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APPLICATION NUMBER:

214012Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Summary Review for Regulatory Action

Date	(electronic stamp)
From	Laura Higginbotham, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Summary Review
NDA/BLA # and Supplement #	NDA 214012, Class 2 Complete Response Resubmission
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	July 1, 2021
PDUFA Goal Date	January 1, 2022
Proprietary Name	LEQVIO
Established or Proper Name	Inclisiran (formerly ALN-PCSSC)
Dosage Form(s)	Subcutaneous injection
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)
Action or Recommended Action:	Approval
Approved/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)

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Eileen Craig, M.D.
Pharmacology Toxicology Review	Elena Braithwaite, Ph.D.
OPQ Review – Technical Lead	Muthukumar Ramaswamy, Ph.D.
OPQ Review – Drug Substance	Daniel Jansen, Ph.D.
OPQ Review – Drug Product	Muthukumar Ramaswamy, Ph.D.
OPQ Review – Manufacturing	Vidya Pai, Ph.D.
Microbiology Review	Avital Shimanovich, Ph.D. / Erika Pfeiler, Ph.D.
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OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OBP=Office of Biotechnology Products
 DPMH=Division of Pediatrics and Maternal Health
 OPDP=Office of Prescription Drug Promotion
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRM=Division of Risk Management
 DEPI=Division of Epidemiology I

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Inclisiran is a double-stranded small interfering RNA (siRNA) that reduces LDL-C by inhibiting production of PCSK9. The Applicant, Novartis Pharmaceuticals Corporation, submitted a New Drug Application (NDA) for inclisiran in December 2019, supported primarily by three randomized, double-blind, placebo-controlled, 18-month trials in patients with heterozygous familial hypercholesterolemia (HeFH), established atherosclerotic cardiovascular disease (ASCVD), and ASCVD risk equivalents who were on maximally tolerated statin therapy. In December 2020, the application received a complete response action because of deficiencies at the (b) (4) manufacturing site. Aside from the manufacturing deficiencies, the application would have been approvable according to Dr. John Sharretts' Division Director Summary Review. With this Class 2 Complete Response resubmission, the Applicant submitted updated manufacturing site information and a safety update from ongoing inclisiran trials.

Hyperlipidemia is a modifiable risk factor for the development of atherosclerosis and ASCVD, which continues to be a leading cause of death and disability worldwide. The goal of lipid-lowering therapy is to reduce cardiovascular (CV) risk. Current treatment guidelines for CV risk reduction through lipid management emphasize 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 who require additional LDL-C reduction.

Consistent with current published guidelines, recent approvals of LDL-lowering agents have limited the initial indication to the two higher CV risk populations (HeFH and ASCVD), as an adjunct to diet and maximally tolerated statin therapy in those patients who require additional lowering of LDL-C. Given the availability of therapies with proven outcomes benefit for lower-risk populations, the indications have been broadened only after the successful completion of a cardiovascular outcomes trial (CVOT) demonstrating clinical benefit.

The phase 3 trials submitted with the initial application, ORION-9, ORION-10, and ORION-11, evaluated the effects of inclisiran on LDL-C levels and other lipid parameters. The study populations included patients with relevant comorbidities, such as increased age, diabetes, hypertension, and renal impairment.

The data demonstrated a clinically meaningful, statistically significant, and durable LDL-C reduction with inclisiran. Consistent effects were observed across various subpopulations defined by demographics and baseline disease characteristics.

The submitted data represent substantial evidence of effectiveness consisting of adequate and well-controlled trials to support an indication for LDL-C lowering in high-risk populations (ASCVD and HeFH). The primary endpoint and observed treatment effect were clinically meaningful, and the analyses were statistically robust. The indication could potentially be expanded to lower risk populations in the future if the ongoing CVOT demonstrates favorable effects on clinical endpoints.

