Cerebrovascular accident	0 (0.0)	2 (0.1)
Dementia	1 (0.1)	0 (0.0)
Dementia Alzheimer's type	0 (0.0)	1 (0.1)
Dizziness	2 (0.1)	1 (0.1)
Headache	2 (0.1)	2 (0.1)
Hypoaesthesia	0 (0.0)	1 (0.1)
Ischaemic stroke	0 (0.0)	1 (0.1)
Memory impairment	0 (0.0)	1 (0.1)
Neuralgia	0 (0.0)	1 (0.1)
Neuropathy peripheral	1 (0.1)	0 (0.0)
Tremor	1 (0.1)	0 (0.0)
Renal and urinary disorders	1 (0.1)	2 (0.1)
Chronic kidney disease	1 (0.1)	0 (0.0)
Renal cyst	0 (0.0)	1 (0.1)
Renal impairment	0 (0.0)	1 (0.1)
Reproductive system and breast disorders	0 (0.0)	1 (0.1)
Erectile dysfunction	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.1)	2 (0.1)
Asthma	0 (0.0)	1 (0.1)
Cough	0 (0.0)	1 (0.1)
Emphysema	1 (0.1)	0 (0.0)
Pulmonary embolism	1 (0.1)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.1)
Dermatitis	0 (0.0)	1 (0.1)

Source: Table 14.3.1.14.

Reviewer Comment: Neoplasms benign, malignant and unspecified was the SOC category that was most frequently reported as a reason for withdrawal from study drug; the incidence was 0.5% (n=10) on placebo and 0.7% (n=13) on inclisiran.

Most reported neoplasms occurred with a n of 1, with the exception of prostate cancer with a n=4 and incidence rate of 0.2% on inclisiran. Prostate cancer was reported in 2 patients on placebo, at 0.1%. Therefore, the incidence rate for prostate cancer was similar between arms.

The next most commonly reported SOC that lead to withdrawal of treatment was Nervous system disorders, which was similar between arms at 0.4% (n=7) on placebo and 0.4% (n=8) on inclisiran. There were 3 stroke-related events (ischemic stroke and cerebrovascular accident) in the inclisiran treatment arm as compared to 1 stroke-related event (cerebral infarction) on placebo, but the numbers were too small to make any definitive conclusions.

Musculoskeletal and connective tissue disorders was the third most commonly reported SOC that lead to permanent study drug discontinuation with 0.2% (n=4) on placebo and 0.4% (n=7) on inclisiran. The difference between arms was small, and no definitive conclusions can be made.

The most common preferred term reported as reason for withdrawal of treatment was injection site reaction, 0.2% (n=3), with inclisiran versus 0 events on placebo. In this reviewer's opinion, injection site hypersensitivity should be combined with injection site reaction and reported on the product labeling as 0.2%, n=4.

8.4.4. Significant Adverse Events

The applicant defined adverse events of special interest as: injection site reactions; drug-related hepatic disorders (standardized MedDRA queries); acute kidney injury (SMQ), new-onset/worsening of diabetes; hypersensitivity, neurological/ neurocognitive events; and ophthalmologic events. The applicant also examined abuse liability.

Drug-Related Hepatic Disorders

The applicant conducted a comprehensive search for drug related hepatic disorders using standardized MedDRA queries, (SMQs), both broad and narrow.

As per the pre-defined hepatic disorders SMQ, TEAEs were similar between the placebo-treated and inclisiran-treated patients. There were approximately 76 (4.2%) patients on placebo and 70 (3.8%) on inclisiran who reported these events. The following table shows a sample of the preferred terms under the hepatic disorders SMQ.

Table 53. Treatment Emergent Adverse Events Related to Hepatic Disorders SMQ, Safety Pool

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of Subjects with at least one TEAE	76 (4.2)	70 (3.8)	146 (4.0)
Alanine aminotransferase increased	7 (0.4)	9 (0.5)	16 (0.4)

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Aspartate aminotransferase increased	5 (0.3)	8 (0.4)	13 (0.4)
Blood alkaline phosphatase increased	0	6 (0.3)	6 (0.2)
Blood bilirubin increased	4 (0.2)	6 (0.3)	10 (0.3)
Gamma-glutamyltransferase increased	18 (1.0)	17 (0.9)	35 (1.0)
Hepatic steatosis	14 (0.8)	14 (0.8)	28 (0.8)
International normalized ratio increased	7 (0.4)	4 (0.2)	11 (0.3)

Source: Table 26, ISS.

Reviewer Comment: Incidence of hepatic related disorders were similar between inclisiran and placebo.

Clinically significant changes in ALT, AST, alkaline phosphatase, and bilirubin were also followed and summarized in the following tables.

Table 54. Incidence of Clinically Significant Increases in ALT, AST, Alkaline Phosphatase and Total Bilirubin, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Alanine Aminotransferase (U/L)			
>3X ULN	7 (0.4)	9 (0.5)	16 (0.4)
> 3 and <=5X ULN	6 (0.3)	5 (0.3)	11 (0.3)
> 5 and <=10X ULN	1 (0.1)	4 (0.2)	5 (0.1)
>10 and <=20X ULN	0	0	0
> 20X ULN	0	0	0
Aspartate Aminotransferase (U/L)			
>3X ULN	10 (0.5)	8 (0.4)	18 (0.5)
> 3 and <=5X ULN	8 (0.4)	5 (0.3)	13 (0.4)
> 5 and <=10X ULN	1 (0.1)	3 (0.2)	4 (0.1)
>10 and <=20X ULN	1 (0.1)	0	1 (0.0)
> 20X ULN	0	0	0
Alkaline Phosphatase (U/L)			
>2XULN	5 (0.3)	8 (0.4)	13 (0.4)
Total Bilirubin (mg/dL)			

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
>2XULN	14 (0.8)	14 (0.8)	28 (0.8)

Source: Table 19, ISS and Table 14.3.3.1.2.2. Post 1.

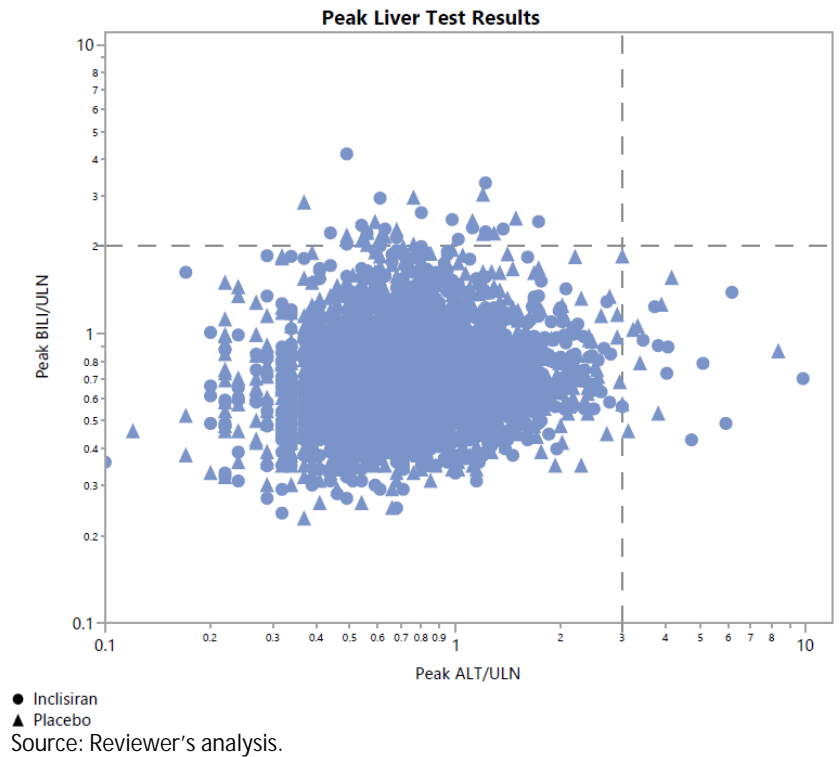
Reviewer Comments: Elevations in ALT, AST, alkaline phosphatase, and total bilirubin above baseline were similar between the two treatment arms. Trends in elevations above various threshold were inconsistent. Elevations of ALT or AST >3X ULN but ≤5X ULN were greater in placebo, but elevations of ALT or AST >5X ULN were greater in the inclisiran group. The overall incidence of AST/ALT elevations >5X ULN was small. No patients experienced AST or ALT elevations above 10X in the Inclisiran arm, while one placebo patient experienced an AST elevation >10X ULN.

Hy's Law was defined as

- Any elevated post-baseline aminotransferases defined as:
 - ALT >3 x ULN or
 - AST >3 x ULN
- Elevated post-baseline serum total bilirubin >2 x ULN and serum ALP levels <2 x ULN

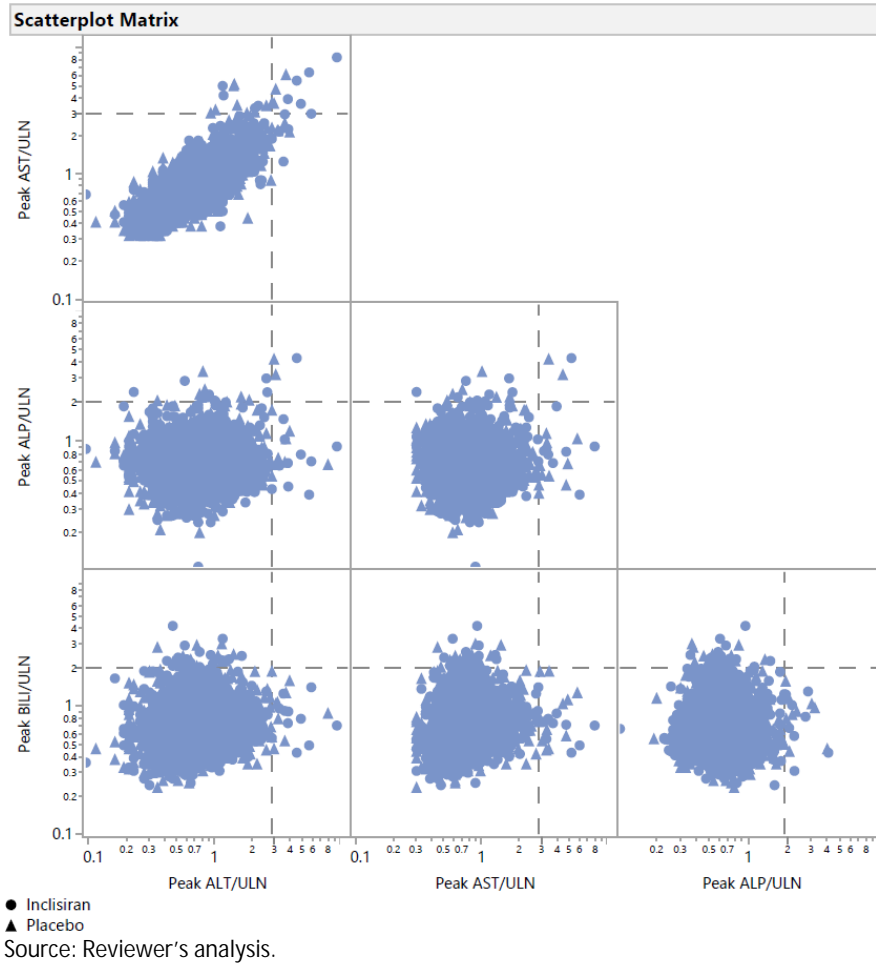
Patients must have met all of the criteria listed above at the same time point and have normal lab parameters (ALT, AST, total bilirubin) at baseline to be considered a Hy's Law case. Per FDA feedback, the applicant presented a second summary that included all subjects who met all of the criteria listed above at the same time point without regard to the baseline lab parameter (ALT, AST, total bilirubin) results. There were no cases meeting the Hy's Law definition in either treatment arm.

Figure 19. Hy's Law Screening Test: Peak ALT and Peak Total Bilirubin



Reviewer Comment: In the figure above, no patient's ALT or bilirubin fell in Quadrant II (right upper quadrant), indicating there were no values that met Hy's Law parameters.

Figure 20. Hy's Law Screening Test: Peak ALT, AST, Total Bilirubin and Alkaline Phosphatase



Reviewer Comment: No Hy's Law cases were found based on ALT or AST $\geq 3XULN$ and Total bilirubin $\geq 2XULN$ within 0 days of ALT or AST elevation.

Renal Function

In the Safety Pool, TEAEs associated with renal safety identified by the predefined SMQ search by PTs were balanced between the placebo-treated and inclisiran-treated subjects.

Table 55. Treatment Emergent Adverse Event Related to Renal Event SMQ, Safety Pool

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of subjects with at least one TEAE Related to Renal Events	60 (3.3)	60 (3.3)	120 (3.3)
Acute kidney injury	17 (0.9)	19 (1.0)	36 (1.0)
Blood creatinine abnormal	1 (0.1)	0	1 (0.0)
Blood creatinine increased	5 (0.3)	7 (0.4)	12 (0.3)
Blood urea increased	1 (0.1)	1 (0.1)	2 (0.1)
Glomerular filtration rate abnormal	0	2 (0.1)	2 (0.1)
Glomerular filtration rate decreased	10 (0.5)	9 (0.5)	19 (0.5)
Nephropathy toxic	2 (0.1)	0	2 (0.1)
Protein urine present	1 (0.1)	0	1 (0.0)
Proteinuria	3 (0.2)	4 (0.2)	7 (0.2)
Renal failure	7 (0.4)	4 (0.2)	11 (0.3)
Renal impairment	16 (0.9)	23 (1.3)	39 (1.1)

Source: Table 27, ISS.

The incidence of patients with clinically significant changes in creatinine was similar in the placebo and inclisiran treatment arms (see table below). For example, in the category “≥50% increase from baseline or >2 mg/dL”, the incidence was 5.1% in placebo and 4.8% in inclisiran patients.

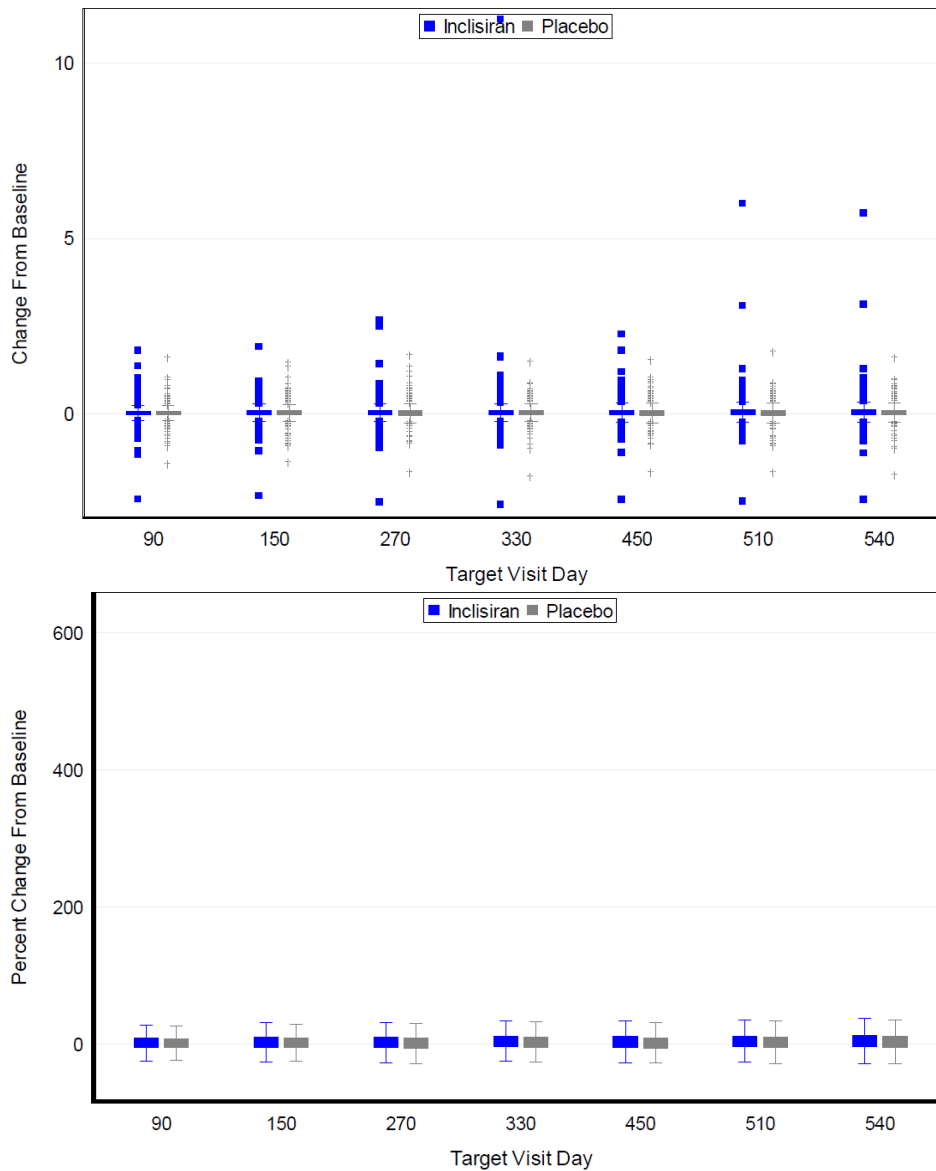
Table 56. Incidence of Clinically Significant Serum Creatinine, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Subjects with at least one clinically significant lab value	93 (5.1)	88 (4.8)	181 (5.0)
Creatinine (mg/dL)			
≥50% increase from baseline (not >2mg/dL)	51 (2.8)	52 (2.8)	103 (2.8)
>2 mg/dL	42 (2.3)	36 (2.0)	78 (2.1)
≥50% increase from baseline or >2mg/dL	93 (5.1)	88 (4.8)	181 (5.0)

Source: Table 20, ISS. and Table 14.3.3.1.2.2.Post1. Clinically significant criteria are met when both of the following occur: 1) Post-baseline values meet the thresholds, 2) Baseline values or any prior post-baseline values do not meet the thresholds. The worst post-baseline value was utilized in the analyses.

The figure below shows the box and whisker plot for absolute change in serum creatinine from baseline to post-baseline visits.

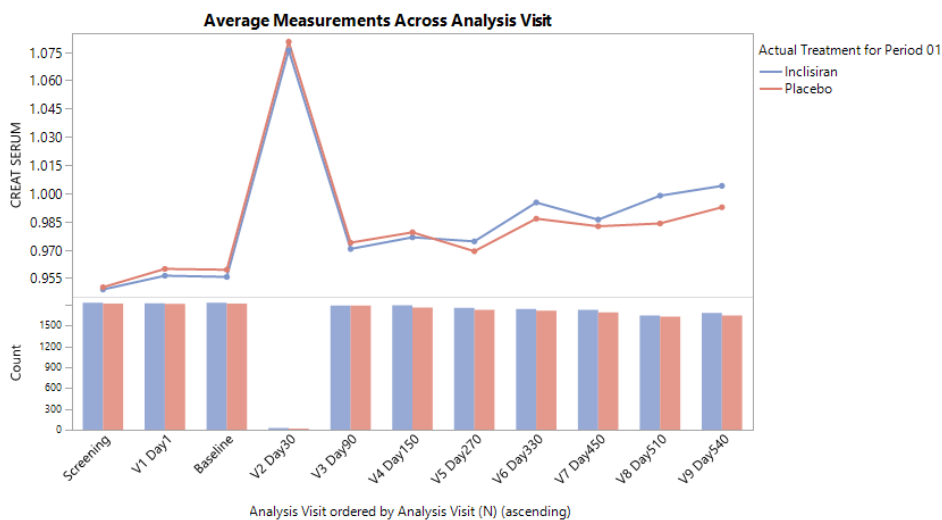
Figure 21. Absolute Change and Percent Change from Baseline for Serum Creatinine (mg/dL), Safety Pool



Source: Figure 14.3.1.2.1, Figure 14.3.1.3/ Figure 4 ISS.

Reviewer Comment: There were two patients on inclisiran with increases in creatinine approximately 5.5 mg/dL and 3.0 mg/dL from Baseline; one patient on inclisiran decreased approximately 2.5 mg/dL from Baseline. In the placebo arm, the greatest outlier was an increase of approximately 1.8 mg/dL from Baseline. Overall, the proportion of patients with $\geq 50\%$ increase from Baseline or >2 mg/dL in serum creatinine was 5.1% on placebo and 4.8% on inclisiran.

The figure below shows the average result of serum creatinine (mg/dL) over the course of the studies.



Reviewer Comment: There were no clinically significant differences between inclisiran and placebo in mean serum creatinine during course of trials.

The table below shows the shifts of maximal change from Baseline in eGFR to worst post-Baseline value.

Table 57. Shift from Baseline to Maximum Change Post-Baseline in eGFR, Safety Pool

Treatment	Baseline	Post-Baseline				Total
		Normal	Mild	Moderate	Severe	
Placebo	Normal	203 (11.3)	269 (14.9)	19 (1.1)	0 (0.0)	491 (27.2)
	Mild	198 (11.0)	582 (32.3)	235 (13.0)	4 (0.2)	1019 (56.5)
	Moderate	3 (0.2)	89 (4.9)	166 (9.2)	26 (1.4)	284 (15.8)
	Severe	0 (0.0)	1 (0.1)	6 (0.3)	2 (0.1)	9 (0.5)
	Total	404 (22.4)	941 (52.2)	426 (23.6)	32 (1.8)	1803 (100.0)
Inclisiran	Normal	192 (10.6)	303 (16.7)	14 (0.8)	0 (0.0)	509 (28.1)
	Mild	181 (10.0)	593 (32.7)	230 (12.7)	1 (0.1)	1005 (55.4)
	Moderate	4 (0.2)	90 (5.0)	173 (9.5)	23 (1.3)	290 (16.0)
	Severe	1 (0.1)	0 (0.0)	5 (0.3)	4 (0.2)	10 (0.6)
	Total	378 (20.8)	986 (54.4)	422 (23.3)	28 (1.5)	1814 (100.0)

Source: Table 14.3.3.1.4 * Worst post-baseline value is used for the categorization. Severe: <30 mL/min/1.73m²; Moderate: >=30-60 mL/min/1.73m²; Mild: >=60-90 mL/min/1.73m²; Normal: >=90 mL/min/1.73m². The denominator for each percentage is from the overall total for each treatment.

Reviewer Comment: Shift table from Baseline to maximum change in post-Baseline eGFR show similar incidence between placebo and inclisiran and no clinically significant difference between the two treatment arms.

Myopathy

The following table summarizes increases in creatinine kinase in the Safety Pool. There were 4 inclisiran-treated patients and 2 placebo-treated patients who had creatinine kinase >10X ULN and ≤20X ULN. Four placebo-treated subjects had creatine kinase >20 XULN as compared to none on inclisiran. No inclisiran treated patient with a clinically significant creatinine kinase increase had an associated treatment emergent adverse event related to musculoskeletal complaints.

Table 58. Incidence of Creatinine Kinase Increases, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Subjects with at least one Clinically Significant lab value	22 (1.2)	24 (1.3)	46 (1.3)
Creatine Kinase (U/L)			
>5X ULN	22 (1.2)	24 (1.3)	46 (1.3)
>5X ULN and ≤10X ULN	16 (0.9)	20 (1.1)	36 (1.0)
>10 and ≤20X ULN	2 (0.1)	4 (0.2)	6 (0.2)
>20X ULN	4 (0.2)	0 (0.0)	4 (0.1)

Source: Table 23, ISS. Clinically significant criteria are met when both of the following occur:

- Post-baseline values meet the thresholds, and
- Baseline values or any prior post-baseline values do not meet the thresholds.

The worst post-baseline value was utilized in the analyses.

Reviewer Comment: Overall, the incidence of changes with creatinine kinase were similar between the two treatment arms.

Approximately 22.7% of placebo-treated patients vs. 23.1% of inclisiran-treated patients reported at least one TEAE that mapped to the SOC of musculoskeletal and connective tissue disorders. There were no SAEs or severe AEs of rhabdomyolysis. After review of the complete data, this reviewer summarized the preferred terms under this category reported at higher incidences in the following table.

Table 59. Treatment Emergent Adverse Event Related to Musculoskeletal Adverse Events, Safety Pool

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of subjects with at least one TEAE under Musculoskeletal and connective tissue disorder	414 (22.7)	424 (23.1)	838 (22.9)
Arthralgia	72 (4.0)	91 (5.0)	163 (4.5)
Back pain	77 (4.2)	83 (4.5)	160 (4.4)
Flank pain	4 (0.2)	10 (0.5)	14 (0.4)
Muscle spasms	25 (1.4)	28 (1.5)	53 (1.5)
Muscular weakness	8 (0.4)	7 (0.4)	15 (0.4)
Musculoskeletal chest pain	39 (2.1)	37 (2.0)	76 (2.1)
Myalgia	39 (2.1)	37 (2.0)	76 (2.1)
Myopathy	0 (0.0)	2 (0.1)	2 (0.1)
Neck pain	15 (0.8)	18 (1.0)	33 (0.9)
Pain in extremity	47 (2.6)	60 (3.3)	107 (2.9)

Source: Table 14.3.1.2, ISS.

Reviewer Comment: "Arthralgia" was reported at 1% higher incidence on Inclisiran than placebo, and should be listed in Section 6, Adverse Reactions. "Pain in extremity" was also reported at 0.7% higher incidence on inclisiran and is recommended for labeling.

New Onset Diabetes/ Worsening of Diabetes

Baseline glycemic status

At baseline, approximately 36.0% of patients overall had a reported medical history of diabetes mellitus and about 64% of patients did not have diabetes mellitus per report.

Table 60. Summary of Diabetes Status by Medical History, Safety Pool

	Placebo N=1822 n/N (%)	Inclisiran N=1833 n/N (%)	Total N=3655 n/N(%)
Diabetes mellitus			
Yes	630/1822 (34.6)	687/1833(37.5)	1317/3655 (36.0)
Type 1	16/630 (2.5)	16/687 (2.3)	32/1317 (2.4)
Type 2	614/630 (97.5)	671/687 (97.7)	1285/1317 (97.6)
No	1192/1822 (65.4)	1146/1833 (62.5)	2338/3655 (64.0)

Source: Table 10, ISS.

Reviewer Comment: Looking at the proportion of patients with a medical history of diabetes at baseline by treatment arm, there was a slightly higher proportion in the inclisiran treatment arm at 37.5% compared to 34.6% on placebo.

New Onset Diabetes

New onset diabetes was defined by combining information from AEs, medications and laboratory parameters. In the subset of patients without a prior medical history of diabetes, new onset diabetes was defined to have occurred when any of the following occurred:

- at least one post-baseline HbA1C $\geq 6.5\%$ or
- two consecutive values of fasting plasma glucose ≥ 126 mg/dL or
- if a new concomitant medication for control of plasma glucose was added or
- diabetic treatment emergent adverse events identified by SMQ search

The following tables summarizes the incidence of new onset diabetes in patients without a history of diabetes mellitus at baseline and those who had a baseline fasting glucose of < 100 mg/dL. No diabetes at baseline was defined as no medical history diabetes in the case report form, HbA1c < 6.5% at baseline, and fasting glucose < 126 at baseline.

Table 61. Incidence of New-Onset Diabetes in Subset of Patients Without Diabetes at Baseline and Fasting Glucose < 100 mg/dL, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
No diabetes at Baseline	1138/1822 (62.5)	1088/1833 (59.4)
Patients with Baseline Fasting Glucose < 100 mg/dL	709/1138 (62.3)	698/1088 (64.2)
Diabetic TEAEs by SMQ search	21/709 (3.0)	13/698 (1.9)
Post-Baseline Fasting Glucose ≥ 126 mg/dL on 2 consecutive occasions	6/709 (0.8)	5/698 (0.7)
Initiation of anti-diabetic medication at any time post-baseline	4/709 (0.6)	4/698 (0.6)
At least one post-baseline HbA1C $\geq 6.5\%$	14/709 (2.0)	16/698 (2.3)
One or more of diabetic criteria (New Onset Diabetes)	33/709 (4.7)	30/698 (4.3)

Source: Table 31, ISS. No diabetes at baseline was defined as no medical history diabetes in the case report form,

HbA1c < 6.5% at baseline, and fasting glucose < 126 at baseline.

Reviewer Comment: In patients with no diabetes at baseline and fasting glucose < 100 mg/dL, approximately 4.7% of patients on placebo and 4.3% of patients on inclisiran had one or more criteria fulfilling the definition of new onset diabetes. Therefore, in this subset of patients without diabetes mellitus at Baseline, using the applicant-defined criteria for new onset diabetes, there was no clinically meaningful increased risk with inclisiran.

The following table shows the incidence of patients impaired fasting glucose who had a baseline fasting glucose between 100 and < 126 mg/dL, and who met the any component criteria for new-onset diabetes mellitus.

Table 62. Incidence of New-Onset of Diabetes in Subset of Patients with Impaired Fasting Glucose, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
No Diabetes at Baseline	1138/1822 (62.5)	1088/1833 (59.4)
Patients with Baseline Fasting Glucose $\geq$ 100 and <126 mg/dL	429/1138 (37.7)	390/1088 (35.8)
Diabetic TEAEs by SMQ search	24/429 (5.6)	27/390 (6.9)
Post-Baseline Fasting Glucose $\geq$ 126 mg/dL on 2 consecutive occasions	30/429 (7.0)	23/390 (2.3)
Initiation of anti-diabetic medication at any time post-baseline	8/ 429 (1.9)	9/ 390 (2.3)
At least one post-baseline HbA1C $\geq$ 6.5%	30/ 429 (7.0)	35/390 (9.0)
One or more of diabetic criteria (New Onset Diabetes)	59/429 (13.8)	57/390 (14.6)

Source: Table 31, ISS. No diabetes at baseline was defined as no medical history diabetes in the case report form, HbA1c < 6.5% at baseline, and fasting glucose < 126 at baseline.

Reviewer Comment: In patients with impaired fasting glucose at baseline, one or more diabetic criteria for new onset diabetes occurred in approximately 13.8% of placebo-treated patients and 14.6% of inclisiran-treated patients. The difference of 0.8% between treatment arms was small but from these analyses, inclisiran may increase the risk of new onset diabetes in patients with impaired fasting glucose. However, the power of the study to detect new onset diabetes in this

small subset of patients (429 patients on placebo and 390 patients on inclisiran) with impaired fasting glucose is poor.

However, when pooling all patients (those with no diabetes and impaired fasting glucose at Baseline) there were 92/1138 (8.1%) on placebo and 87/1088 (8.0%) on inclisiran who met the definition of new onset diabetes. Thus overall, the incidence of new onset diabetes was similar in the two treatment arms.

The following table summarized the time to new onset diabetes for patients in the Safety Pool.

Table 63. Time to New Onset Diabetes, Safety Pool

	Placebo (N=1822) n (%)	Inclisiran (N=1833) n (%)
Number of Subjects without Diabetes at Baseline* n (%)	1138/ 1822(62.5)	1088/ 1833(59.4)
Number of Subjects with New-Onset Diabetes** n (%)	92/ 1138(8.1)	87/ 1088(8.0)
Number of Weeks to New-Onset Diabetes		
n	92	87
Mean ± SD	42.6 ± 24.16	44.9 ± 24.73
Median	39.1	46.3
Q1, Q3	22, 64	21, 65
Min, Max	1, 79	6, 80
<4 Weeks	1/ 92(1.1)	0/ 87(0.0)
4 to <8 Weeks	5/ 92(5.4)	2/ 87(2.3)
8 to <12 Weeks	0/ 92(0.0)	3/ 87(3.4)
12 to <16 Weeks	13/ 92(14.1)	16/ 87(18.4)
>=16 Weeks	73/ 92(79.3)	66/ 87(75.9)

Source: Table 32, ISS and Table 14.3.4.5. * No diabetes at baseline is defined as no medical history of diabetes in the targeted medical history, HbA1c <6.5% at baseline, and fasting glucose <126 mg/dL at baseline. ** A 4-component definition of new-onset diabetes will be utilized. The 4 components are provided below. 1) Diabetic TEAEs identified by the SMQ search, or 2) Post-baseline fasting glucose >=126 mg/dL on 2 consecutive occasions, or 3) Initiation of anti-diabetic medication at any time post-baseline, or 4) At least 1 post-baseline Hba1c >=6.5%.

Reviewer Comment: The incidence of subjects who did not have diabetes at baseline, and who subsequently developed new onset diabetes was 8.1% on placebo and 8.0% on inclisiran. Time to new onset diabetes was similar in both placebo-treated (mean of 43 days) and inclisiran-treated (mean of 45 days) patients.

The following table summarizes the mean change in fasting glucose from baseline to last glucose value in patients by their baseline glucose-control status.

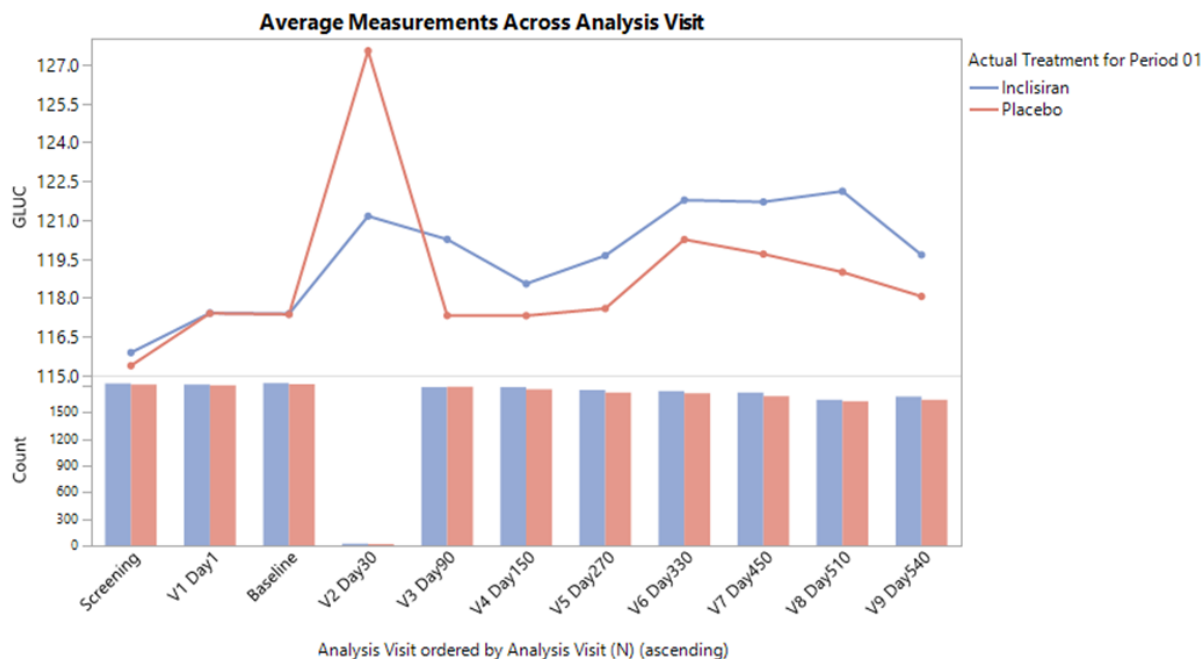
Table 64. Change from Baseline to Last On-Treatment Glucose, by Baseline Glucose-Control Status

	Placebo N=1822	Inclisiran N=1833
Fasting glucose mg/dL		
Baseline glucose-control status		
Normal		
n	768	784
Mean Change in Glucose ± SD	8.3 ± 19.03	8.9 ± 18.12
Impaired		
n	645	623
Mean Change in Glucose ± SD	4.1 ± 28.18	4.6 ± 22.58
Diabetes		
n	390	407
Mean Change in Glucose ± SD	-18.5 ± 68.49	-10.1 ± 71.84
Overall		
n	1803	1814
Mean Change in Glucose ± SD	1.0 ± 39.48	3.2 ± 39.07

Source: Table 14.3.4.2.1 Note: Change from baseline is summarized in the table. For fasting glucose, only confirmed FASTING samples are used for this analysis.* Fasting glucose control ranges are Normal <100 mg/dL; Impaired ≥100 to <126 mg/dL, and Diabetes ≥126 mg/dL.

Reviewer Comment: There was a slightly higher change in mean glucose from Baseline in the inclisiran treatment group as compared to placebo, mostly driven by patients with diabetes.

Figure 22. Average Fasting Glucose (mg/dL) Over Time, by Treatment Arm, Safety Pool



Source: Reviewer Created, JMP Clinical.

Reviewer Comment: For the overall population, the mean change in fasting glucose was 1.0 mg/dL on placebo compared to 3.2 mg/dL on inclisiran, not considered a clinically significant difference between the treatment arms.

The following table shows the mean change in hemoglobin A1c from baseline to last A1c value in patients by their baseline HbA1c-control status.

Table 65. Change in HbA1c from Baseline to Last On-Treatment HbA1c, by Baseline HbA1c-Control Status

	Placebo N=1822	Inclisiran N=1833
HbA1c (%)		
Baseline HbA1c-Control Status		
Normal		
n	569	572
Mean Change in HbA1c ± SD	0.0 ± 0.28	0.1 ± 0.28
Impaired		
n	768	758
Mean Change in HbA1c ± SD	0.0 ± 0.35	0.1 ± 0.44

	Placebo N=1822	Inclisiran N=1833
Diabetes		
n	459	480
Mean Change in HbA1c ± SD	-0.1 ± 1.30	0.1 ± 1.37
Overall		
n	1796	1810
Mean Change in HbA1c ± SD	0.0 ± 0.71	0.1 ± 0.78

Source: Table 14.3.4.2.1 Note: Change from baseline is summarized in the table. HbA1c ranges are Normal <5.7%; Impaired >=5.7 to <6.5%, and Diabetes >=6.5%.

Reviewer Comment: For the overall population, the mean change from Baseline in HbA1c was 0.0% on placebo compared to +0.1% on inclisiran.

The following table shows the shifts in glucose control category from baseline to the worst on-treatment category.

Table 66. Shifts from Baseline in Glucose Control Category Using Worst On-Treatment Values, Safety Population

Shift category	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Normal to Normal (no change)	232 (12.7)	194 (10.6)
Normal to Impaired	242 (13.3)	280 (15.3)
Normal to Diabetes	7 (0.4)	13 (0.7)
Impaired to Normal	26 (1.4)	27 (1.5)
Impaired to Impaired (no change)	663 (36.4)	632 (34.5)
Impaired to Diabetes	146 (8.0)	168 (9.2)
Diabetes to Normal	0 (0.0)	0 (0.0)
Diabetes to Impaired	15 (0.8)	12 (0.7)
Diabetes to Diabetes (no change)	470 (25.8)	486 (26.5)
Missing	21 (1.2)	21 (1.1)
Summary of Changes Overall		
No Change	1365 (74.9)	1312 (71.6)
Worsened	395 (21.7)	461 (25.2)
Improved	41 (2.3)	39 (2.1)
Missing	21 (1.2)	21 (1.1)

Source: Table 14.3.4.3.1.

Reviewer Comment: In the shift table slightly more patients on inclisiran had a worsened glucose control category (25.2%) compared to placebo (21.7%), while shifts to an improved

category were similar between arms. More patients shifted from normal to diabetes on inclisiran (0.7%) than on placebo (0.4%). More patients who had impaired fasting glucose shifted to diabetes on inclisiran (9.2%) than on placebo (8.0%).

In summary, mean changes in fasting glucose and HbA1C were small, and not clearly different between inclisiran and placebo. Shift analyses indicated a small, but consistent greater incidence of worsening glycemia (normal to pre-diabetes, pre-diabetes to diabetes) with inclisiran compared to placebo.

Hypersensitivity

The applicant defined hypersensitivity events for analysis using the Hypersensitivity SMQ, (broad) but excluding preferred terms that included infusion site and injection site reactions. Using the above definition, a summary table was created as shown below.

Table 67. Treatment Emergent Adverse Events Related to Hypersensitivity, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Number of subjects with at least one TEAE	137 (7.5%)	136 (7.4%)
Acute respiratory failure	6 (0.3)	5 (0.3)
Asthma	15 (0.8)	20 (1.1)
Conjunctivitis	9 (0.5)	8 (0.4)
Conjunctivitis allergic	2 (0.1)	2 (0.1)
Dermatitis	7 (0.4)	9 (0.5)
Dermatitis allergic	1 (0.1)	2 (0.1)
Dermatitis atopic	0 (0.0)	2 (0.1)
Dermatitis contact	4 (0.2)	3 (0.2)
Drug hypersensitivity	5 (0.3)	1 (0.1)
Eczema	9 (0.5)	10 (0.5)
Eye swelling	3 (0.2)	0 (0.0)
Flushing	2 (0.1)	1 (0.1)
Hypersensitivity	3 (0.2)	0 (0.0)
Mouth ulceration	2 (0.1)	2 (0.1)
Pruritus	13 (0.7)	6 (0.3)
Pruritus generalized	2 (0.1)	3 (0.2)
Rash	22 (1.2)	17 (0.9)
Rash generalized	0 (0.0)	3 (0.2)
Rash pruritic	2 (0.1)	3 (0.2)
Respiratory failure	1 (0.1)	3 (0.2)
Rhinitis allergic	9 (0.5)	11 (0.6)
Seasonal allergy	7 (0.4)	13 (0.7)
Urticaria	4 (0.2)	6 (0.3)
Wheezing	5 (0.3)	3 (0.2)

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	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Allergic cough	1 (0.1)	0 (0.0)
Allergic sinusitis	1 (0.1)	1 (0.1)
Allergy to vaccine	1 (0.1)	0 (0.0)
Anaphylactic reaction	1 (0.1)	0 (0.0)
Angioedema	1 (0.1)	0 (0.0)
Bronchospasm	2 (0.1)	0 (0.0)
Choking	1 (0.1)	1 (0.1)
Circulatory collapse	2 (0.1)	0 (0.0)
Dermatitis exfoliative	1 (0.1)	1 (0.1)
Erythema	1 (0.1)	1 (0.1)
Exfoliative rash	0 (0.0)	1 (0.1)
Eyelid oedema	1 (0.1)	1 (0.1)
Face oedema	0 (0.0)	1 (0.1)
Generalized oedema	1 (0.1)	1 (0.1)
Iodine allergy	0 (0.0)	1 (0.1)
Laryngospasm	0 (0.0)	1 (0.1)
Lip swelling	0 (0.0)	2 (0.1)
Localised oedema	0 (0.0)	1 (0.1)
Multiple allergies	0 (0.0)	1 (0.1)
Rash vesicular	1 (0.1)	1 (0.1)
Scrotal oedema	0 (0.0)	1 (0.1)
Skin oedema	0 (0.0)	1 (0.1)
Sneezing	0 (0.0)	1 (0.1)
Stomatitis	0 (0.0)	1 (0.1)
Swollen tongue	0 (0.0)	2 (0.1)
Blister	1 (0.1)	0 (0.0)
Capillaritis	1 (0.1)	0 (0.0)
Conjunctival oedema	1 (0.1)	0 (0.0)
Eosinophilia	1 (0.1)	0 (0.0)
Eye allergy	1 (0.1)	0 (0.0)
Genital rash	1 (0.1)	0 (0.0)
Interstitial lung disease	1 (0.1)	0 (0.0)
Neurodermatitis	1 (0.1)	0 (0.0)
Pruritus allergic	1 (0.1)	0 (0.0)
Rash pustular	1 (0.1)	0 (0.0)
Skin exfoliation	1 (0.1)	0 (0.0)
Vessel puncture site rash	1 (0.1)	0 (0.0)
Vulval ulceration	1 (0.1)	0 (0.0)

Source: Table 14.3.2.3./ Table 35 ISS.