The benefit-risk consideration is favorable, as safety issues associated with inclisiran are monitorable and generally reversible. Injection-site reactions (ISRs) were the most notable safety issue in clinical trials submitted with the initial NDA application, occurring in 8.2% of patients in the inclisiran arm and 1.8% on placebo. No ISR was categorized as a serious or severe adverse event (AE). Other AEs that occurred more frequently with inclisiran than placebo included arthralgia, urinary tract infections, diarrhea, and bronchitis. The incidence of anti-drug antibodies (ADA) was low, and there was no meaningful difference in mean changes in LDL-C or PCSK9 or the pattern of individual responses among patients with confirmed positive ADA compared to patients with negative ADA. The Complete Response resubmission included updated safety information from two open-label trials, ORION-3 and ORION-8, and from the placebo-controlled and open-label periods of ORION-5. The safety profile of inclisiran was consistent with that of the initial review, and no new safety concerns were identified.

Reviewers from all review disciplines support approval. As with the initial review cycle, the Office of Biotechnology supports approval but recommends a postmarketing commitment to reassess assay sensitivity for detection of anti-drug antibodies and reanalysis of clinical samples.

In summary, the Applicant submitted data demonstrating substantial evidence of effectiveness to support an indication 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. Weighing the magnitude of inclisiran's LDL-C lowering effects against the relatively small incidence of adverse reactions and their non-serious nature, the benefit-risk consideration is favorable. Safety issues were mostly minor or self-limited and can be addressed in labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the US and worldwide. • Hypercholesterolemia is a major modifiable risk factor for the development of ASCVD, and LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes. <ul style="list-style-type: none"> ○ A meta-analysis of statin trials demonstrated that an absolute reduction of 39 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). • Current treatment guidelines emphasize reducing the risk of ASCVD through lipid lowering, considering individual risk for a CV event. <ul style="list-style-type: none"> ○ Primary prevention: Reduction of the risk for developing ASCVD in patients without established disease ○ Secondary prevention: Reduction of the risk for additional CV events in patients with established ASCVD • 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 monoclonal antibody proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk who may benefit from additional LDL-C reduction. 	<p>LDL-C reduction with therapies targeting upregulation of the LDL-C receptor is the cornerstone of preventive treatment for ASCVD.</p> <p>Statin are considered first-line, standard-of-care therapy for lowering LDL-C with the goal of reducing CV risk.</p> <p>Current guidelines emphasize an individualized approach that considers the risk for a CV event.</p> <p>There is unmet medical need among high-risk patients with HeFH or established ASCVD with elevated LDL-C levels despite maximally tolerated statin therapy, with or without adjunctive therapies, such as ezetimibe or PCSK9 inhibitors.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	<ul style="list-style-type: none"> • High-intensity statins reduce LDL-C by $\geq 50\%$. • Moderate-intensity statins reduce LDL-C by 30% to 49%. • PCSK9 inhibitors lower LDL-C by 45% to 60% and have proven CV benefit, but their use is limited by expense and lack of payer coverage. • Ezetimibe lowers LDL-C by 18% to 20% as monotherapy and 12% to 15% as add-on to moderate- or high-intensity statin. • Bempedoic acid lowers LDL-C by 18 to 19% as an adjunct to maximally tolerated statin but was approved after the most recent guideline update. A CVOT is ongoing. • 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 statin. 	<p>Statin and PCSK9 inhibitors reduce LDL-C and have proven CV outcome benefit.</p> <p>Guidelines recommend additional LDL-C lowering in very-high-risk patients on high-intensity (or maximally tolerated) statin therapy who have persistent LDL-C elevation above targets for their risk category.</p>
Benefit	<ul style="list-style-type: none"> • In patients with HeFH or established ASCVD on maximally tolerated statin therapy, inclisiran lowered LDL-C by 48% to 52% from baseline to Day 510 compared to placebo. • LDL-C lowering is a surrogate endpoint for risk reduction of CVD that has served as the basis for conventional approval of other products. • Changes in secondary endpoints were supportive of the primary endpoint. • The treatment effect was relatively stable over the 18-month trials. • There were no major statistical issues identified in the clinical trials, and the efficacy findings were robust because of the large treatment effect and small amount of missing data. • A cardiovascular outcomes trial to evaluate the benefit of inclisiran as an adjunct to statin therapy is ongoing. 	<p>The clinical trials submitted represent substantial evidence of effectiveness consisting of adequate and well-controlled trials for LDL-C lowering in high-risk populations.</p> <p>The phase 3 trials demonstrated a clinically meaningful, statistically robust, and durable LDL-C reduction with inclisiran in high-risk patients who required additional lowering of LDL-C.</p> <p>Given the 15% relative risk reduction in major adverse cardiovascular events observed with PCSK9 inhibitor monoclonal antibodies, one might expect comparable risk reduction from inclisiran; the absolute risk reduction would be a function of the underlying cardiovascular risk in the population.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none"> • The major safety issue was ISRs, which occurred more frequently with inclisiran (8.2% of patients) than placebo (1.8%). • Other adverse events occurring more frequently in patients assigned to inclisiran included arthralgia, urinary tract infections, diarrhea, and bronchitis. None of these adverse events caused irreversible harm. • The incidence of anti-drug antibodies (ADA) was low, and there was no evidence of reduced efficacy in patients with positive ADA. 	<p>Injection site reactions were mild to moderate in severity. The risk for ISR is monitorable and can be adequately addressed in labeling.</p> <p>Other safety issues may be addressed in labeling and do not alter the overall favorable benefit-risk consideration.</p>

2. Background

Inclisiran (proposed trade name Leqvio) is a double-stranded small interfering ribonucleic acid (siRNA) that inhibits hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9), resulting in decreased circulating low-density lipoprotein cholesterol (LDL-C) levels. Reduction in intrahepatic PCSK9 levels leads to increased recycling and expression of the LDL-C receptor (LDLR) on the hepatocyte cell surface, which in turn increases LDL-C uptake, thus reducing circulating LDL-C.

The proposed product is provided in 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, and then every 6 months.

The Applicant proposes an indication 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.

Analysis of Condition

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease (CVD), the leading cause of death and disability worldwide. Hypercholesterolemia is a major modifiable risk factor for the development of atherosclerosis and CVD.

Many large-scale, randomized cardiovascular outcomes trials (CVOTs) have shown that reducing LDL-C levels with statins reduces the risk of CVD. A meta-analysis¹ of statin trials concluded that lowering LDL-C by 1 mmol/L (39 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 approximately 22%, and that statin regimens using higher doses or more-potent agents – resulting in greater reductions in LDL-C – reduce the risk of vascular events more than less-intensive statin regimens in high-risk patients. More recently, CVOTs of the two approved monoclonal antibody PCSK9 inhibitors, alirocumab² and evolocumab,³ demonstrated that reducing LDL-C levels with these agents led to a reduction in risk of CV events.

Moderate-intensity and high-intensity statins reduce LDL-C by 30% to 49% and $\geq 50\%$, respectively. PCSK9 inhibitors lower LDL-C by an additional 50% to 70%. Ezetimibe lowers LDL-C by 15% to 20%. Other drug categories, such as fibrates or niacin, are not considered mainstays of LDL-C lowering therapy because of mild LDL-lowering ability and clinical trial

¹ 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.

² Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018; 379: 2097-107.

³ 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.

data that show no benefit in reducing CV morbidity or mortality among patients already treated with a statin.

Current treatment guidelines emphasize reducing the risk of atherosclerotic cardiovascular disease (ASCVD) through lipid management, considering an individual 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 risk category. Low-intensity statins are not recommended for any population.

Ezetimibe and 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 may benefit from additional LDL-C reduction.