Reviewer Comment: This reviewer replicated the applicant's method for Hypersensitivity SMO analysis and confirmed the numbers the applicant generated. There was no difference in TEAEs related to hypersensitivity in placebo-treated 137 (7.5%) patients compared with inclisiran-treated 136 (7.4%) patients based on assessments of preferred terms in the Hypersensitivity

SMQ (broad).

The most common AEs reported were asthma (1.1% on inclisiran vs. 0.8% on placebo), rash (0.9% on inclisiran vs. 1.2% on placebo), allergic rhinitis (0.6% on inclisiran vs. 0.5% on placebo), seasonal allergy (0.7% on inclisiran vs. 0.4% on placebo), eczema (0.5% on inclisiran vs. 0.5% on placebo), dermatitis (0.5% on inclisiran vs. 0.4% on placebo), and pruritus (0.3% on inclisiran vs. 0.7% on placebo).

Only asthma and seasonal allergy were reported at a slightly higher incidence in patients on inclisiran than placebo. Most of the reported events were mild or moderate in severity. Asthma was reported as serious in 0.2%, n=4 on inclisiran and 0.2%, n=3 on placebo.

This reviewer explored other ways to analyze the data for hypersensitivity reactions including an FDA Medical Query using terms under the “Rash, narrow” grouping. The following table was obtained.

Table 68. FDA Medical Query, Rash, Narrow, Safety Pool

Preferred Term	Inclisiran (N = 1833)	Placebo (N = 1822)
	52 (2.8%)	40 (2.2%)
Blister	0 (0%)	1 (0.1%)
Dermatitis	9 (0.5%)	7 (0.4%)
Exfoliative rash	1 (0.1%)	0 (0%)
Fungal skin infection	1 (0.1%)	1 (0.1%)
Genital rash	0 (0%)	1 (0.1%)
Injection site rash	13 (0.7%)	0 (0%)
Miliaria	1 (0.1%)	1 (0.1%)
Rash	17 (0.9%)	22 (1.2%)
Rash generalised	3 (0.2%)	0 (0%)
Rash pruritic	3 (0.2%)	2 (0.1%)
Rash pustular	0 (0%)	1 (0.1%)
Rash vesicular	1 (0.1%)	1 (0.1%)
Skin exfoliation	0 (0%)	1 (0.1%)
Urticaria	6 (0.3%)	4 (0.2%)
Vessel puncture site rash	0 (0%)	1 (0.1%)

Source: Reviewer created from ISS ADAE dataset and JMP Clinical software.

Reviewer Comment: “Injection site rash” was significantly different for inclisiran treated patients vs. placebo. Excluding this preferred term, there was no imbalance in rash using this query. Individual preferred terms were similar between the two treatment arms. I recommend a subsection in the inclisiran labeling for injection site reactions to highlight the difference from

placebo.

Discontinuations due to Hypersensitivity Reactions

There was 1 discontinuation from treatment for dermatitis with inclisiran (vs. 0 with placebo), and 1 discontinuation from treatment for asthma with inclisiran (vs. 0 with placebo). The following are the narratives for these two patients:

Subject ID: (b) (6) (ORION-10), Treatment Group: Inclisiran 300 mg Dose
On (b) (6) (66 days after receiving the first dose of blinded study drug [Day 67]), this 67-year-old female assigned to the inclisiran 300 mg dose group experienced a nonserious adverse event of dermatitis and was discontinued from the study drug. The event was ongoing at the time of discontinuation. The investigator considered the event to be mild and not reasonably possibly attributable to study drug. Subject remained on the study and reported identical event in a year, next spring.

Reviewer Comment: Although drug-related hypersensitivity cannot be excluded, the temporal pattern described in the history, and occurrence both on and off study drug are more consistent with dermatitis associated with seasonal allergens.

Subject ID: (b) (6) (ORION-11), Treatment Group: Inclisiran 300 mg
On (b) (6) (95 days after receiving the first dose of blinded study drug [Day 96]), this 71-year-old female with a prior history of asthma, experienced a nonserious adverse event of asthma and was discontinued from the study drug. The event was resolved at the time of discontinuation. The investigator considered the event to be moderate and reasonably possibly attributable to study drug. Concomitant medications included budesonide, cefuroxime axetil, codeine phosphate; sulfogaiacol, fexofenadine hydrochloride, salbutamol.

Reviewer Comment: The exacerbation of asthma in patients with a known asthma could occur in response to a "trigger" such as viral upper respiratory infection, allergen or irritant exposure, lack of adherence to controller medication or other stimulant alternative to study treatment. Drug-related exacerbation cannot be entirely excluded, but the relatively long time between dosing and onset of the adverse reaction suggests an alternate etiology.

Anaphylaxis

This reviewer conducted an analysis for the MedDRA SMQ "anaphylactic reaction", narrow search using MAED software. There were 3 patients with 3 events on placebo compared to no patients on inclisiran with this search.

Table 69. MedDRA Anaphylaxis SMQ, Safety Pool

	Placebo N=1822	Inclisiran N=1833

	n (%)	n (%)
Anaphylactic reaction SMQ, narrow	3 (0.2)	0 (0.0)
Anaphylactic reaction	1 (0.1)	0 (0.0)
Circulatory collapse	2 (0.11)	0 (0.0)

Source: Reviewer created from ISS ADAE dataset and MedDRA Based Adverse Event Diagnostics software.

Reviewer Comments: From the submitted data, there was no concern about anaphylactic reactions with inclisiran.

Angioedema

This reviewer conducted an analysis for the MedDRA SMO "Angioedema", narrow search which resulted in 12 patients with 12 events on inclisiran and 10 patients with 11 events on placebo. The results are shown in the following table.

Table 70. MedDRA Angioedema Narrow SMQ, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Angioedema SMQ, narrow	10 (0.5)	12 (0.7)
Urticaria	4 (0.2)	6 (0.3)
Conjunctival oedema	1 (0.1)	0 (0)
Eyelid oedema	1 (0.1)	1 (0.1)
Eye Swelling	3 (0.2)	0 (0)
Swollen tongue	0 (0)	2 (0)
Lip swelling	0 (0)	2 (0)
Face oedema	0 (0)	1 (0.1)
Angioedema	1 (0.1)	0 (0)

Source: Reviewer created from ISS ADAE dataset and MedDRA Based Adverse Event Diagnostics software.

Reviewer Comment: There were slightly more patients on inclisiran (0.7%) than on placebo (0.5%) who reported an adverse reaction under the Angioedema SMQ. This reviewer further examined narratives of those patients on inclisiran who reported reactions such as swollen lips, tongue, or face.

Patient ID# [REDACTED] (b) (6), Treatment Group: Inclisiran 300 mg Dose: 64 y.o. male had a medical history of coronary heart disease atrial fibrillation, Gilbert's syndrome, hyperparathyroidism, thyroidectomy. Concomitant medications were acetylsalicylic acid, amlodipine, atorvastatin calcium, bisoprolol, omeprazole, tamsulosin. On [REDACTED] (b) (6) (Day 1), patient received first dose of study medication. On [REDACTED] (b) (6) (Day 89) patient received second dose of study medication. On [REDACTED] (b) (6) (Day 89) patient experienced a nonserious adverse event of injection site hypersensitivity, moderate in severity, symptoms included pain, swelling, and red spots. The event resolved on [REDACTED] (b) (6) and patient was discontinued from

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the study drug on [REDACTED] (b) (6). Patient continued in the study and reported swollen tongue on [REDACTED] (b) (6), which resolved on [REDACTED] (b) (6).

Reviewer Comment: Event of swollen tongue occurred almost one year after discontinuation of inclisiran; therefore, causality with inclisiran unlikely.

Patient ID# [REDACTED] (b) (6), Treatment Group: Inclisiran 300 mg Dose: 79 y.o. male had a medical history of coronary heart disease, dry eyes, hiatal hernia and hyperlipidemia. Concomitant medications were acetylsalicylic acid, carbomer, cod-liver oil, ketoprofen, lansoprazole, ramipril and simvastatin. On [REDACTED] (b) (6) (Day 1), the patient received first dose of study drug. On [REDACTED] (b) (6) (4 days after receiving the first dose of study drug), the patient experienced swollen tongue moderate in severity which resolved on [REDACTED] (b) (6). Dose of inclisiran was not changed and patient received second dose of study drug on [REDACTED] (b) (6). On [REDACTED] (b) (6) (172 days after receiving the second dose of blinded study drug [Day 453] patient experienced chest pain. On the same day, the subject was admitted to the hospital where he was diagnosed with gallstones (serious adverse event preferred term: cholelithiasis). Laboratory tests were performed (results not provided). A cholecystectomy was scheduled for [REDACTED] (b) (6). The event resolved on [REDACTED] (b) (6).

Reviewer Comment: Rechallenge with a second dose of inclisiran did not produce another hypersensitivity event. Therefore, a causal relationship is not established.

Patient ID # [REDACTED] (b) (6), Treatment Group: Inclisiran 300 mg Dose: 69 y.o. female had a medical history of coronary heart disease, percutaneous coronary intervention, hypertension, hyperlipidemia, generalized atherosclerosis, angina pectoris, mitral regurgitation, tricuspid valve insufficiency, tonsillectomy, gastritis, fatty liver, gastro-esophageal reflux disease, generalized osteoarthritis, root syndrome, dizziness, headache, problems falling asleep, and allergy to aspirin and penicillin. Concomitant medications included Ridlip (rosuvastatin), Nitromint (nitroglycerin), Coronal (bisoprolol), Tritace (ramipril), and Aclotin (ticlopidine). On [REDACTED] (b) (6) (Day 1), the patient received the first dose of study drug. On [REDACTED] (b) (6) (seven days after receiving the first dose of study drug), the patient experienced skin edema, face edema, lower abdominal pain, musculoskeletal pain, insomnia, and worsening of pre-existing dizziness and headache; all were of moderate severity. No action was taken with the study drug and no treatment was reported. On [REDACTED] (b) (6), Ridlip (rosuvastatin) was stopped due to symptoms of intolerance. On [REDACTED] (b) (6), the patient recovered from headache, dizziness, and insomnia. On [REDACTED] (b) (6) (Visit 3, Day 90), the patient received the last dose of study drug. On [REDACTED] (b) (6), the patient had mild intra-abdominal pain. No treatment was reported. On [REDACTED] (b) (6), the patient withdrew consent. The events (skin edema, face edema, lower abdominal pain, musculoskeletal pain, intra-abdominal pain) were ongoing at the time of last

available report.

Reviewer Comment: Drug-related causation for skin edema, face edema, lower abdominal pain, musculoskeletal pain, intra-abdominal pain is not clear.

Patient ID# [REDACTED] (b) (6), Treatment Group: Inclisiran 300 mg Dose: 65 y.o. had a medical history of cerebrovascular disease, ischemic stroke, hypertension, and hyperlipidemia. The patient was a former smoker and was intolerant to atorvastatin with the symptoms of muscle ache and ankle swelling. Concomitant medications included atorvastatin, clopidogrel, bendroflumethiazide, and lisinopril. On [REDACTED] (b) (6) (Day 1), the patient received the first dose of study drug. On [REDACTED] (b) (6) (Visit 3, Day 90), the patient received the second dose of study drug. On [REDACTED] (b) (6) (99 days after receiving the recent dose of study drug), the patient experienced lip swelling of mild severity. No action was taken with the study drug and no treatment was reported. Lip swelling resolved on the same day after 10 hours. On [REDACTED] (b) (6) (Visit 5, Day 270) the patient received the third dose of study drug, and last dose on [REDACTED] (b) (6) (Visit 7, Day 450). On [REDACTED] (b) (6) the patient completed the study.

Reviewer Comment: The event (lip swelling) was considered non-serious and did not reoccur on continuation of treatment with inclisiran. Therefore, the event may not be attributable to study drug.

Patient ID# [REDACTED] (b) (6), Treatment Group Inclisiran 300 mg Dose: 72 y.o. woman had a medical history of coronary heart disease, percutaneous coronary intervention, angina, hypertension, and hyperlipidemia. The patient was a smoker and had a family history of coronary artery disease. Concomitant medications included atorvastatin, atenolol, and aspirin. On [REDACTED] (b) (6) (Day 1), the patient received the first dose of study drug. On [REDACTED] (b) (6) (Visit 3, Day 90), the patient received the second dose of study drug. On [REDACTED] (b) (6), the patient experienced mild myalgia. On the same day, the patient discontinued atorvastatin and started rosuvastatin due to discomfort and myalgia. On [REDACTED] (b) (6), myalgia resolved. The patient received the third dose of study drug on [REDACTED] (b) (6) (Visit 5, Day 270), and last dose on [REDACTED] (b) (6) (Visit 7, Day 450). On [REDACTED] (b) (6) (one day after receiving the last dose of the study drug), the patient experienced lower eyelid edema (left and right eyelids) of mild severity, and had mild generalized pruritus. No treatment was reported. On [REDACTED] (b) (6), the patient recovered from lower eyelid edema and generalized pruritus. On [REDACTED] (b) (6) (Visit 9), the patient completed the study.

Reviewer Comment: It is unclear if the mild eyelid swelling was attributable to inclisiran.

Patient ID# [REDACTED] (b) (6), Treatment Group Inclisiran 300 mg Dose; 20 y.o. male who had

medical history of hyperlipidemia and angioedema. The patient had risk score of >20% for 10 year-risk of cardiovascular event and had a family history of dyslipidemia. On (b) (6) (Day 1), the patient received the first dose of study drug. On (b) (6), the patient experienced mild pityriasis versicolor rash on arms and chest. On (b) (6), almost one hour before receiving the study drug, the patient experienced swollen lip of mild severity. The patient received the second dose of the study drug (Visit 3, Day 90) and also received topical Dermol (antimicrobial and emollient) and ketoconazole for the above mentioned rash on arm and chest. No action was taken with the study drug and no treatment was reported for the swollen lip. Lip swelling resolved on the same day of its onset. On (b) (6), pityriasis versicolor rash on arms and chest was resolved. On (b) (6) (Visit 5, Day 270) the patient received the third dose of study drug, and last dose on (b) (6) (Visit 7, Day 450). On (b) (6), the patient completed the study. The Investigator considered the event (swollen lip) as non-serious and was not reasonably attributable to study drug.

Reviewer Comment: The event of lip swelling is considered non-serious as it did not require treatment and resolved on the same day of onset. The event also did not reoccur on continuation of treatment with inclisiran.

Reviewer comment: In conclusion, there was no clear imbalance in events of angioedema between inclisiran and placebo. Review of case narratives of inclisiran patients were inconclusive regarding a causal relationship between inclisiran and the events.

Severe Cutaneous Adverse Reactions

The MedDRA SMQ “Severe Cutaneous Adverse Reaction, narrow” was used to summarize potentially important skin reactions. There were 2 patients on inclisiran who reported adverse reactions that mapped to this SMQ as compared to 1 patient on placebo. None of these reactions were reported as serious.

Table 71. MedDRA Severe Cutaneous Adverse Reaction, Narrow SMQ, Safety Pool

Study	Arm	Narrow SMQ	Preferred Term	Patient ID#
ORION-10	Inclisiran	Severe Cutaneous Adverse Reaction	Exfoliative rash	(b) (6)
			Rash scaly	
ORION-11	Inclisiran	Severe Cutaneous Adverse Reaction	Dermatitis exfoliative	
			Erythroderma	
ORION-10	Placebo	Severe Cutaneous Adverse Reaction	Dermatitis exfoliative	
			Exfoliative dermatitis	

Source: Reviewer created from ISS ADAE dataset and JMP Clinical software.

Reviewer Comment: Overall, the incidence of serious hypersensitivity reactions such as anaphylaxis, angioedema, and severe cutaneous adverse reaction was low and similar to placebo.

Injection Site Reactions

Injection site reactions were identified using preferred terms that mapped to the MedDRA high-level term "injection site reactions". In the Safety Pool, the proportion of subjects with TEAE (High Level Term) at the injection site was 8.2% (150/1833) for the inclisiran treatment arm vs. 1.8% (33/1822) for the placebo treatment arm.

The most frequently reported preferred terms were "injection site reaction," 3.1% on inclisiran vs. 0.1% on placebo; "injection site pain" 2.2% on inclisiran vs. 0.5% on placebo; "injection site erythema" 1.6% on inclisiran vs. 0.2% on placebo and "injection site rash," 0.7% on inclisiran vs. 0% on placebo.

The following table summarizes treatment emergent preferred terms reported in the Safety Pool.

Table 72. Summary of Treatment Emergent Adverse Events at the Injection Site by Preferred Term, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Subjects with at Least One TEAE at the Injection Site	33 (1.8)	150 (8.2)	183 (5.0)
Injection site bruising	7 (0.4)	9 (0.5)	16 (0.4)
Injection site discoloration	0 (0.0)	4 (0.2)	4 (0.1)
Injection site discomfort	1 (0.1)	1 (0.1)	2 (0.1)
Injection site erythema	4 (0.2)	30 (1.6)	34 (0.9)
Injection site haematoma	1 (0.1)	4 (0.2)	5 (0.1)
Injection site hypersensitivity	0 (0.0)	2 (0.1)	2 (0.1)
Injection site induration	1 (0.1)	5 (0.3)	6 (0.2)
Injection site oedema	1 (0.1)	1 (0.1)	2 (0.1)
Injection site pain	9 (0.5)	41 (2.2)	50 (1.4)
Injection site pallor	0 (0.0)	1 (0.1)	1 (0.1)
Injection site paresthesia	0 (0.0)	4 (0.2)	4 (0.1)
Injection site pruritus	6 (0.3)	8 (0.4)	14 (0.4)
Injection site rash	0 (0.0)	13 (0.7)	13 (0.4)
Injection site reaction	2 (0.1)	56 (3.1)	58 (1.6)
Injection site swelling	1 (0.1)	0 (0.0)	1 (0.0)
Injection site warmth	0 (0.0)	2 (0.1)	2 (0.1)

Source: Table 14.3.1.12.1

Reviewer Comment: The proportion of subjects with TEAEs at the injection site in the overall

population was 4.5-fold higher in the inclisiran group (8.2%) compared to the placebo group (1.8%). A description of this adverse reaction should be included in safety labeling in the prescribing information.

The following table shows the time to first TEAE at the injection site for patients in the Safety Pool.