Recent approvals of novel LDL-lowering therapies, in the absence of outcomes data and in the context of available therapy, have been influenced by the magnitude of LDL-C lowering, mechanism of action, and evidence for off-target toxicity. FDA approved the monoclonal antibody PCSK9 inhibitors in 2015 prior to the completion of their CVOTs, but the initial indications were restricted to a higher CV-risk population, as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CVD, who require additional lowering of LDL-C. The indication was broadened after the successful completion of their CVOTs, which demonstrated reassuring long-term safety data in addition to demonstrating CV benefit.

Brief Regulatory History

The initial inclisiran NDA 21402 was submitted on December 23, 2019. A 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. 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.

After the Complete Response action, the Applicant submitted several Content and Format Package proposals, and FDA provided advice on the proposed content of the safety update and the overall proposed content and format to be included in the Complete Response Resubmission.

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 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. Updated safety data, including all deaths, serious adverse events (SAEs), adverse events (AEs) leading to drug withdrawal, treatment-emergent adverse events (TEAEs), and laboratory data, from three ongoing inclisiran trials are also included in the resubmission.

There is an ongoing randomized, placebo-controlled trial (Study CTSU-MDCO-PCS-17-01) to evaluate the effects of inclisiran on CV outcomes in patients with ASCVD. The trial, also known as HPS-4/TIMI 65/ORION-4 (NCT03705234), is being conducted at approximately 180 clinical sites in the UK and the US and is expected to enroll approximately 15,000 participants aged 55 years or older with atherosclerotic cardiovascular disease randomized to inclisiran sodium 300 mg or matching placebo in a 1:1 ratio for a planned median duration of about 5 years. The estimated primary completion date is December 2024, with results expected by 2025.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends approval. Refer to the OPQ Integrated Quality Assessment authored by the application technical lead, Dr. Muthukumar Ramaswamy, for details. I concur with Dr. Ramaswamy's recommendation.

Inclisiran is an siRNA duplex that contains a 21-nucleotide long sense strand linked to a triantennary acetyl galactosamine (GalNAc) on the 3' end and a 23-nucleotide long anti-sense strand. Modifications at the 2' ribose moiety and a phosphodiester backbone confer stability and protect the siRNA from nucleases. The molecular formula is $C_{529}H_{664}F_{12}N_{176}Na_{43}O_{316}P_{43}S_6$, and the molecular weight of the salt form is 17,284.75 g/mol. Inclisiran sodium is a white to pale white powder that is freely soluble in water.

During the initial NDA review cycle, a Complete Response action was taken because the Office of Process Manufacturing Assessment (OPMA) inspection recommendation was to "withhold approval" due to deficiencies related to the (b) (4) drug product manufacturing facility. There were no outstanding issues related to drug substance, drug product, manufacturing process, and microbiology sections of the original NDA submission. Refer to the OPQ integrated quality assessments dated October 1, 2020 and December 17, 2020 in DARRTS.

In the Complete Response resubmission, there are no major changes to the drug substance, drug product composition, drug product manufacturing process, drug product release and end-of-life specifications, analytical procedure, or drug product primary container closure system. The resubmission contains a minor update to the container closure system that was deemed acceptable by Dr. Ramaswamy. The resubmission also contains a minor update to the drug substance starting material specification that was found adequate by Dr. Daniel Jensen.

The Applicant replaced the drug product manufacturing facility, (b) (4), with Sandoz GmbH facility in Langkampfen, Austria. The Applicant also replaced the drug product analytical testing site used for release and stability from (b) (4) to Sandoz GmbH, Langkampfen, Austria and Sandoz GmbH, Kundl, Austria. The overall manufacturing process remains the same, but minor changes were implemented to adapt the process to equipment available at the new facility. The manufacturing process and process control information included in the resubmission were found acceptable by Dr. Vidya Pai.

Facility compliance information for the drug product and drug substance manufacturing and testing facilities were reviewed by Dr. Vidya Pai. The facility review concluded that the facilities associated with this application are compliant. Thus, the manufacturing inspection recommendation from OPMA for this NDA is approval.

4. Nonclinical Pharmacology/Toxicology

During the initial NDA review cycle, the Pharmacology/Toxicology reviewer, Dr. Elena Braithwaite, concluded that the nonclinical data submitted by the Applicant were adequate, and she recommended approval. Refer to Dr. Braithwaite's review for details. No new nonclinical data were included with the Complete Response resubmission. The nonclinical team continues to recommend approval of inclisiran; see Dr. Calvin Elmore's tertiary review for the Complete Response resubmission in DARRTS. I concur with the recommendation for approval.

5. Clinical Pharmacology

During the initial NDA review cycle, the Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) reviewed the clinical pharmacology data and recommended approval. Refer to Dr. Sang Chung's review for details. No new clinical pharmacology data were included with the Complete Response resubmission; the clinical pharmacology team continues to recommend approval. I concur with the recommendation for approval.

6. Clinical/Statistical-Efficacy

The clinical effectiveness of inclisiran was evaluated in three similarly designed, randomized, double-blind, placebo-controlled trials, ORION-9 (NCT03397121), ORION-10 (NCT03399370), and ORION-11 (NCT3400800). During the initial NDA review cycle, the clinical reviewer, Dr. Eileen Craig, and the statistical reviewer, Dr. Jennifer Clark, both concluded that the submitted data constitute substantial evidence of effectiveness to support approval, and I concur with their recommendations. For details, refer to the original clinical review authored by Dr. Craig and the original statistical review authored by Dr. Clark. No new efficacy data were submitted with the Complete Response resubmission.

7. Safety

During the original NDA review, Dr. Iffat Chowdhury concluded that the identified safety issues did not individually or collectively outweigh the observed efficacy in the intended population. The most notable safety issues were injection-site reactions (ISRs) and small shifts suggesting worsening glycemia (normal to pre-diabetes, pre-diabetes to diabetes) with inclisiran compared to placebo. At the time of the original NDA review, Dr. Chowdhury supported approval, and Dr. John Sharretts, Deputy Director of DDLO, agreed with her recommendation. For details of the original safety evaluation, refer to Dr. Chowdhury's clinical review.

In the Complete Response resubmission, the Applicant submitted a safety update that included new and updated safety information from ongoing open-label trials ORION-3 and ORION-8 and from the recently completed double-blind portion (Part 1) of ORION-5 through a data cutoff date of May 10, 2021. All deaths, treatment-emergent SAEs, AEs leading to drug discontinuation, AEs at the injection site, treatment-emergent AEs, and clinical laboratory values were included. The safety profile of inclisiran in the resubmission remains consistent with that previously identified during review of the initial NDA submission.

Safety Database

The overall safety population included in the safety update, defined as patients who received at least one dose of investigational product, consisted of 3417 patients. ORION-3 and ORION-8 were open-label extension trials of ORION-1 (ASCVD or ASCVD risk equivalents) and

ORION-9/10/11 (ASCVD, ASCVD risk equivalents, HeFH, or HoFH), respectively. ORION-5 was a two-part, 6-month double-blind followed by 18-month open-label period, study in patients with HoFH. The mean treatment exposure across all submitted data was 27 months (ORION-3 mean exposure: 35 to 44 months depending on group; ORION-8: 25 months; ORION-5: 18 to 22 months). Patients were required to be on maximally tolerated statin at baseline in all three trials.

Across ORION-3 and ORION-8, the mean age ranged from 63 to 64 years, 64% to 68% of subjects were male, and 93% were white. In ORION-5 (HoFH), the mean age was 43 years, 61% of subjects were female, and 86% were white. Refer to Dr. Craig's clinical review for details of the population.

In ORION-3, 85% (318/374) of subjects are ongoing, 1% (4/374) completed the study, and 14% (52/374) discontinued the study. The most common reason for discontinuation was withdrawal of consent. Only 8 subjects (2%) discontinued because of an AE.