Table 73. Time to First Treatment Emergent Adverse Event at Injection Site, Safety Pool

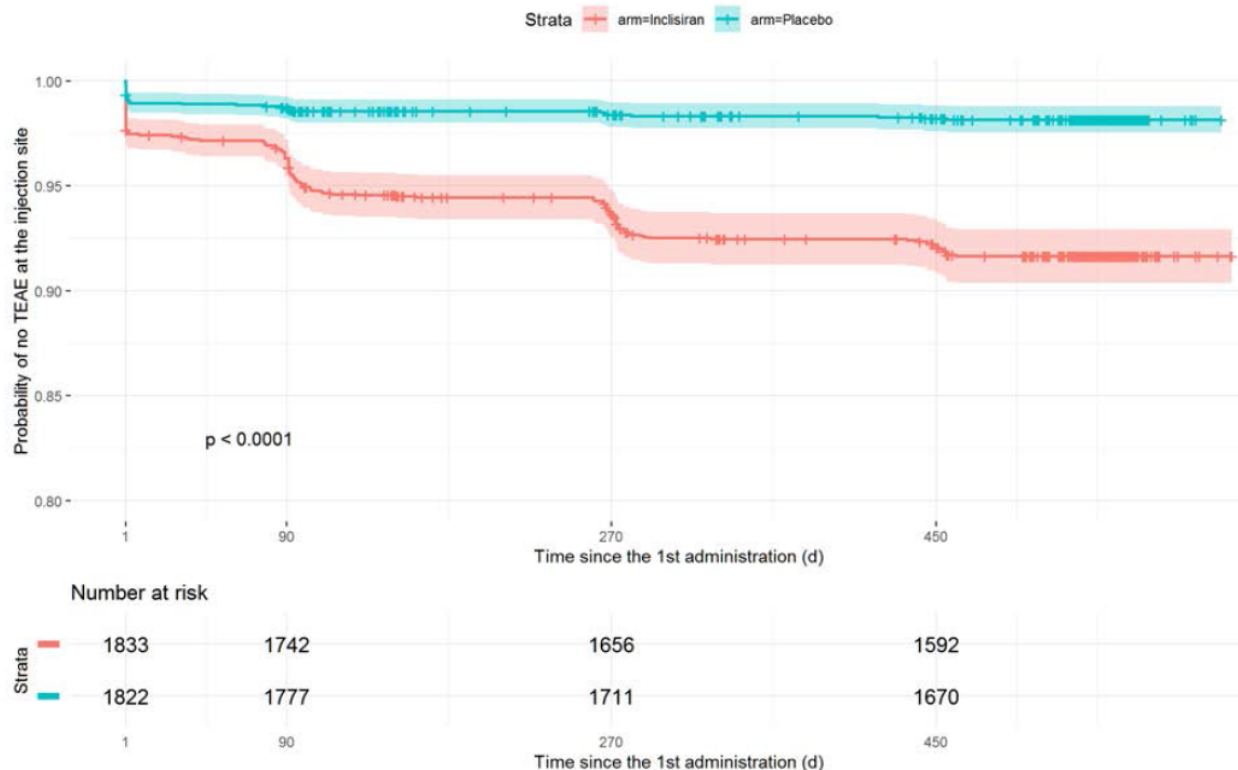
	Placebo N=1822	Inclisiran N=1833
Number of Subjects with any TEAE at the injection site n(%)	33 (1.8%)	150 (8.2%)
Time to first TEAE at injection site		
n	36	182
Mean ± SD (hours)	81 ± 271	84 ± 192
Duration of First TEAE at injection site		
n	35	169
Mean ± SD (hours)	36 ± 140	134 ± 439

Source: Table 14.3.1.13.1 Only subjects with a TEAE at the injection site were included in the analysis. The time (hours) was calculated from the date of the most recent administration of study drug.

Reviewer Comment: Injection site reactions occurred approximately 3.5 days (mean) after inclisiran administration and lasted approximately 5.6 days (mean) for those patients reporting a reaction. Reactions on placebo were of much shorter duration (1.5 days).

The following figure shows the time to first injection site reaction for patients in the Safety Pool. Patients received study drug at Day 1, 90, and every 6 months.

Figure 23. Kaplan-Meier Plot of Time to First Treatment Emergent Adverse Event at the Injection Site Following Administration of Study Drug, Safety Pool



Source: ISS, Appendix 1, Section 7.4. Note: Shade area represent 95%CI of the Kaplan-Meier curves within each strata. Number at risk for each strata is provided for each dosing day (Day 1, 90 and every 6 months).

Reviewer Comment: More patients on inclisiran developed a treatment emergent adverse event at the injection site than on placebo. For example, at time 450 days after first dose, approximately 8% of patients on inclisiran reported a TEAE at injection site compared to 2% on placebo. Therefore, an injection site reaction is more likely with inclisiran treatment.

Of the 183 total subjects with a TEAE at the injection site, the majority had a mild event, a minority had a moderate event, and none had a severe event.

The following table shows the severity of the injection site reaction in patients who had an injection site reaction by the individual Phase 3 trials.

Table 74. Reported Severity of Injection Site Reactions, Phase 3 trials

Severity	ORION-10		ORION-11		ORION-9		Overall	
	Inclisiran n=47	Placebo n=15	Inclisiran n=62	Placebo n=14	Inclisiran n=41	Placebo n=4	Inclisiran n=150	Placebo n=33
Mild	42	15	49	12	38	4	129	31

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Severity	ORION-10		ORION-11		ORION-9		Overall	
	Inclisiran n=47	Placebo n=15	Inclisiran n=62	Placebo n=14	Inclisiran n=41	Placebo n=4	Inclisiran n=150	Placebo n=33
	(89%)	(100%)	(79%)	(86%)	(93%)	(100%)	(86%)	(84%)
Moderate	5 (11%)	0 (0%)	13 (21%)	2 (14%)	3 (7%)	0 (0%)	21 (14%)	2 (6%)

Source: ISS, Appendix 1, Section 7.2. Only first occurrence of the TEAE at the injection site were retained in the overall count.

Reviewer Comment: Of the inclisiran-treated patients with an injection site reaction, most patients (86%) reported a mild reaction, with 14% reporting a moderate reaction. There were no severe or serious injection site reactions.

Four inclisiran-treated patients withdrew from study drug due to non-serious TEAEs at the injection site as compared to no withdrawals in the placebo arm due to injection sites TEAEs; their patient narratives are as follows:

ORION-11; Patient ID# [REDACTED] (b) (6); Inclisiran 300 mg dose; 67 y.o. woman with medical history of coronary heart disease, hyperlipidemia, and hypertension. Concomitant medications were acetylsalicylic acid, bisoprolol fumarate, fish oil, levothyroxine, pantoprazole, potassium chloride, ramipril, rosuvastatin. On [REDACTED] (b) (6) (1 day after receiving the third dose of blinded study drug [Day 269]), patient experienced a nonserious adverse event of injection site reaction and was discontinued from the study drug. Symptoms included erythema, pruritus, and rash. The event resolved on [REDACTED] (b) (6).

ORION-10; Patient ID# [REDACTED] (b) (6); Inclisiran 300 mg dose; 78 y.o. man with medical history of coronary heart disease, hyperlipidemia, rhinitis and type 2 diabetes mellitus. Concomitant medications atorvastatin, fluticasone, metformin, metoprolol and ramipril. Patient received first dose of study medication on [REDACTED] (b) (6). On [REDACTED] (b) (6) (2 minutes after receiving the second dose of blinded study drug [Day 87]), patient experienced a nonserious adverse event of injection site reaction. Symptoms included tenderness and sensation of fullness over the injection site. The event resolved on the same day, [REDACTED] (b) (6). On an unspecified date, the subject decided to stop study drug since he gets very apprehensive with the injection.

ORION-9; Patient ID# [REDACTED] (b) (6); Inclisiran 300 mg dose; 54 y.o. woman with a medical history of familial hypercholesteremia (HeFH); anxiety, and migraine. Concomitant medication included clotrimazole, ezetimibe, and fluvastatin sodium. On [REDACTED] (b) (6) (approximately 8.5 hours after receiving the first dose of blinded study drug [Day 1]), patient experienced a nonserious adverse event of injection site reaction. Symptoms included erythema and induration. The event resolved on [REDACTED] (b) (6). The subject remained in the study; she refused further study treatment administration.

ORION-9; Patient ID# (b) (6); Inclisiran 300 mg dose; 52 yo woman with a medical history of familial hypercholesterolemia (HeFH); depression, attention deficit/hyperactivity disorder. Concomitant medications included ezetimibe, ibuprofen, rosuvastatin. On (b) (6), patient received first dose of study drug. On (b) (6) (1 day after receiving the second dose of blinded study drug [Day 96]), patient experienced a nonserious adverse event of injection site reaction and was discontinued from the study drug. Symptoms included erythema, warmth, and pruritus. Patient received terbinafine and methylprednisone. The event resolved on (b) (6).

Reviewer Comment: There were no adverse reactions within the patient narratives to indicate other reactions such as anaphylaxis, angioedema, or Stephen-Johnson's syndrome associated with injection site reactions that would indicate a more serious/life-threatening event.

Injection site reactions were further examined by race, gender and age. The following table shows injection site reactions by gender.

Table 75. Treatment Emergent Adverse Events at the Injection Site by Gender, Safety Pool

	Male		Female	
	Placebo N=1240, n (%)	Inclisiran N=1228, n(%)	Placebo N=582, n (%)	Inclisiran N=605, n (%)
Subjects with at least one TEAE at Injection Site	23 (1.9%)	80 (6.5%)	10 (1.7%)	70 (11.6%)

Table 14.3.1.12.1.1. TEAEs at the injection site include all TEAEs identified as being an injection site reaction on the AE CRF or with 'Injection Site' in the HLT name.

Reviewer Comment: There was a numerical difference in the occurrence of TEAEs at the injection site by gender in patients on inclisiran, 6.5% male and 11.6% female.

Table 76. Treatment Emergent Adverse Events at the Injection Site by Age < 65 and >= 65 years old, Safety Pool

	Patients < 65 years old		Patients >= 65 years old	
	Placebo N=882, n (%)	Inclisiran N=852, n(%)	Placebo N=940, n (%)	Inclisiran N=981, n (%)
Subjects with at least one TEAE at Injection Site	19 (2.2%)	85 (10.0%)	14 (1.5%)	65 (6.6%)

Table 14.3.1.12.1.2. TEAEs at the injection site include all TEAEs identified as being an injection site reaction on the AE CRF or with 'Injection Site' in the HLT name. * Denominator based upon events

Reviewer Comment: There was a numerical difference in the occurrence of TEAEs at the

injection site by age in patients on inclisiran, 6.6% of patients >=65 years of age and 10.0% of patients < 65 years of age. A possible explanation for the difference may be that younger patients mount a greater immune response than older patients

Table 77. Treatment Emergent Adverse Events at Injection Site by Race, Safety Pool

	White		Black	
	Placebo N=1704, n (%)	Inclisiran N=1669, n (%)	Placebo N=101, n (%)	Inclisiran N=131, n (%)
Subjects with at least one TEAE at Injection Site	30 (1.8)	143 (8.6)	2 (2.0)	4 (3.1)

Table 14.3.1.12.1.6 TEAEs at the injection site include all TEAEs identified as being an injection site reaction on the AE CRF or with 'Injection Site' in the HLT name. * Denominator based upon events

Reviewer Comment: There was a numerical difference in the occurrence of TEAEs at the injection site by race in patients on inclisiran, 3.1% of black patients and 8.6% of white patients. However, interpretation of this difference is limited because the sample size and number of black patients with events was small.

The following table shows the number and percent of patients with and without a history of allergies who had at least one TEAE at the injection site.

Table 78. Treatment Emergent Adverse Events at the Injection Site by History of Allergy, Safety Pool

	Allergy History		No Allergy History	
	Placebo N=344, n (%)	Inclisiran N=324, n (%)	Placebo N=1478, n (%)	Inclisiran N=1509, n (%)
Subjects with at least one TEAE at Injection Site	7 (2.0)	39 (12.0)	26 (1.8)	111 (7.4)

Source: Table 14.3.1.12.1.16

A history of allergy was identified using the following high-level group term: allergic conditions.

Reviewer Comment: As shown in the table above, patients in the inclisiran-treated arm, who reported a history of allergy (identified using the high-level group term "allergic conditions"), had a higher incidence of injection site reactions 12% vs. 7.4%. In the placebo arm, patients who had a history of allergy had a similar incidence of injection site reactions as compared to those without an allergy history, 2.0% vs. 1.8%, respectively. This may indicate that patients with prior history of allergic conditions may have higher likelihood of an injection site reaction with inclisiran. Interpretation is limited by the relatively small subset and low number of events with

a history of allergy.

Neurologic Events

Neurological events related to myelin-sheath disorders or neuropathies were collected as AEs of special interest based on theoretical concerns that low LDL-C concentrations may impair myelination. Specifically, neurologic events were identified using Demyelination, (SMQ, broad and narrow) and Peripheral neuropathy, (SMQ, broad and narrow). The incidence of AEs related to neurological disorders was similar between treatment groups, 2.9% on placebo vs 2.3% on inclisiran.

Table 79. TEAE- Neurologic Events, Safety Pool

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of subjects with at least one TEAE	53 (2.9)	43 (2.3)	96 (2.6)
Hypoaesthesia	11 (0.6)	9 (0.5)	20 (0.5)
Paraesthesia	8 (0.4)	10 (0.5)	18 (0.5)
Neuropathy peripheral	6 (0.3)	10 (0.5)	16 (0.4)
Muscular weakness	8 (0.4)	7 (0.4)	15 (0.4)
Neuralgia	5 (0.3)	4 (0.2)	9 (0.2)
Hyporeflexia	5 (0.3)	1 (0.1)	6 (0.2)
Gait disturbance	3 (0.2)	2 (0.1)	5 (0.1)
Polyneuropathy	0 (0.0)	3 (0.2)	3 (0.1)
Sensory loss	0 (0.0)	3 (0.2)	3 (0.1)
Burning sensation	2 (0.1)	1 (0.1)	3 (0.1)
Areflexia	1 (0.1)	1 (0.1)	2 (0.1)
Axonal neuropathy	2 (0.1)	0 (0.0)	2 (0.1)
Trigeminal neuralgia	2 (0.1)	0 (0.0)	2 (0.1)
Hypergammaglobulinaemia benign monoclonal	0 (0.0)	1 (0.1)	1 (0.1)
Muscle atrophy	0 (0.0)	1 (0.1)	1 (0.1)
Decreased vibratory sense	1 (0.1)	0 (0.0)	1 (0.1)
Mononeuropathy	1 (0.1)	0 (0.0)	1 (0.1)
Myelopathy	1 (0.1)	0 (0.0)	1 (0.1)
Peripheral nerve paresis	1 (0.1)	0 (0.0)	1 (0.1)
Peripheral sensorimotor neuropathy	1 (0.1)	0 (0.0)	1 (0.1)
Sensory disturbance	1 (0.1)	0 (0.0)	1 (0.1)

Source: Table 14.3.2.4.

Neurocognitive Events

Neurocognitive disorders were identified using the following SMQs:

- Deliria (including confusion), (HLGT)
- Cognitive and attention disorders and disturbances, (HLGT)
- Dementia and amnesic conditions, (HLGT)
- Disturbances in thinking and perception (HLGT)
- Mental impairment disorders (HLGT)

Table 80. Treatment Emergent Adverse Events Related to Neurocognitive Events, Safety Pool

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of subjects with at least one TEAE	19 (1.0)	13 (0.7)	32 (0.9)
Memory impairment	5 (0.3)	3 (0.2)	8 (0.2)
Dementia	4 (0.2)	2 (0.1)	6 (0.2)
Amnesia	3 (0.2)	1 (0.1)	4 (0.1)
Confusional state	1 (0.1)	2 (0.1)	3 (0.1)
Cognitive disorder	0 (0.0)	2 (0.1)	2 (0.1)
Attention deficit/hyperactivity disorder	1 (0.1)	1 (0.1)	2 (0.1)
Disorientation	1 (0.1)	1 (0.1)	2 (0.1)
Vascular dementia	2 (0.1)	0 (0.0)	2 (0.1)
Dementia Alzheimer's type	0 (0.0)	1 (0.1)	1 (0.0)
Disturbance in attention	1 (0.1)	0 (0.0)	1 (0.0)
Hallucination	1 (0.1)	0 (0.0)	1 (0.0)
Mixed dementia	1 (0.1)	0 (0.0)	1 (0.0)

Source: Table 14.3.2.4

Reviewer Comment: There was no difference from placebo in neurocognitive events with inclisiran using the pre-defined SMQs.

The Division requested a second FDA customized MedDRA query (CMQ) of neurocognitive disorders based on a list of terms from published literature. The MedDRA terms are listed in the table below.

Table 81. MedDRA Terms Comprising FDA Neurocognitive CMO

MedDRA level	MedDRA Code	MedDRA Term Label
PTCD	10001949	Amnesia
PTCD	10061423	Amnesic disorder
PTCD	10002711	Anterograde Amnesia
PTCD	10066842	Behavioural and Psychiatric Symptoms of Dementia
PTCD	10008398	Change in sustained attention
LLTCD	10009843	Cognitive Deterioration
PTCD	10057668	Cognitive Disorder
LLTCD	10010300	Confusion
LLTCD	10048321	Confusion Aggravated
PTCD	10010305	Confusional State
PTCD	10012218	Delirium
PTCD	10012267	Dementia
PTCD	10012271	Dementia Alzheimer's type
LLTCD	10012290	Dementia Nos
LLTCD	10012291	Dementia Nos Aggravated
LLTCD	10012292	Dementia of the Alzheimer's type NOS
PTCD	10067889	Dementia with Lewy Bodies
PTCD	10013395	Disorientation
PTCD	10013496	Disturbance in attention
PTCD	10070246	Executive dysfunction
PTCD	10068968	Frontotemporal Dementia
LLTCD	10058669	Global Amnesia
PTCD	10021402	Illogical Thinking
PTCD	10071176	Impaired reasoning
PTCD	10021630	Incoherent
PTCD	10023236	Judgement impaired
PTCD	10027175	Memory Impairment
PTCD	10027374	Mental Impairment
LLTCD	10027376	Mental Impairment Nos
LLTCD	10048345	Mental State Abnormal Aggravated
PTCD	10048294	Mental Status Changes
PTCD	10065424	Mini Mental Status Examination Abnormal
PTCD	10036631	Presenile Dementia
PTCD	10038965	Retrograde Amnesia
PTCD	10039966	Senile Dementia

MedDRA level	MedDRA Code	MedDRA Term Label
LLTCD	10039967	Senile Dementia Nos
LLTCD	10040602	Short-term Memory Loss
PTCD	10043431	Thinking Abnormal
LLTCD	10043438	Thinking Slowed
PTCD	10044380	Transient Global Amnesia
PTCD	10057678	Vascular Dementia

The incidence table using the customized MedDRA query related to neurocognitive events in the Safety Pool yielded the following table.

Table 82. TEAEs Related to Neurocognitive Events, FDA CMO, Safety Pool

Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Number of subjects with at least one TEAE	19 (1.0)	13 (0.7)	32 (0.9)
Nervous system disorders	14 (0.8)	9 (0.5)	23 (0.6)
Memory impairment	5 (0.3)	3 (0.2)	8 (0.2)
Dementia	4 (0.2)	2 (0.1)	6 (0.2)
Amnesia	3 (0.2)	1 (0.1)	4 (0.1)
Cognitive disorder	0 (0.0)	2 (0.1)	2 (0.1)
Vascular dementia	2 (0.1)	0 (0.0)	2 (0.1)
Dementia Alzheimer's type	0 (0.0)	1 (0.1)	1 (0.0)
Disturbance in attention	1 (0.1)	0 (0.0)	1 (0.0)
Psychiatric disorders	5 (0.3)	4 (0.2)	9 (0.2)
Mental status changes	3 (0.2)	1 (0.1)	4 (0.1)
Confusional state	1 (0.1)	2 (0.1)	3 (0.1)
Disorientation	1 (0.1)	1 (0.1)	2 (0.1)

Source: Applicant response to information request, 6/4/2020.

Reviewer Comment: Using the FDA customized MedDRA query, there were no clinically meaningful differences from placebo in the incidence of neurocognitive events with inclisiran.

Psychiatric Disorders

A post-marketing review of PCSK9 inhibitor monoclonal antibodies (evolocumab and alirocumab) noted various psychiatric adverse events reported with the use of those drug products. Inclisiran is a double-stranded small interfering ribonucleic acid that inhibits translation of PCSK9 protein and has selectivity for the liver. According to Pharm/tox reviewer, quantitative whole body autoradiography studies performed with ¹⁴C-labeled inclisiran in rats and monkeys showed there was minimal distribution to the brain and spinal cord in both rats and monkeys.

However, because PCSK9 levels are reduced with inclisiran (similar pharmacodynamic effect to PCSK9 antibody inhibitors, which bind circulating PCSK9 and reduce free PCSK9 levels) this reviewer examined the reported adverse events related to psychiatric disorders.

The following table summarizes the more common adverse events related to Psychiatric disorders SOC submitted by the applicant.

Table 83. Summary of Most Common Preferred Terms Under Psychiatric Disorders, Safety Pool

System Organ Class/ Preferred Term	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Number (%) of Patients with Psychiatric Disorders	86 (4.7)	83 (4.5)
Anxiety	14 (0.8)	16 (0.9)
Anxiety disorder	0	1 (0.1)
Depressed mood	3 (0.2)	4 (0.2)
Depression	29 (1.6)	25 (1.4)
Insomnia	19 (1.0)	20 (1.1)
Mental status changes	3 (0.2)	1 (0.1)
Sleep disorder	3 (0.2)	2 (0.1)

Source: Table 14.3.1.2

Reviewer Comment: There were 83 (4.5%) patients on inclisiran compared to 86 (4.7%) patients on placebo who reported adverse events related to Psychiatric disorders. To confirm there was no concerning signal, this reviewer conducted additional analyses (see below).

This reviewer also conducted FDA customized queries using the “Anxiety, Narrow” grouping.

Table 84. Customized FDA Query, “Anxiety, Narrow”, Safety Pool

FDA Medical Query, Narrow	Dictionary-Derived Term	Inclisiran (N = 1833)	Placebo (N = 1822)
<i>Anxiety</i>		20 (1.1%)	17 (0.9%)
<i>Anxiety</i>	Anxiety	16 (0.9%)	14 (0.8%)
<i>Anxiety</i>	Anxiety disorder	1 (0.1%)	0 (0%)
<i>Anxiety</i>	Cardiovascular somatic symptom disorder	1 (0.1%)	0 (0%)
<i>Anxiety</i>	Neurosis	1 (0.1%)	1 (0.1%)
<i>Anxiety</i>	Panic attack	0 (0%)	1 (0.1%)
<i>Anxiety</i>	Panic disorder	0 (0%)	1 (0.1%)
<i>Anxiety</i>	Stress	1 (0.1%)	0 (0%)

Source: Reviewer created from ADAE dataset and FDA Medical Query Explorer, JMP Clinical

Reviewer Comment: Using the “Anxiety, Narrow” FDA Query, there were 20 (1.1%) patients on inclisiran versus 17 (0.9%) patients on placebo. The data do not suggest an increased risk of anxiety related disorders with inclisiran.

This reviewer also conducted FDA customized queries using the “Depression, Narrow”

grouping.

Table 85. Customized FDA Query, "Depression, Narrow", Safety Pool

FDA Medical Query, Narrow	Dictionary-Derived Term	Inclisiran (N = 1833)	Placebo (N = 1822)
<i>Depression</i>		34 (1.9%)	34 (1.9%)
<i>Depression</i>	Adjustment disorder with depressed mood	1 (0.1%)	0 (0%)
<i>Depression</i>	Depressed mood	4 (0.2%)	(0.2%)
<i>Depression</i>	Depression	25 (1.4%)	29 (1.6%)
<i>Depression</i>	Major depression	2 (0.1%)	2 (0.1%)
<i>Depression</i>	Persistent depressive disorder	2 (0.1%)	0 (0%)

Source: Reviewer created from ADAE dataset and FDA Medical Query Explorer, JMP Clinical

Reviewer Comment: Using the "Depression, Narrow" FDA Query, there were 34 (1.9%) patients on inclisiran versus 34 (1.9%) patients on placebo. The data do not suggest an increased risk of depression related disorders with inclisiran.

Ophthalmologic Events

An early nonclinical study suggested papilledema findings in a two female monkeys in a 15-week study. However, further investigation showed no findings of papilledema in the 40-week toxicology study in monkeys, which used a board-certified veterinary ophthalmologist. The applicant stated that the use of the term papilledema was inappropriately used to capture optic disc variations. Since papilledema specifically refers to optic disc swelling that occurs secondarily to increased intracranial pressure and the finding of papilledema was not verified by the board-certified veterinary ophthalmologist, the Agency pharmacology/toxicology team agreed with the applicant that this finding was mislabeled. Additionally, there was no papilledema noted in the histopathology evaluation of the eye.

The applicant conducted an analysis of ophthalmologic events in the Phase 3 clinical trials using the following MedDRA SMQs:

- Optic nerve disorders, (SMQ, broad and narrow)
- Retinal disorders, (SMQ, narrow)
- Corneal disorders, (SMQ, narrow)

The number of patients who reported a TEAE related to ophthalmological events was n=21 (1.2%) in placebo compared to n=27 (1.5%) in inclisiran.

Table 86. Treatment Emergent Adverse Events Related to Ophthalmologic Events, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Number of patients with at least one TEAE	21 (1.2)	27 (1.5)
Age-related macular degeneration	0	1 (0.1)
Blindness unilateral	1 (0.1)	1 (0.1)
Corneal lesion	0	1 (0.1)
Diabetic retinal oedema	0	1 (0.1)
Dry age-related macular degeneration	0	1 (0.1)
Macular degeneration	3 (0.2)	1 (0.1)
Macular oedema	0	1 (0.1)
Maculopathy	0	1 (0.1)
Optic ischaemic neuropathy	0	1 (0.1)
Photopsia	1 (0.1)	0
Punctate keratitis	0	1 (0.1)
Retinal artery embolism	1 (0.1)	0
Retinal artery occlusion	0	1 (0.1)
Retinal degeneration	1 (0.1)	0
Retinal detachment	2 (0.1)	2 (0.1)
Retinal tear	2 (0.1)	2 (0.1)
Retinal vein occlusion	0	3 (0.2)
Visual acuity reduced	0	1 (0.1)
Visual impairment	6 (0.3)	5 (0.3)
Vitreous adhesions	1 (0.1)	0
Vitreous detachment	2 (0.1)	1 (0.1)
Vitreous floaters	2 (0.1)	0
Vitreous haemorrhage	0	1 (0.1)

Source: Table 37, ISS.

Reviewer Comment: Overall number of patients in the study with ophthalmologic events was small and precludes making a definitive conclusion. The difference between placebo and inclisiran is also small.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

This section focuses on the common adverse events reported in the Safety Pool. This reviewer searched for the most frequently reported preferred terms for adverse events as well as conducted an analysis for terms that mapped to Standardized MedDRA SMQ queries.

Common Adverse Events- Search of Preferred Terms

In an analysis of all preferred terms, 78.0% of patients randomized to inclisiran and 77.3% of patients randomized to placebo reported at least one TEAE during the trial. The listing by SOC with the most common AE (PT in inclisiran group $\geq 3\%$) are as follows:

Table 87. Treatment Emergent Adverse Events by SOC, Most Common PT, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Cardiac disorders		
Angina pectoris	57 (3.1)	58 (3.2)
Gastrointestinal disorders		
Diarrhoea	66 (3.5)	71 (3.9)
General disorders and administration site		
Injection site reaction	2 (0.1)	56 (3.1)
Infections and infestations		
Bronchitis	50 (2.7)	78 (4.3)
Nasopharyngitis	134 (7.4)	140 (7.6)
Upper respiratory tract infection	103 (5.7)	105 (5.7)
Urinary tract infection	66 (3.6)	81 (4.4)
Metabolism and nutrition disorders		
Diabetes mellitus	207 (11.4)	212 (11.6)
Musculoskeletal and connective tissue disorder		
Arthralgia	72 (4.0)	91 (5.0)
Back pain	77 (4.2)	83 (4.5)
Pain in extremity	47 (2.6)	60 (3.3)
Nervous system disorder		
Dizziness	55 (3.0)	59 (3.2)
Headache	56 (3.1)	59 (3.2)
Respiratory, thoracic and mediastinal disorders		
Cough	54 (3.0)	61 (3.3)
Dyspnoea	47 (2.6)	59 (3.2)
Vascular disorders		
Hypertension	104 (5.7)	104 (5.7)

Source: Table 14.3.1.2

Reviewer Comment: As shown in the table above, common adverse events were $\geq 3\%$ for inclisiran and greater than placebo would be appropriate to list in Section 6.1 of the inclisiran label. This would include injection site reactions, arthralgia and bronchitis.

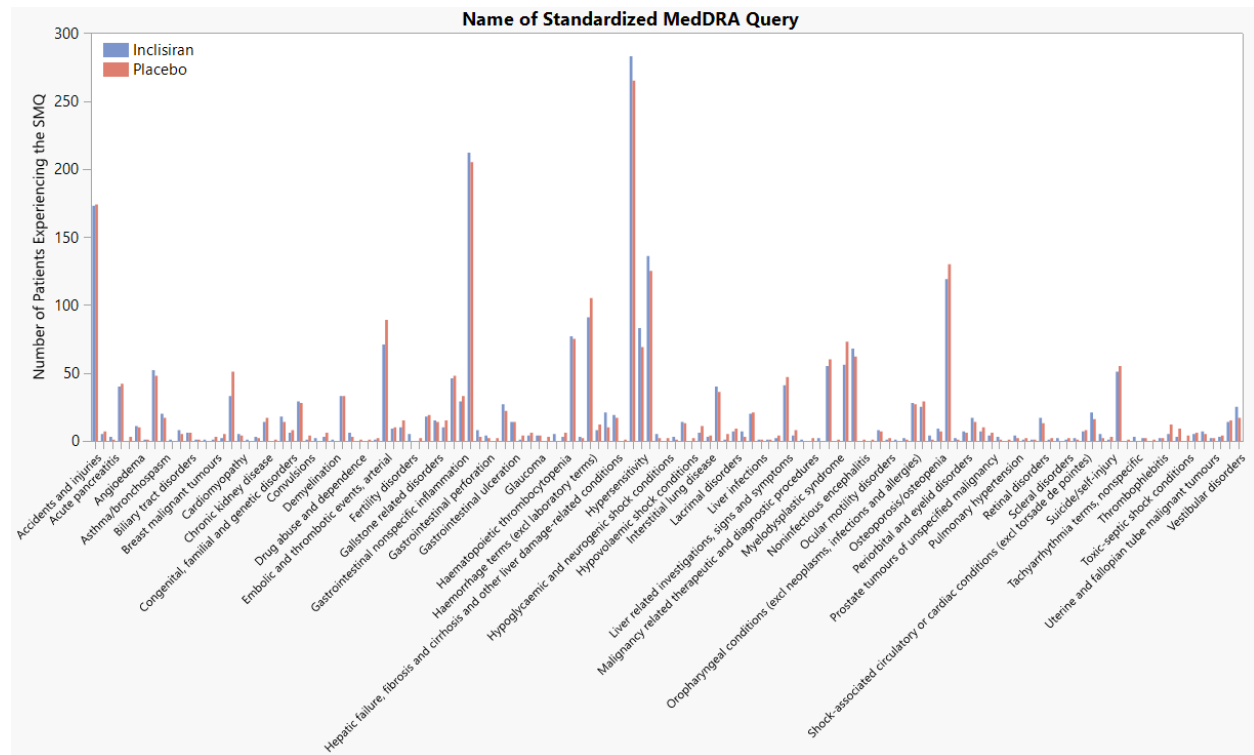
This reviewer conducted a search with the following standard MedDRA SMQs, narrow query with the Safety Pool using the following terms:

Accidents and injuries; Acute central respiratory depression; Acute pancreatitis; Acute renal failure; Agranulocytosis; Anaphylactic reaction; Angioedema; Anticholinergic syndrome; Arthritis; Asthma/bronchospasm;

Biliary disorders; Breast neoplasms, malignant and unspecified; Cardiac arrhythmias; Cardiac failure; Cardiomyopathy; Cerebrovascular disorders; Chronic kidney disease; Congenital, familial and genetic disorders; Conjunctival disorders; Convulsions; Corneal disorders; Dementia; Demyelination; Depression and suicide/self-injury; Drug abuse, dependence and withdrawal; Dyslipidaemia; Embolic and thrombotic events; Eosinophilic pneumonia; Extrapyrimal syndrome; Extravasation events (injections, infusions and implants); Fertility disorders; Gastrointestinal nonspecific inflammation and dysfunctional conditions; Gastrointestinal perforation, ulceration, haemorrhage or obstruction; Generalised convulsive seizures following immunization; Glaucoma; Guillain-Barre syndrome; Haematopoietic cypenias; Haemodynamic oedema, effusions and fluid overload; Haemolytic disorders; Haemorrhages; Hearing and vestibular disorders; Hepatic disorders; Hostility/aggression; Hyperglycaemia/new onset diabetes mellitus; Hypersensitivity; Hypertension; Hyponatraemia/SIADH; Hypotonic-hyporesponsive episode; Interstitial lung disease; Ischaemic colitis; Ischaemic heart disease; Lacrimal disorders; Lactic acidosis; Lens disorders; Lipodystrophy; Malignancies; Malignant lymphomas; Myelodysplastic syndrome; Neuroleptic malignant syndrome; Noninfectious diarrhea; Noninfectious encephalitis; Noninfectious encephalopathy/delirium; Noninfectious meningitis; Ocular infections; Ocular motility disorders; Optic nerve disorders; Oropharyngeal disorders; Osteonecrosis; Osteoporosis/osteopenia; Periorbital and eyelid disorders; Peripheral neuropathy; Pregnancy and neonatal topics; Premalignant disorders; Prostate neoplasms, malignant and unspecified; Pseudomembranous colitis; Psychosis and psychotic disorders; Pulmonary hypertension; Renovascular disorders; Retinal disorders; Retroperitoneal fibrosis; Rhabdomyolysis/myopathy; Scleral disorders; Severe cutaneous adverse reactions; Shock; Skin neoplasms, malignant and unspecified; Systemic lupus erythematosus; Taste and smell disorders; Thrombophlebitis; Thyroid dysfunction; Torsade de pointes/QT prolongation; Tumour lysis syndrome; Uterine and fallopian tube neoplasms, malignant and unspecified; Vasculitis

The following graph was generated using these MedDRA SMOs:

Figure 24. MedDRA SMQ Analysis



Source: Reviewer created with ISS ADAE dataset and JMP Clinical

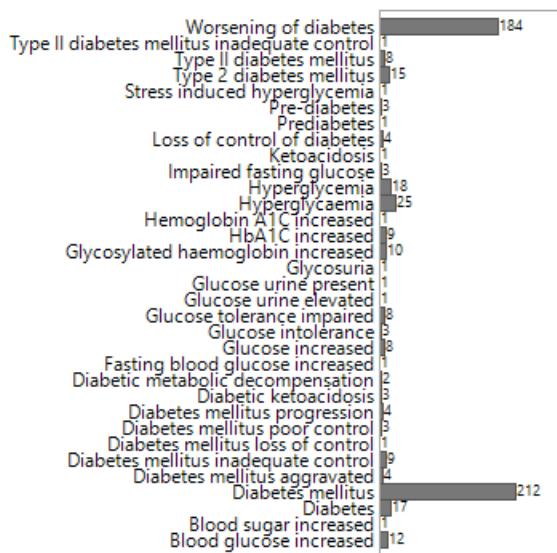
The top four SMQs more frequently reported in inclisiran patients than placebo were as follows:

1. Hyperglycemia SMQ- 290/1833 patients on inclisiran vs. 278/1822 patients on placebo
2. Gastrointestinal SMQ-222/1833 patients on inclisiran vs 211/1822 patients on placebo
3. Hypertension SMQ -136/1833 patients on inclisiran vs. 125/1822 patients on placebo
4. Hypersensitivity SMQ- 94/1833 patients on inclisiran vs. 83/1822 patients on placebo

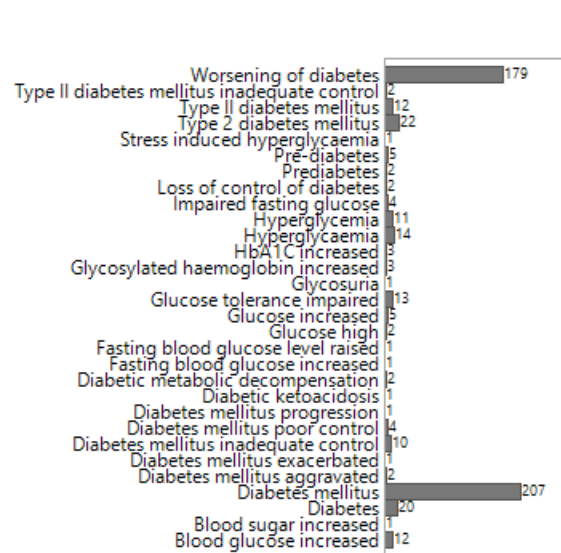
The following figures show the lower level terms and the preferred terms that mapped to the MedDRA SMQs.

Figure 25. MedDRA Hyperglycemia SMQ, Safety Pool

Inclisiran- Hyperglycemia, SMQ, Narrow



Placebo-Hyperglycemia SMQ, Narrow



Source: Reviewer created with ISS ADAE dataset and JMP Clinical 7.1. Includes both Preferred terms and Lower Level terms.

Reviewer Comment: Adverse reactions related to Hyperglycemia SMQ were reported at a similar rate between the two treatment arms, approximately 15.8% on inclisiran vs. 15.3% on placebo. See section on new onset diabetes in Adverse Reactions of Special Interest for further analysis.

Figure 26. MedDRA Gastrointestinal Nonspecific symptoms and therapeutic procedures SMQ, Safety Pool

Inclisiran-Gastro NOS and Therapeutic SMQ Placebo-Gastro NOS and Therapeutic SMQ

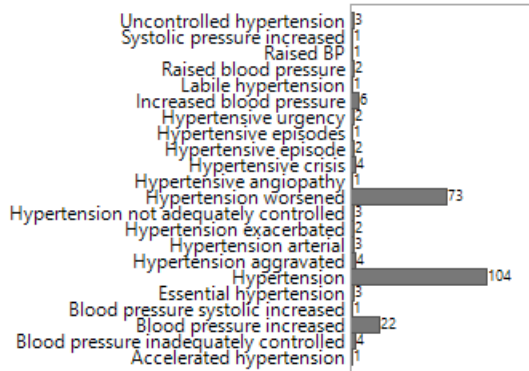


Source: Reviewer created with ISS ADAE dataset and JMP Clinical 7.1. Includes both Preferred terms and Lower Level terms.

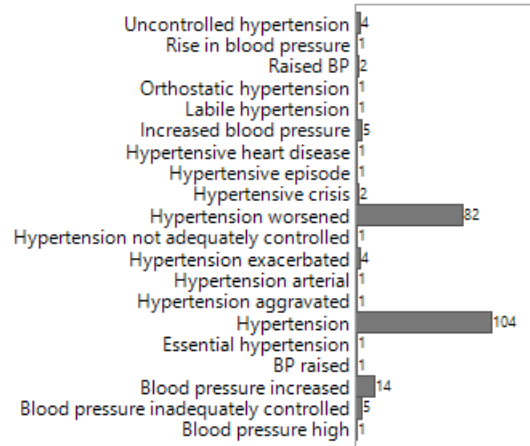
Reviewer Comment: Adverse reactions related to Gastrointestinal nonspecific symptoms SMQ were reported approximately <1% greater on inclisiran than placebo

Figure 27. MedDRA Hypertension SMQ, Safety Pool

Inclisiran – Hypertension SMQ



Placebo- Hypertension SMQ



Source: Reviewer created with ISS ADAE dataset and JMP Clinical 7.1. Includes both Preferred terms and Lower Level terms.

Reviewer Comment: Eight more patients on inclisiran reported “Blood pressure increased” than on placebo. However, 9 more patients on placebo reported “Hypertension worsened” on placebo than on inclisiran. Furthermore, analysis of blood pressure data do not indicate a higher frequency of worsening blood pressure with inclisiran.

Figure 28. MedDRA Hypersensitivity SMQ, Safety Pool

Inclisiran- Hypersensitivity SMO

Placebo-Hypersensitivity- SMO



Source: Reviewer created with ISS ADAE dataset and JMP Clinical 7.1 Includes both Preferred terms and Lower Level terms.

Reviewer Comment: Injection site rash, injection site hypersensitivity, and injection site allergic reaction are all reported with inclisiran compared to none on placebo. Injection site reaction is recommended for labeling. Other allergic/hypersensitivity reactions seem to occur in inclisiran with the same frequency as placebo. Please see section on Adverse Events of Special Interest for further analysis of hypersensitivity and injection site reactions.

8.4.6. Laboratory Findings

Liver, muscle, and glycemc parameters are presented and discussed in other sections of this

safety review. The incidence of patients with other abnormal laboratory values are described in this section.

The following table summarizes the potentially clinically significant abnormal values with hematology laboratory tests.

Table 88. Incidence of Potentially Clinically Significant Tests in Hematology Parameters, ORION 9, 10, and 11

ORION-9	Placebo N=240 n (%)	Inclisiran N=241 n (%)
Subjects with at least one Hematology PCS Lab Value	0 (0.0)	1 (0.4)
Hematocrit (%)		
≤0.8xLLN	0 (0.0)	0 (0.0)
Hemoglobin (g/dL)		
≤10	0 (0.0)	1 (0.4)
Leukocytes (10 ⁹ /L)		
≤2.8	0 (0.0)	0 (0.0)
≥16	0 (0.0)	0 (0.0)
Platelets (10 ⁹ /L)		
≤75	0 (0.0)	0 (0.0)
≥700	0 (0.0)	0 (0.0)
ORION-10	Placebo N=778 n (%)	Inclisiran n=781 n (%)
Subjects with at least one Hematology PCS Lab Value	32 (4.1)	23 (2.9)
Hematocrit (%)		
≤0.8xLLN	17 (2.2)	9 (1.2)
Hemoglobin (g/dL)		
≤10	23 (3.0)	13 (1.7)
Leukocytes (10 ⁹ /L)		
≤2.8	2 (0.3)	2 (0.3)
≥16	2 (0.3)	4 (0.5)
Platelets (10 ⁹ /L)		
≤75	0 (0.0)	1 (0.0)
≥700	0 (0.0)	0 (0.0)
ORION-11	Placebo N= 804 n (%)	Inclisiran N=811 n (%)
Subjects with at least one Hematology PCS Lab Value	6 (0.7)	16 (2.0)
Hematocrit (%)		
≤0.8xLLN	4 (0.5)	7 (0.9)

ORION-9	Placebo N=240 n (%)	Inclisiran N=241 n (%)
Subjects with at least one Hematology PCS Lab Value	0 (0.0)	1 (0.4)
Hemoglobin (g/dL)		
≤10	1 (0.1)	9 (1.1)
Leukocytes (10 ⁹ /L)		
≤2.8	0 (0.0)	3 (0.4)
≥16	2 (0.2)	3 (0.4)
Platelets (10 ⁹ /L)		
≤75	1 (0.1)	0 (0.0)
≥700	0 (0.0)	0 (0.0)

Source: ORION-9: Table 14.3.5.1.2.1; ORION-10: Table 14.3.5.1.2.2; ORION-11: Table 14.3.5.1.2.1

Reviewer Comment: There were no consistent trends of imbalances or trends in hematologic parameters. For the parameter hemoglobin ≤10g/dL, there were 24/1822 (1.3%) placebo-treated patients and 23/1833 (1.3%) inclisiran treated patients for the three phase 3 trials combined; i.e. the incidence was the similar in both treatment arms overall, with inconsistent trends (higher in placebo in ORION-10, higher with inclisiran in ORION-11, no difference in ORION-9) across the three trials. All other potentially clinically significant hematology parameters were similar between treatment arms in all 3 trials.

The following tables summarize shifts from Baseline to a maximum change post-Baseline for laboratory tests for the Safety Pool (all three Phase 3 studies pooled).

Table 89. Shift from Baseline to Maximum Change Post-Baseline in Albumin (g/dL), Safety Pool

Parameter	Treatment	Baseline	Post-Baseline*			Total
			< 1xLLN	Normal	>1xULN	
Albumin (g/dL)	Placebo	<1xLLN	4 (0.2)	7 (0.4)	0 (0.0)	11 (0.6)
		Normal	10 (0.6)	1671 (98.7)	1 (0.1)	1682 (99.4)
		>1xULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Total	14 (0.8)	1678 (99.1)	1 (0.1)	1693 (100.0)
	Inclisiran	<1xLLN	1 (0.1)	6 (0.3)	0 (0.0)	7 (0.4)
		Normal	7 (0.4)	1705 (99.1)	1 (0.1)	1713 (99.5)
		>1xULN	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
		Total	8 (0.5)	1712 (99.5)	1 (0.1)	1721 (100.0)

Source: Response to information request, submitted on May 06, 2020

Table 90. Shift from Baseline to Maximum Change Post-Baseline in Blood Urea Nitrogen (mg/dL), Safety Pool

Parameter	Treatment	Baseline	Post-Baseline*			Total
			< 1xLLN	Normal	>1xULN	
Blood Urea Nitrogen (mg/dL)	Placebo	<1xLLN	0 (0.0)	2 (0.1)	0 (0.0)	2 (0.1)
		Normal	0 (0.0)	1266 (74.8)	184 (10.9)	1450 (85.6)
		>1xULN	0 (0.0)	103 (6.1)	138 (8.2)	241 (14.2)
		Total	0 (0.0)	1371 (81.0)	322 (19.0)	1693 (100.0)
	Inclisiran	<1xLLN	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
		Normal	1 (0.1)	1280 (74.4)	168 (9.8)	1449 (84.2)
		>1xULN	0 (0.0)	113 (6.6)	158 (9.2)	271 (15.7)
		Total	1 (0.1)	1394 (81.0)	326 (18.9)	1721 (100.0)

Source: Response to information request, submitted on May 06, 2020.

Table 91. Shift from Baseline to Maximum Change Post-Baseline in Glucose (mg/dL), Safety Pool

Parameter	Treatment	Baseline	Post-Baseline*			Total
			< 1xLLN	Normal	>1xULN	
Glucose (mg/dL)	Placebo	<1xLLN	0 (0.0)	2 (0.1)	3 (0.2)	5 (0.3)
		Normal	3 (0.2)	912 (50.6)	355 (19.7)	1270 (70.4)
		>1xULN	7 (0.4)	188 (10.4)	333 (18.5)	528 (29.3)
		Total	10 (0.6)	1102 (61.1)	691 (38.3)	1803 (100.0)
	Inclisiran	<1xLLN	0 (0.0)	1 (0.1)	3 (0.2)	4 (0.2)
		Normal	3 (0.2)	848 (46.7)	426 (23.5)	1277 (70.4)
		>1xULN	10 (0.6)	169 (9.3)	354 (19.5)	533 (29.4)
		Total	13 (0.7)	1018 (56.1)	783 (43.2)	1814 (100.0)

Source: Response to information request, submitted on May 06, 2020.

Table 92. Shift from Baseline to Maximum Change Post Baseline in Potassium (mmol/L), Safety Pool

Parameter	Treatment	Baseline	Post-Baseline*			Total
			< 1xLLN	Normal	>1xULN	
Potassium (mmol/L)	Placebo	<1xLLN	3 (0.2)	8 (0.5)	0 (0.0)	11 (0.7)
		Normal	13 (0.8)	1555 (93.2)	49 (2.9)	1617 (96.9)
		>1xULN	0 (0.0)	31 (1.9)	10 (0.6)	41 (2.5)
		Total	16 (1.0)	1594 (95.5)	59 (3.5)	1669 (100.0)
	Inclisiran	<1xLLN	2 (0.1)	10 (0.6)	0 (0.0)	12 (0.7)
		Normal	10 (0.6)	1580 (94.0)	40 (2.4)	1630 (97.0)
		>1xULN	0 (0.0)	32 (1.9)	6 (0.4)	38 (2.3)
		Total	12 (0.7)	1622 (96.5)	46 (2.7)	1680 (100.0)

Source: Response to information request, submitted on May 06, 2020.

Table 93. Shift from Baseline to Maximum Change Post Baseline in Sodium (mmol/L), Safety Pool

Parameter	Treatment	Baseline	Post-Baseline*			Total
			< 1xLLN	Normal	>1xULN	
Sodium (mmol/L)	Placebo	<1xLLN	11 (0.6)	16 (0.9)	1 (0.1)	28 (1.7)
		Normal	23 (1.4)	1588 (93.8)	25 (1.5)	1636 (96.6)
		>1xULN	1 (0.1)	22 (1.3)	6 (0.4)	29 (1.7)
		Total	35 (2.1)	1626 (96.0)	32 (1.9)	1693 (100.0)
	Inclisiran	<1xLLN	6 (0.3)	21 (1.2)	0 (0.0)	27 (1.6)
		Normal	19 (1.1)	1601 (93.0)	53 (3.1)	1673 (97.2)
		>1xULN	0 (0.0)	17 (1.0)	4 (0.2)	21 (1.2)
		Total	25 (1.5)	1639 (95.2)	57 (3.3)	1721 (100.0)

Source: Response to information request, submitted on May 06, 2020.

Reviewer Comment: Shifts of maximal change in various laboratory parameters show that the majority of inclisiran treated patients who were normal at Baseline had a maximal change from Baseline that was also within the normal range. The incidence of maximum change with inclisiran for laboratory parameters was similar to placebo. There were no laboratory changes of concern in patients treated with inclisiran as compared to those treated with placebo.

8.4.7. Vital Signs

Vital sign measurements included heart rate and blood pressure. The following two tables show change in heart rate and blood pressure from Baseline between inclisiran and placebo treatment groups.

Table 94. Shift from Baseline in Systolic BP and Diastolic BP at the End of Study, Safety Pool

Change from Baseline in SBP (mmHg)	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
<=-20	203 (11.1)	191 (10.4)
> -20 to <=-10	311 (17.1)	272 (14.8)
> -10 to <= -5	181 (9.9)	210 (11.5)
>=-5 to < +5	382 (21.0)	396 (21.6)
>=+5 to <+10	197 (10.8)	183 (10.0)
>=+10 to <+20	237 (13.0)	269 (14.7)
>= +20	176 (9.7)	197 (10.7)
Missing	135 (7.4)	115 (6.3)
Change from Baseline in DBP (mmHg)		
<=-10	298 (16.4)	301 (16.4)
>-10 to <=-5	303 (16.6)	286 (15.6)
>-5 to <=-3	138 (7.6)	116 (6.3)

> -3 to < +3	370 (20.3)	400 (21.8)
>=+3 to <5	115 (6.3)	118 (6.4)
>=+5 to <+10	237 (13.0)	218 (11.9)
>=+10	226 (12.4)	279 (15.2)
Missing	135 (7.4)	115 (6.3)

Source: Table 14.3.5.6

Reviewer Comment: There were no consistent differences or trends in blood pressure between inclisiran and placebo treatment groups.

Table 95. Change from Baseline to End of Study in Heart Rate, Safety Pool

Change from Baseline in heart rate (beats/min)	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
<=-20	53 (2.9)	54 (2.9)
> -20 to <=-10	220 (12.1)	179 (9.8)
> -10 to < +10	1199 (65.8)	1242 (67.8)
>=+10 to < +20	168 (9.2)	188 (10.3)
>= +20	47 (2.6)	55 (3.0)
Missing	135 (7.4)	115 (6.3)

Source: Response to Information Request, 5/6/20

Reviewer Comment: There were no clinically meaningful differences in heart rate between inclisiran and placebo treatment groups.

8.4.8. Electrocardiograms (ECGs)

A 12-lead ECG was conducted at Randomization and End of Study visit. A small number of study patients who did not come in for a final on-site visit (4 patients in ORION-9, 23 patients in ORION-10, 34 patients in ORION-11) did not have ECG. Cardiac evaluation in these study patients for adverse events (AEs) or change from baseline was not be available due to no ECG assessment.

The percentage of patients with abnormal ECG findings reported as AEs was summarized by treatment in the following table.

Table 96. ECG Abnormalities Reported as Treatment Emergent Adverse Events by Treatment Arm, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)
Cardiac arrhythmias (HLGT)	103 (5.7)	103 (5.6)
Cardiac conduction disorders (HLT)	14 (0.8)	18 (1.0)
Atrioventricular block	1 (0.1)	6 (0.3)
Atrioventricular block complete	0 (0.0)	2 (0.1)
Atrioventricular block first degree	3 (0.2)	4 (0.2)
Atrioventricular block second degree	4 (0.2)	1 (0.1)
Bifascicular block	0 (0.0)	1 (0.1)
Bundle branch block left	6 (0.3)	2 (0.1)
Bundle branch block right	1 (0.1)	1 (0.1)
Conduction disorder	0 (0.0)	1 (0.1)
Defect conduction intraventricular	1 (0.1)	0 (0.0)
Rate and rhythm disorders NEC (HLT)	26 (1.4)	25 (1.4)
Supraventricular arrhythmias (HLT)	58 (3.2)	58 (3.2)
Arrhythmia supraventricular	1 (0.1)	0 (0.0)
Atrial fibrillation	42 (2.3)	38 (2.1)
Atrial flutter	4 (0.2)	6 (0.3)
Atrial tachycardia	0 (0.0)	2 (0.1)
Sinus arrhythmia	0 (0.)	1 (0.1)
Sinus bradycardia	2 (0.1)	5 (0.3)
Sinus node dysfunction	3 (0.2)	1 (0.1)
Sinus tachycardia	3 (0.2)	2 (0.1)
Supraventricular extrasystoles	5 (0.3)	2 (0.1)
Supraventricular tachycardia	4 (0.2)	4 (0.2)
Ventricular arrhythmias and cardiac arrest (HLT)	16 (0.9)	19 (1.0)
ECG investigations (HLT)	5 (0.3)	1 (0.1)
Electrocardiogram T wave inversion	0 (0.0)	1 (0.1)
Electrocardiogram abnormal	4 (0.2)	0 (0.0)
QRS axis abnormal	1 (0.1)	0 (0.0)

Source: Table 14.3.1.3.3; HLGT=High Level Group Term; HLT=High Level Term

Reviewer Comment: The incidence of patients with ECG abnormalities reported as adverse events was similar in the two treatment arms.

8.4.9. QT

The QT Consultation team determined that there was no significant QTc prolongation effect for

inclisiran.

The effect of inclisiran was evaluated in a thorough QT study (Study # ORION-12), a phase 1, randomized, double-blind, double-dummy, placebo- and positive-controlled, 3-way crossover study in healthy subjects. The highest dose evaluated was 900 mg single dose (administered as 3 subcutaneous injections), which covers the worst-case exposure scenario. The data were analyzed using the by-time analysis as the primary analysis, which did not suggest that inclisiran is associated with significant QTc prolonging effect. The study included moxifloxacin as a positive control and assay sensitivity was established using by time analysis. The findings of this analysis were further supported by the available nonclinical data and exposure response analysis.

Below are proposed edits to the label submitted to SDN001 ([link](#)) from the IRT. Our changes are highlighted (**addition**, ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 3 times the maximum recommended dose, inclisiran does not prolong the QT interval to any clinically relevant extent.

(b) (4)

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

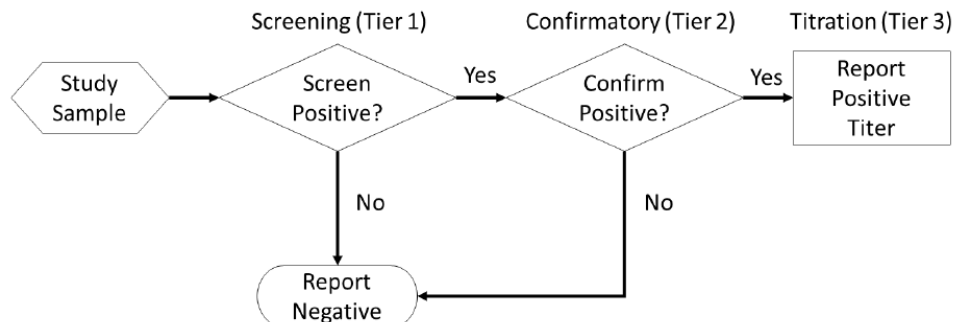
8.4.10. Immunogenicity

Anti-Drug Antibody positivity

According to the applicant, in nonclinical studies, there were incidences of the development of anti-drug antibody (ADA), but they were generally low titer responses in a small number of animals and were not dose related. There was no association between the presence of ADA and changes in either systemic drug exposure or PCSK9 levels in repeat-dose studies in monkeys. Additionally, inclisiran did not stimulate pro-inflammatory cytokines in mice or monkeys or activate complement in monkeys. Please see the pharmacology/toxicology review for the Agency’s assessment of ADA in nonclinical studies.

In the Phase 3 clinical program, samples for ADA assessment were collected for all patients at all study visits including at Baseline (prior to injection). However, ADA samples collected at Baseline, Day 30, Day 150, Day 330, and Day 510 visits were *analyzed* in the screening assay for inclisiran treated patients only. If an inclisiran treated patient had a positive sample in the screening assay, stored samples from that patient for all other time points were also analyzed in the screening assay in order to provide a complete time course of the ADA profile for that patient. Each positive sample in the screening assay was subsequently analyzed in the confirmatory assay, and if positive in the confirmatory assay then the sample was analyzed in the titration assay to determine the ADA titer.

Figure 29. Diagram of Anti-Drug Antibody Hierarchical Testing



The number and percent of inclisiran treated patients in the Safety Pool with a confirmed positive ADA sample at Baseline (prior to injection) and those who developed a confirmed post-Baseline ADA response are shown in the following table.

Table 97. Frequency of Patients with Confirmed Positive ADA by Visit, Safety Pool

Visit	Subjects on Inclisiran (N=1833) n/m (%)
Baseline (Prior to Injection)	33/1827 (1.8)
Any of Day 30, 150, 330, and 510	90/1820 (4.9)
Day 30	43/1816 (2.4)
Day 150	28/1773 (1.6)
Day 330	31/1736 (1.8)
Day 510	22/1691 (1.3)

Source: Applicant response to Information Request, 9/2/20. n: number of subjects with confirmed ADA responses
 m: number of subjects with sample data collected at each visit (used as the denominator)

Reviewer Comment: The detection of anti-inclisiran binding antibodies in the confirmatory assay occurred at a low frequency in the phase 3 trials (ORION 9, 10, and 11). Furthermore, titers of

ADA samples positive in the confirmatory assay were low (50 – 800).

This reviewer sent a request to the applicant to submit the number and percent of patients who had persistent ADA response. ‘Persistent’ ADA response was defined as any confirmed positive ADA at the subject’s last sample obtained up to Day 510. ‘Transient’ ADA was defined as confirmed positive ADA at any time point during the study but negative at their last sample obtained up to Day 510.

Table 98: Type of Anti-Drug Antibody Response, Safety Pool

ADA Response	Patients on Inclisiran N=1833 n/m (%)
Persistent	24/1830 (1.3)
Transient	66/1830 (3.6)
No response	1740/1830 (95.1)

Source: Applicant response to Information Request, 9/2/20. m: number of subjects with any ADA sample data collected and analyzed (used as the denominator).

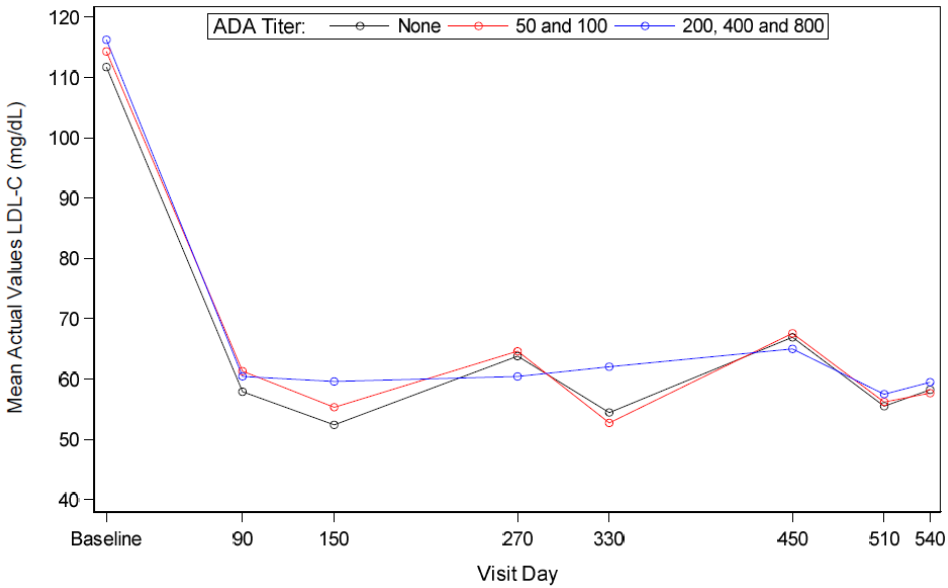
Note: ‘Persistent’ ADA response is defined as any confirmed positive ADA at the subject’s last sample obtained up to Day 510.

‘Transient’ ADA is defined as confirmed positive ADA at any time point during the study but negative at their last sample obtained up to Day 510.

Reviewer Comment: Of those 90 patients who had positive ADA response at any time point, including Baseline, the majority (66) had a transient response.

An information request was sent to the applicant to evaluate LDL-C, PCSK9 level, and neutralizing antibody titer over time, according to ADA titer levels in patients on inclisiran. In response, the applicant submitted the following figures of the observed LDL-C and PCSK9 level. The following figure shows the observed LDL-C level during the trial in patients with and without ADA, divided into three groups according to titer level. There were approximately 1740 patients with no confirmed positive ADA (black line in the figure below), 49 subjects with confirmed post-baseline positive ADA with a maximum titer level of 50 and 100 (red line in the figure below), and 41 subjects with a confirmed post-baseline positive ADA with a maximum titer level of 200, 400, and 800 (blue line in the figure below).

Figure 30: Mean LDL-C (mg/dL) by Visit and Maximum Post-Baseline ADA Titer, Safety Pool

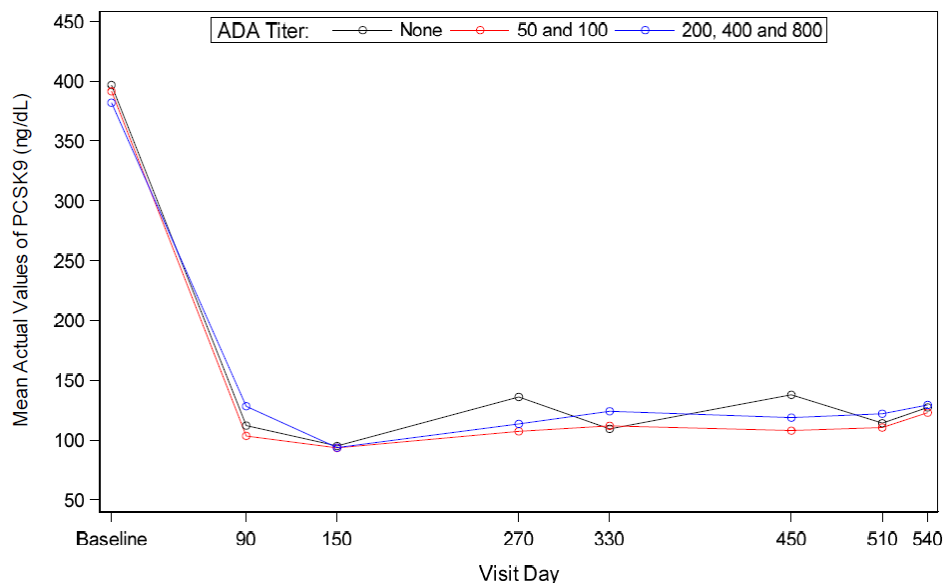


Source: Response to Information Request, April 27, 2020

Reviewer Comment: The number of patients with very low (titer of 50 and 100) and low ADA (titer of 200, 400 and 800) was small, approximately 49 and 41 patients, respectively. At some time points, there seems to be a slight attenuation of efficacy (about 5 mg/dL) in LDL-C lowering in the group with titer of 200, 400 and 800. However, at other time points, there was no difference between the three groups of patients. Overall, there was no clinically significant difference in LDL-C lowering between the ADA titer groups.

The following figure shows the PCSK9 level during the course of the trial in patients with and without ADA, divided into three groups according to titer level (none, 50 and 100, and 200, 400 and 800).

Figure 31: Mean PCSK9 level (ng/dL) by Visit and Maximum Post-Baseline ADA Titer, Safety Pool



Source: Response to Information Request, April 27, 2020

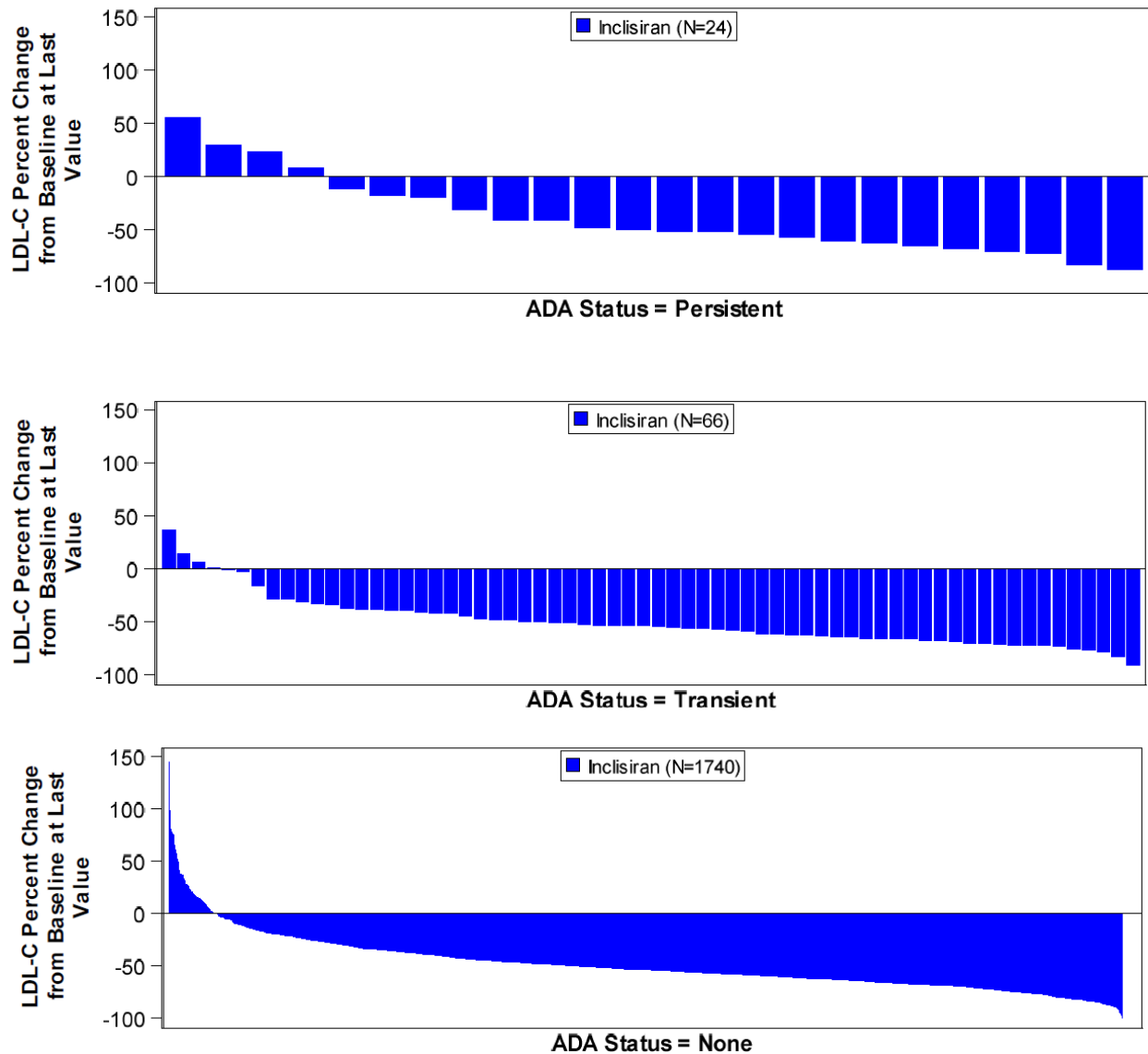
Reviewer Comment: There was no clinically significant difference in PCSK9 levels between patients with or without ADA. Therefore, the presence of ADA by titer level was not associated with a loss of effect for PCSK9 levels.

This reviewer requested the applicant to conduct waterfall plots of percent change from Baseline in LDL-C at Last Value during the treatment period according to persistent or transient ADA status, in patients on inclisiran in the Safety Pool.

- 'Persistent' ADA was defined as any confirmed positive ADA at their last sample obtained up to Day 510.
- 'Transient' ADA was defined as confirmed positive ADA at any time point during the study but negative at their last sample obtained up to Day 510.

The following three figures show waterfall plots of percent change from Baseline in LDL at Last Value by ADA status (persistent, transient, or no ADA).

Figure 32: Waterfall Plots of Percent Change from Baseline in LDL-C at Last Value by ADA Status



Source: Response to Information Request, April 27, 2020

Reviewer Comment: The pattern of individual patient responses between patients with no confirmed positive ADA, transient confirmed ADA and persistent confirmed ADA appears similar.

The applicant submitted individual patient profiles of patients who were ADA positive. This reviewer examined all treatment emergent AEs of ADA positive patients. No systemic allergic reactions, and no signs or symptoms suggestive of systemic allergic reactions were seen in ADA positive subjects. Five patients who were positive for ADA also had injection site reactions.

The OPO/OBP team (refer to review by Dr. Takahasi, in DARRTS dated 8/14/20; Reference ID: 4656320) reviewed the immunogenicity assay validation report for ELISA method for the detection of anti-inclisiran-reactive IgG/IgM antibodies in human serum. All the validation parameters were appropriately evaluated except for deficiencies where two separately prepared unpurified positive controls were used in the assay validation. The OBP team recommends that the assay sensitivity and all other assay validation parameters of the ELISA method for the detection of anti-inclisiran-reactive IgG/IgM antibodies in human serum except the cut-points using an affinity-purified anti-inclisiran antibody positive control should be re-determined to ensure the assay is a sensitive, specific, and selective assay to measure ADA responses. All existing clinical samples should be re-analyzed using the appropriately validated assay. The OBP team recommends approval with possible PMC as described above.

8.5. Analysis of Submission-Specific Safety Issues

Most submission specific safety issues are discussed under Section 8.4, Significant Adverse Events. Theoretical risks associated with low LDL-C, but not specifically identified in this submission as adverse events of special interest include cerebrovascular hemorrhage, primary adrenal insufficiency, primary gonadal insufficiency, and fat-soluble vitamin related disorders are explored in this section.

8.5.1. Cerebrovascular hemorrhage

The following table summarizes the number and percent of patients with AEs that mapped to the MedDRA SMQ “cerebrovascular hemorrhage”.

Table 99. Number (%) of Patients with Treatment Emergent Adverse Events, MedDRA SMQ Cerebrovascular Hemorrhage

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Cerebrovascular hemorrhage	12 (0.7)	8 (0.4)	20 (0.5)
Cerebrovascular accident	3 (0.2)	4 (0.2)	7 (0.2)
Cerebrovascular disorder	1 (0.1)	2 (0.1)	3 (0.1)
Cerebral haemorrhage	0	1 (0.1)	1 (0.0)
Subdural haematoma	4 (0.2)	1 (0.1)	5 (0.1)
Haemorrhagic stroke	1 (0.1)	0	1 (0.0)
Spinal subdural haematoma	1 (0.1)	0	1 (0.0)
Subarachnoid haemorrhage	1 (0.1)	0	1 (0.0)
Subdural haemorrhage	1 (0.1)	0	1 (0.0)

Source: Response to Information Request, July 14, 2020. Cerebrovascular hemorrhage is searched using

“Haemorrhagic central nervous system vascular conditions (SMQ)”.

Reviewer Comment: The incidence of AEs that mapped to the SMQ cerebrovascular hemorrhage was 0.4% on inclisiran and 0.7% on placebo. There does not appear to be a signal for cerebrovascular hemorrhage for inclisiran based on AE reporting.

8.5.2. Primary adrenal insufficiency

The sponsor conducted the analysis for adverse events related to primary adrenal insufficiency with a search for terms under the High Level Term: “Adrenal Cortical Hypofunctions”. No adverse events were found with this search in either treatment arm.

8.5.3. Primary gonadal insufficiency

The sponsor conducted the analysis for adverse events related to primary gonadal insufficiency with a search for terms under the High Level Term: “Endocrine Abnormalities of Gonadal Function NEC”. There was one patient in inclisiran arm with hypogonadism.

8.5.4. Fat soluble vitamin related disorders

As there are no SMQ for fat-soluble vitamin deficiency, the applicant developed a list of relevant PTs related to vitamin deficiencies:

“conjunctival deposit, night blindness, vitamin a, vitamin a abnormal, vitamin a decreased, vitamin a deficiency, vitamin a deficiency eye disorder, vitamin a deficiency related conjunctival disorder, vitamin a deficiency related corneal disorder, xerophthalmia, hyperparathyroidism secondary, hypocalcaemia, hypophosphataemia, myopathy, osteomalacia, pathological fracture, tetany, vitamin d, vitamin d abnormal, vitamin d decreased, vitamin d deficiency, vitamin e, vitamin e decreased, vitamin e deficiency, international normalised ratio, international normalised ratio abnormal, international normalised ratio fluctuation, international normalised ratio increased, prothrombin time, prothrombin time abnormal, prothrombin time prolonged, prothrombin time ratio, prothrombin time ratio abnormal, prothrombin time ratio increased, vitamin k, vitamin k decreased, vitamin k deficiency, abdominal wall haematoma, adrenal haematoma, aortic intramural haematoma, application site haematoma, arteriovenous fistula site haematoma, arteriovenous graft site haematoma, auricular haematoma, blood urine, blood urine present, breast haematoma, broad ligament haematoma, catheter site haematoma, cephalhaematoma, cerebellar haematoma, cerebral haematoma, cervix haematoma uterine, choroidal haematoma, colonic haematoma, ecchymosis, extradural haematoma, gingival bleeding, haematoma, haematoma evacuation, haematoma infection, haematuria, hepatic haematoma, implant site haematoma, incision site haematoma, infusion site haematoma, injection site haematoma, intestinal haematoma, intra-abdominal haematoma, intracerebral haematoma evacuation, intracranial haematoma, lip haematoma, mediastinal haematoma, melaena, ovarian haematoma, paranasal sinus haematoma, pelvic haematoma, pelvic haematoma obstetric, perineal haematoma, periorbital haematoma, perirenal haematoma, peritoneal haematoma, pharyngeal haematoma, post procedural haematoma, pulmonary haematoma, renal haematoma, retroperitoneal haematoma retroplacental haematoma, scrotal haematoma, spinal cord haematoma, splenic haematoma, spontaneous haematoma, subcutaneous haematoma, subdural haematoma, subdural haematoma evacuation, subgaleal haematoma, tongue haematoma, traumatic haematoma, umbilical haematoma, uterine haematoma, vaccination site haematoma, vaginal haematoma, vessel puncture site haematoma, vulval haematoma, vulval haematoma evacuation, hypovitaminosis, multi-vitamin deficiency”

The following table summarizes the number and percent of patients with AEs that mapped to these terms as specified in the table.

Table 100. Number (%) of Patients with Fat-Soluble Vitamin Related Disorders, Safety Pool

	Placebo N=1822 n (%)	Inclisiran N=1833 n (%)	Total N=3655 n (%)
Fat soluble vitamin related disorders	54 (3.0)	49 (2.7)	103 (2.8)
Vitamin D deficiency	10 (0.5)	14 (0.8)	24 (0.7)
Haematuria	16 (0.9)	9 (0.5)	25 (0.7)
Injection site haematoma	1 (0.1)	4 (0.2)	5 (0.1)
International normalized ration increased	7 (0.4)	4 (0.2)	11 (0.3)
Blood urine present	1 (0.1)	3 (0.2)	4 (0.1)
Haematoma	7 (0.4)	3 (0.2)	10 (0.3)
Subcutaneous haematoma	0	3 (0.2)	3 (0.1)
Ecchymosis	3 (0.2)	2 (0.1)	5 (0.1)
Hypocalcaemia	1 (0.1)	2 (0.1)	3 (0.1)
Myopathy	0	2 (0.1)	2 (0.1)
Hypophosphataemia	1 (0.1)	1 (0.1)	2 (0.1)
Melaena	1 (0.1)	1 (0.1)	2 (0.1)
Subdural haematoma	4 (0.2)	1 (0.1)	5 (0.1)
Tetany	0	1 (0.1)	1 (0.0)
Traumatic haematoma	1 (0.1)	1 (0.1)	2 (0.1)
Vitamin D decreased	0	1 (0.1)	1 (0.0)
Breast haematoma	1 (0.1)	0	1 (0.0)
Hyperparathyroidism secondary	1 (0.1)	0	1 (0.0)
Prothrombin time prolonged	2 (0.1)	0	2 (0.1)

Source: Response to Information Request, July 14, 2020.

Reviewer Comment: The incidence of AEs that mapped to the terms related to fat soluble deficiencies was 2.7% on inclisiran and 3.0% on placebo. Although, this evaluation was limited by the lack of prospective testing for fat-soluble vitamin deficiencies, there does not seem to be a signal in this area with inclisiran based on AE reporting.

8.6. Safety Analyses by Demographic Subgroups

The following table summarizes treatment emergent adverse events by sex, age, and race.

Table 101. Treatment Emergent Adverse Events by Sex, Age and Race, Safety Pool

	Placebo N= 1822	Inclisiran N= 1833
Subjects with at least one TEAE by various subgroups		
Sex		
Male	952/1240 (76.8)	949/1228 (77.3)
Female	457/582 (78.5)	481/605 (79.5)
Age		
<65	656/ 882 (74.4)	651/852 (76.4)
>=65	753/940 (80.1)	779/981 (79.4)
<75	1193/1570 (76.0)	1235/1594 (77.5)
>=75	216/252 (85.7)	195/239 (81.6)
Race		
White	1332/1704 (78.2)	1312/1669 (78.6)
Black or African American	65/101 (64.4)	93/131 (71.0)
Other	12/17 (70.6)	25/33 (75.8)

Source: Tables 14.3.1.2.1; 14.3.1.2.2; 14.3.1.2.6,14.3.1.2.3

Reviewer Comment: There were no significant differences in treatment emergent adverse events with inclisiran when compared to placebo when examined by sex, age (<65, ≥65), or race. However, as expected, older patients who were ≥75 years of age reported a higher incidence of TEAEs on both treatment arms as compared to younger patients. The interpretation of the small imbalances for the subgroups of African American and Other races is limited by small sample size and small number of events.

Serious treatment emergent adverse events were also evaluated by sex, age, and race.

Table 102: Serious Adverse Events by Sex, Age and Race, Safety Pool

	Placebo N=1822	Inclisiran N=1833
Subjects with at least one SAE by various subgroups		
Sex		
Male	287/1240 (23.1)	267/1228 (21.7)
Female	132/582 (22.7)	107/605 (17.7)
Age		
<65	179/882 (20.3)	142/852 (16.7)
>=65	240/940 (25.5)	232/981 (23.6)
< 75	333/1570 (21.2)	305/1594 (19.1)
>=75	86/252 (34.1)	69/239 (28.9)
Race		
White	394/ 1704 (23.1)	342/1669 (20.5)
Black or African American	22/101 (21.8)	28/131 (21.4)
Other	3/17 (17.6)	4/33 (12.1)

Source: Table 14.3.1.4.1; 14.3.1.4.2; 14.3.1.4.6, 14.3.1.4.3.

Reviewer Comment: There were no clinically significant differences in serious adverse events with inclisiran when compared to placebo when examined by sex, age, or race. Serious adverse events were generally numerically lower in the inclisiran arm across subgroups.

8.7. Specific Safety Studies/Clinical Trials

Phase 2 trials

The Phase 2 trials included ORION-1 (dose-finding study), ORION-2 (pilot study in HoFH), and ORION-3 (extension study of ORION-1).

ORION-1

ORION-1 was a Phase 2, placebo-controlled, double-blind, randomized study to compare the effect of inclisiran administered as either a single-dose (200 mg, 300 mg, or 500 mg) or as 2

doses (100 mg, 200 mg, or 300 mg) on Day 1 and Day 90 in approximately 501 patients ≥ 18 years of age with high CV risk and elevated LDL-C. Most patients in the single-dose and double-dose parts of the study were male (67.2% and 62.9%, respectively), White (92.0% and 94.4%, respectively), and on statins (80.6% and 81.5%, respectively). Overall, 93.3% and 94.0% of patients completed the single-dose and double-dose parts of the study.

There were two deaths in the study. One death occurred in the 500 mg inclisiran single dose group due to an MI. This subject had a history of previous MI and CHD. A second death occurred in the 200 mg inclisiran double dose group due to sepsis and pneumonia following surgery for aortic disease.

In the single-dose groups, 3 (4.6%) placebo-treated patients, and 30 (16.1%) of the inclisiran-treated patients experienced SAEs. All SAEs were reported as single cases with the exception of MI (2 patients in the 500 mg inclisiran group and one patient in the 200 mg inclisiran group), angina pectoris (one in each of the 3 inclisiran groups), prostate cancer (2 subjects in the 200 mg inclisiran group), and syncope (1 patient in each the 200 mg and 300 mg inclisiran groups).

In the double-dose groups, overall, 7 (11.3%) placebo-treated patients, and 30 (16.3%) inclisiran-treated patients experienced SAEs. All SAEs were reported as single cases, with the exception for acute MI (2 patients in the 300 mg inclisiran group), atrial tachycardia (one patient in the 100 mg and 200 mg groups), CHD (2 patients in the 300 mg inclisiran group), post procedural complication (2 patients in the 200 mg inclisiran group), and syncope (one patient in the 200 mg and 300 mg inclisiran dose groups, and 1 placebo-treated patient).

No patient withdrew from treatment due to an AE in the single-dose groups. In the double-dose groups, one placebo-treated subject and one subject in the inclisiran 100 mg group withdrew due to an AE.

For the double-dose group, a total of 2 subjects discontinued study drug through Day 360 due to AEs:

- A placebo-treated patient had an AE of Herpes zoster that resulted in discontinuation of study drug prior to Day 90.
- A patient in the 100 mg inclisiran group had AEs of influenza-like illness, nasopharyngitis, back pain and myalgia that resulted in discontinuation of study drug prior to Day 90.

In the placebo-treated and inclisiran-treated patients, TEAEs occurred in 83.9% and 78.5% of subjects in the single-dose group, respectively, and 83.7% and 82.3% of subjects in the double dose group, respectively.

In the single-dose group, the most common AEs in the inclisiran-treated patients ($\geq 5\%$ of subjects who received inclisiran) were nasopharyngitis (26 patients [14.9%]), influenza, back pain and arthralgia (12 patients [6.5%], each), upper respiratory tract infection, and myalgia (11 patients [5.9%] each), and angina pectoris (10 patients [5.4%]).

In the double-dose group, the most common AEs in the inclisiran-treated patients ($\geq 5\%$ of patients who received inclisiran) were nasopharyngitis (24 patients [13.9%]), myalgia (17 patients [9.2%]), diarrhea (15 patients [8.2%]), influenza (12 patients [6.5%]), headache and back pain (11 patients [6.0%] each), and arthralgia (10 patients [5.5%]).

ORION-3

ORION-3 is an ongoing, open-label, multicenter, long-term (4 year) extension in patients who completed ORION-1. The study consists of 2 treatment groups; Group 1 (inclisiran only arm) is receiving inclisiran only and Group 2 (switching arm) received evolocumab for 1 year followed by inclisiran for the remainder of the trial. The applicant included all available data up to Day 630 of the study.

Patients entering the study were not randomly assigned to treatment arms. There were 436 patients from ORION-1 eligible to participate in ORION-3 and 382 (87.6%) patients consented. Of the 382 patients who consented to participate in ORION-3, 290 received inclisiran in ORION-1 and therefore, were assigned to Group 1 (inclisiran only arm) in ORION-3. The remaining 92 consented patients had received placebo in ORION-1 and therefore, were assigned to Group 2 (switching arm) in ORION-3.

In Group 1, there was one death. Patient ID# [REDACTED] ^{(b) (6)} a 78-year-old, White, male died due to ischemic cardiovascular accident. The patient's ischemic cardiovascular accident was subsequent to a traffic accident. This patient had a medical history that included hyperlipidemia, hypertension, peripheral artery disease, prior transient ischemic attack, and right internal carotid artery stenosis.

Overall, 60 (21.1%) Group 1 inclisiran-treated patients experienced a SAE. Treatment emergent SAEs were predominantly CV events typical for patients with dyslipidemia. The majority of SAEs were reported as a single event and there was no specific SAE occurring in more than 3 patients. The SAE occurring in 3 subjects were anemia, angina pectoris, osteoarthritis, prostate cancer, and transient ischemic attack.

Overall, 8 (2.8%) Group 1 inclisiran-treated patients withdrew from treatment due to TEAEs and included an eye contusion, abnormal liver function test, diabetes mellitus, muscle weakness, plasma cell myeloma, tremor, and skin depigmentation.

The most common TEAEs (those occurring in $\geq 2\%$ patients) observed were nasopharyngitis,

influenza, urinary tract infection, and injection site reactions.

In Group 2, there were no deaths reported. Sixteen (17.8%) patients treated with evolocumab for 360 days experienced an SAE. The majority of SAEs were reported as a single event and there was no specific SAE occurring in more than 2 patients. The SAE occurring in 2 patients was hemorrhoidal hemorrhage. After Day 360, 10 (11.5%) patients treated with inclisiran from Day 360 to the data cut-off date experienced a SAE. All SAEs were reported as a single event and there was no specific SAE occurring in more than 1 patient.

One patient (Pt ID# [REDACTED] ^{(b) (6)}) treated with inclisiran from Day 360 to the data cut-off date had a SAE (hepatic enzyme increased) leading to withdrawal from treatment. The patient had hepatitis C and reported recent excessive alcohol consumption.

The most common TEAEs in patients treated with inclisiran from Day 360 to the data cut-off date were similar to TEAEs observed prior to Day 360. These events were hypertension, nasopharyngitis, arthralgia, influenza, and injection site pain.

ORION-2

ORION-2 was a Phase 2, open-label, single-arm, multicenter pilot study to test the efficacy and duration of effect of inclisiran sodium 300 mg in patients with HoFH. Four patients were treated with inclisiran: 3 patients receiving 2 injections and 1 patient received 1 injection.

Three of the 4 patients reported TEAEs [ORION-2 CSR Section 12]. Two patients had 1 TEAE each (unstable angina and acne flare-up). The third patient had several TEAEs, including nasopharyngitis, cystitis, dyspnea, road traffic accident, influenza-like illness, musculoskeletal pain, non-cardiac chest pain, oropharyngeal pain, abdominal pain upper, paresthesia, pain in extremity and limb injury events.

No deaths or TEAEs leading to treatment withdrawal were reported in ORION-2. One SAE was reported (unstable angina) in a 50-year-old White male with a medical history of hyperlipidemia, prior coronary artery bypass graft, and prior percutaneous coronary intervention study.

Reviewer Comments: The overall safety profile for inclisiran in the Phase 2 studies was generally similar to that seen in the Phase 3 studies.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No additional safety studies.

8.8.2. Human Reproduction and Pregnancy

Three inclisiran exposed pregnancies occurred during the Phase 3 trials, with treatment discontinued in all cases. One pregnancy went to term with delivery of a full-term healthy baby, one pregnancy was voluntarily terminated before 12 weeks, and 1 pregnancy was ongoing.

The Division of Pediatric and Maternal Health (DPMH) completed a consult review regarding proposed labeling to comply with the Pregnancy and Lactation labeling rule³⁴. The following summarizes DPMH's conclusions.

Pregnancy

- In animal reproduction studies, no evidence of teratogenic effects was observed in rats and rabbits. There was no evidence of embryoletality, fetotoxicity, or genotoxicity.
- In humans, there are sparse data on use of inclisiran in three pregnant women. Therefore, the data are insufficient to determine a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes.
- Current recommendation is that women who are planning pregnancy or who become pregnant should stop cholesterol reducing drugs therapy. Alternatively, the prescriber should consider the ongoing therapeutic needs of the individual patient.
- DPMH recommends a PMR to conduct a worldwide, single-arm, observational safety study of pregnant women exposed to inclisiran. It is a descriptive study that actively collects prospective and retrospective data in women exposed to inclisiran during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant in all exposed pregnancies of which you become aware. Infant outcomes should be assessed through at least the first year of life. The single arm pregnancy study will collect information for a minimum of 10 years from the date of market approval for inclisiran.
- Contact information for the pregnancy safety study should be added to labeling once the protocol is finalized and enrollment begins.

Lactation

- It is not known if the drug is present in human milk. There is no information on the effects of the drug on the breastfed infant, or the effects of the drug on the milk production.
- Oligonucleotide-based products typically have poor oral bioavailability; therefore, it is considered unlikely that low milk exposure levels will adversely impact neonatal development.

³⁴ Refer to the review by Christos Mastroyannis, M.D., Medical Officer, Maternal Health, Division of Pediatric and Maternal Health (DPMH); submitted to DARRTS on 10/19/2020; Reference ID: 4687201.

- As animal study findings suggest that inclisiran is not systemically absorbed by rat pups, DPMH does not recommend a PMR clinical lactation study. DPMH recommends the standard risk-benefit statement is added to subsection 8.2 of inclisiran labeling.

(b) (4)

8.8.3. Pediatrics and Assessment of Effects on Growth

Safety and efficacy in pediatric patients have not been established.

As a new active ingredient, this application is subject to Pediatric Research Equity Act requirements. Under the iPSP agreed to by the Division and Applicant, the Applicant was granted a partial waiver for pediatric patients, birth to <18 years of age, with non-familial hypercholesterolemia with clinical atherosclerotic cardiovascular disease (b) (4) and elevated LDL-C, birth to <8 years of age (or <6 years of age and on apheresis) with elevated cholesterol with HeFH. The rationale for the partial waiver is based upon "studies would be impossible or highly impractical"

The applicant will be issued postmarketing requirements (PMRs) to conduct phase 3 efficacy and safety studies evaluating inclisiran in patients with HeFH ages 8 years (or ≥6 years of age and on apheresis) to less than 18 years.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Nonclinical studies indicate that inclisiran does not have central nervous system activity and has no abuse potential.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

Inclisiran was well-tolerated, and the most important safety issue was injection site reactions in the Phase 3 trials. Inclisiran will be administered by a health care provider in the clinic setting, as it was during the phase 3 trials. No additional risk management activities in the postmarket setting, e.g., REMS, are anticipated.

8.9.3. Additional Safety Issues From Other Disciplines

Safety issues from other disciplines are discussed in relevant sections throughout this review.

8.10. Integrated Assessment of Safety

Inclisiran was generally well-tolerated, and the most important safety issue was injection site reactions in the Phase 3 trials. Preferred terms that mapped to the High-Level Term “Injection site reactions” occurred in 8.2% of patients on inclisiran as compared to 1.8% on placebo. Injection site reactions occurred on average in approximately 3.5 days after inclisiran administration and lasted on average 5.6 days, and most were mild to moderate in severity. Four inclisiran treated patients withdrew from treatment due to non-serious adverse reactions at the injection site compared to none on placebo.

Overall hypersensitivity reactions occurred in 7.4% on inclisiran and 7.5% of placebo treated patients. The incidence of some individual preferred terms under hypersensitivity disorders was greater with inclisiran, while others were greater in placebo. There was no discernable pattern.

Other frequently reported AEs that occurred with inclisiran greater than placebo were: arthralgia 5.0% on inclisiran and 4.0% on placebo; urinary tract infections 4.4% on inclisiran and 3.6% on placebo; diarrhea 3.9% on inclisiran and 3.5% on placebo and bronchitis 4.3% on inclisiran and 2.7% on placebo.

A total of 54 deaths occurred during the 18 months of the 3 Phase 3 trials. The incidence of deaths on inclisiran and placebo was exactly the same at 27 deaths or 1.5% on each treatment arm. The most common cause of death was in cardiac disorders and occurred at 0.7% on inclisiran as compared to 0.5% on placebo. Inclisiran did not appear to increase the risk of death from any particular cause.

Overall, slightly fewer patients on inclisiran (20%) than on placebo (23%) reported at least one serious adverse event. Most serious adverse events were balanced between groups.

The incidence of adverse events leading to withdrawal of study treatment was 2.5% (45/1833) on inclisiran and 1.9% (35/1822) on placebo. The most common preferred term as a reason for withdrawal of treatment was injection site reaction (n=4, 0.2%) as compared to 0 patients on placebo. Other adverse reactions that led to withdrawal of treatment were in Neoplasms disorders and Musculoskeletal disorders with a difference of approximately 0.2% greater incidence on inclisiran than placebo.

Adverse Events of Special Interest

ALT elevations/hepatic events: A similar proportion of patients in each treatment group experienced elevations in ALT or AST >3X ULN. There were no elevations greater than 10X ULN

on inclisiran. There were no Hy's Law cases. The incidence of hepatic disorders SMQ was 3.8% on inclisiran and 4.2% on placebo.

Renal function: TEAEs associated with renal safety identified by the predefined SMQ search by PTs were balanced between the placebo-treated and inclisiran-treated subjects at 3.3%. There were no clinically significant differences between inclisiran and placebo for change from Baseline in serum creatinine. Shift tables for change in eGFR show similar incidence between inclisiran and placebo and no clinically significant difference between the two treatment arms.

Myopathy: The incidence of elevations in creatinine kinase was similar between the two treatment arms. Preferred terms such as arthralgia and pain in extremity were reported at slightly higher incidence than placebo.

New Onset Diabetes: Overall, the number of subjects who did not have diabetes at baseline and who developed new onset diabetes was 8.0% on inclisiran and 8.1% on placebo. In the subset of patients with no diabetes at Baseline and fasting glucose < 100 mg/dL, approximately 4.3% of patients on inclisiran and 4.7% of patients on placebo developed new onset diabetes. In the subset of patients with impaired fasting glucose, 14.6% on inclisiran and 13.8% on placebo had new onset diabetes.

Overall mean change from Baseline in glucose was +3.2 mg/dL on inclisiran and +1.0 mg/dL on placebo while the mean change HbA1c was +0.1% on inclisiran and 0% on placebo. These differences were driven by changes among patients who had diabetes or impaired fasting glucose.

The similar incidence of new onset diabetes in patients who did not have diabetes at baseline and the magnitude of the changes in glucose and HbA1c in patients with diabetes/impaired fasting glucose subsets suggests that any blood glucose effects of inclisiran are likely to be small.

Neurocognitive Events: Using a number of MedDRA High level group terms, the number of patients with adverse events related to neurocognitive events was 0.7% on inclisiran and 1.0% on placebo. I also conducted a customized query, which resulted in a similar incidence of adverse events between treatment arms. Inclisiran did not appear to increase the risk of neurocognitive events.

Psychiatric Events: Psychiatric related disorders did not occur more frequently in the inclisiran group (n=83, 4.5%) vs. the placebo group (n=86, 4.7%). I conducted FDA customized queries for anxiety and depression and found a similar incidence between groups. Inclisiran did not appear to increase the risk of psychiatric events.

Immunogenicity: In the Phase 3 trials, anti-drug antibodies were analyzed for the patients on inclisiran and not on placebo. The incidence of patients with confirmed positive ADA at any visit was 4.9% and titers were generally low. Approximately 3.6% of patients had transient ADA, while 1.3% had persistent ADA. ADA presence by titer levels did not appear to be associated with loss of LDL-C lowering efficacy or PCSK9 levels.

Theoretical risks associated with low LDL-C such as cerebrovascular hemorrhage, primary adrenal insufficiency, primary gonadal insufficiency, and fat-soluble vitamin related disorders were investigated. There did not appear to be a signal for these events based on adverse events reporting.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not held for this application.

10. Labeling Recommendations

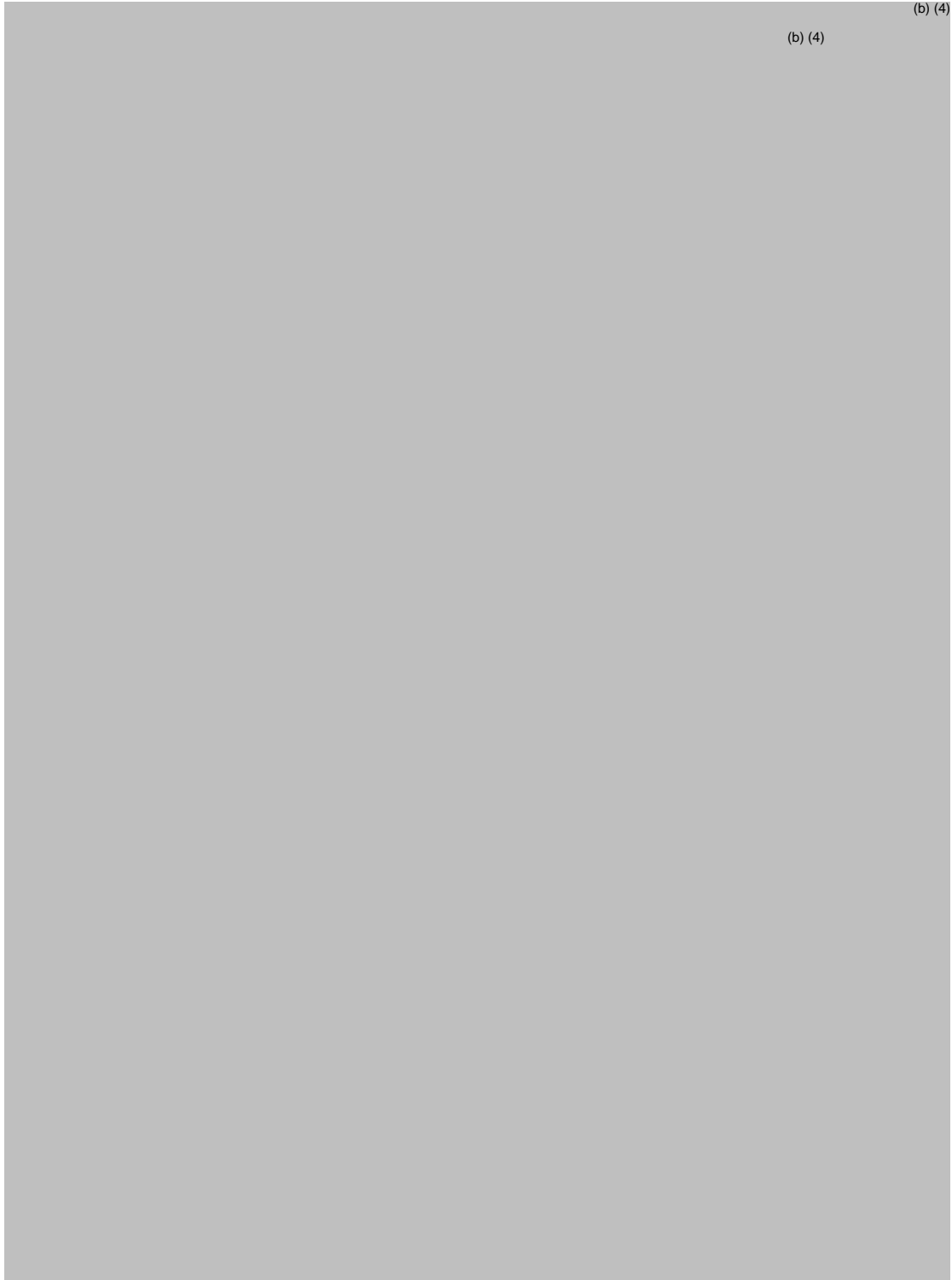
10.1. Prescription Drug Labeling

The following major labeling decisions were conveyed to the Applicant:

- Restriction of the indicated population to patients on maximally tolerated statin with HeFH or clinical atherosclerotic cardiovascular disease, who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- Add a Limitations of Use: The effect of INCLISIRAN on cardiovascular morbidity and mortality has not been determined.
- Section 14: Clinical Studies

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11. Risk Evaluation and Mitigation Strategies (REMS)

A risk management plan, Elements to Assure Safe Use (ETASU) and the Implementation System are not proposed by the applicant and are not recommended by the clinical team.

12. Postmarketing Requirements and Commitments

Postmarketing Requirements

1. Conduct an efficacy and safety study evaluating inclisiran in patients with heterozygous familial hypercholesterolemia (HeFH) aged 12 years to less than 18 years. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 12-month, multicenter efficacy and safety study in 150 patients (randomized 2:1 to inclisiran and placebo), followed by a 12-month open-label extension with all patients assigned to inclisiran in pediatric patients aged 12 years to less than 18 years with HeFH on maximally tolerated, stable lipid-modifying therapy with LDL-C $\geq$ 130 mg/dL.
Draft Protocol Submission: No later than 1st half 2020
Final Protocol Submission: No later than 2nd half 2020
Study Completion: June 2023
Final Report Submission: December 2023
2. Conduct an efficacy and safety study evaluating inclisiran in patients with heterozygous familial hypercholesterolemia (HeFH) aged 6-7 if on plasma apheresis and 8 to <12 years of age. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 12-month, multicenter efficacy and safety study (b) (4), followed by a 12-month open-label extension with all patients assigned to inclisiran in pediatric patients aged 6-7 (if on plasma apheresis or meet eligibility criteria for lipid apheresis from their home country) and 8 years to less than 12 years with HeFH on maximally tolerated, stable lipid-modifying therapy (b) (4).
Draft Protocol Submission: No later than 1st half 2021
Final Protocol Submission: December 2021
Study Completion: June 2024
Final Report Submission: December 2024

Postmarketing Commitments

3. Complete the ongoing randomized, double-blind, placebo-controlled, parallel group, multicenter trial in approximately 15,000 patients (randomized 1:1 to inclisiran and placebo) designed to assess the effects of inclisiran on the occurrence of major

cardiovascular events. The trial will include evaluation of the effects of inclisiran on the occurrence of injection site reactions, hypersensitivity reactions, antibody formation and new onset diabetes mellitus.

13. Appendices

None.

13.1. References

References are listed as footnotes throughout this document.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number):

1. Protocol Number: ALN-PCSSC-01: A phase 1, randomized, single-blind, placebo-controlled, single ascending dose and multiple dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneously administered ALN-PCSSC in subjects with elevated low-density lipoprotein cholesterol (2 principal investigators)
2. Protocol Number: ORION-1 (MDCO-PCS-15-01): A placebo-controlled, double-blind, randomized trial to compare the effect of different doses of ALN-PCSSC given as single or multiple subcutaneous injections in subjects with high cardiovascular risk and elevated low-density lipoprotein cholesterol (LDL-C) (54 principal investigators)
3. Protocol Number: ORION-2 (MDCO-PCS-16-02): An open-label, single-arm, multicenter pilot study to evaluate safety, tolerability, and efficacy of ALN-PCSSC in subjects with homozygous familial hypercholesterolemia (3 principal investigators)
4. Protocol Number: ORION-3 (MDCO-PCS-16-01): An open label, active comparator extension trial to assess the effect of long term dosing of inclisiran and evolocumab given as subcutaneous injections in subjects with high cardiovascular risk and elevated LDL-C (55 principal investigators)
5. Protocol Number: ORION-6 (MDCO-PCS-18-02): A single-dose, open-label, parallel-group study to assess the pharmacokinetics, pharmacodynamics, and safety of inclisiran in subjects with hepatic impairment compared to subjects with normal hepatic function (1 principal investigator)
6. Protocol Number: ORION-7 (MDCO-PCS-16-03): A single-dose, open-label, parallel-group study to assess the pharmacokinetics of inclisiran in subjects with renal impairment compared to subjects with normal renal function (2 principal investigators)

7. ORION-9 (MDCO-PCS-17-03): A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with heterozygous familial hypercholesterolemia (HeFH) and elevated low-density lipoprotein cholesterol (LDL-C) (57 principal investigators)
8. Protocol Number: ORION-10 (MDCO-PCS-17-04): A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) and elevated low-density lipoprotein cholesterol (LDL-C) (154 principal investigators)
9. Protocol Number: ORION-11 (MDCO-PCS-17-08): A placebo-controlled, double-blind, randomized trial to evaluate the effect of 300 mg of inclisiran sodium given as subcutaneous injections in subjects with atherosclerotic cardiovascular disease (ASCVD) or ASCVD-risk equivalents and elevated low-density lipoprotein cholesterol (LDL-C) (84 principal investigators)
10. Protocol Number: ORION-12 (MDCO-PCS-17-09): A double-blind, randomized, placebo-controlled-parallel-design study with an open-label positive-control, to assess the electrocardiographic effects of inclisiran in healthy subjects (1 principal investigator)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of principal investigators identified: <u>413</u>		
Number of investigators who are applicant employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)

Clinical Review
E. Craig and I. Chowdhury
NDA 214012
LEQVIO™ (inclisiran)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EILEEN M CRAIG
11/04/2020 05:00:05 PM

IFFAT N CHOWDHURY
11/05/2020 10:05:49 AM

JOHN M SHARRETTS
11/06/2020 10:53:38 AM
I concur with the findings and conclusions in this review.