In ORION-8, 93% (2769/2990) of subjects are ongoing, 0.2% (5/2990) completed the study, and 7% (216/2990) discontinued the study. The most common reasons for discontinuation were death and withdrawal of consent. Only 1% of subjects discontinued because of an AE.

During the double-blind treatment period of ORION-5, 92% (34/37) of inclisiran-treated subjects and 100% (19/19) of placebo-treated subjects completed the study. The most common reason for discontinuation was withdrawal of consent. No subjects discontinued because of an AE.

General Safety Issues

Deaths, Serious Adverse Events, Withdrawals Due to Adverse Events

In the initial NDA submission, the incidence of death was 1.5% (mean treatment exposure of 18 months) in both the inclisiran- and placebo-treated arms. In new safety data submitted with the Complete Response, the incidence of death was 1.6% (6/371; mean treatment exposure of 35 to 44 months) in ORION-3 (ASCVD or ASCVD risk equivalents) and 2.6% (78/2990; mean treatment exposure of 25 months) in ORION-8 (ASCVD, ASCVD risk equivalents, HeFH, or HoFH). No deaths were reported in ORION-5 (HoFH). Although the death incidence in newly submitted open-label data is slightly higher, this is not unexpected given the longer observation time. Additionally, the higher death incidence in ORION-8, which began in April 2019, appears likely related to the ongoing COVID-19 pandemic; a large number of deaths in the *Infections and infestations* MedDRA System Organ Class (SOC), primarily coronavirus infection, were reported (0.5%). The most common cause of death by SOC was *Cardiac disorders* (0.6% of deaths in ORION-8), as expected for a trial of patients with or at high risk for CVD. This finding is also consistent with data from the initial NDA submission, where 0.6% of deaths (0.7% inclisiran-treated vs. 0.5% placebo-treated) were attributable to *Cardiac disorders*. A cardiovascular outcomes trial, which will assess the effect of inclisiran on major adverse cardiovascular events, is ongoing.).

In the initial NDA submission, the percentage of subjects who reported at least one SAE was 20% amongst inclisiran-treated subjects compared to 23% amongst placebo-treated subjects (mean treatment exposure of 18 months). In safety data included in the Complete Response, a comparably high proportion of subjects (33% in ORION-3, 22% in ORION-8, and 20% in

ORION-5) reported at least one SAE over a mean treatment exposure of 27 months, including 5 to 11% in the *Cardiac disorders* SOC. Overall, the SAE incidence in the Complete Response appears similar to that observed in the original NDA review, with the exception of data from ORION-3, which is higher. This is likely due to the prolonged treatment duration in ORION-3 (mean 35 to 44 months) compared to the other open-label trials (ORION-8, mean 25 months; ORION-5, mean 18 to 22 months) and the placebo-controlled trials included in the initial NDA (mean 18 months). SAEs observed in the safety update were similar to those reported in the initial NDA submission and included cardiovascular-related events (coronary artery disease, angina pectoris, transient ischemic attack, angina unstable, atrial fibrillation) that are expected in a population of subjects with ASCVD or ASCVD risk equivalents, as well as other SAEs commonly observed in an older population (including osteoarthritis, cancer, and infections [pneumonia, coronavirus]). In the double-blind, placebo-controlled treatment period of ORION-5, there were no SAE imbalances between inclisiran-treated and placebo-treated subjects.

The incidence of TEAEs leading to withdrawal of study treatment ranged from 1.8% (55/2990; mean treatment exposure of 25 months) in ORION-8 to 4.9% (18/371; mean treatment exposure of 35 to 44 months) in ORION-3. No subjects discontinued due to an adverse event in ORION-5 (HoFH). There was no discernible pattern to the frequently reported reasons for drug discontinuation, as most were reported by one subject. Notable reasons for withdrawal included musculoskeletal-related AEs (muscle strain, muscular weakness, myalgia, restless legs syndrome), hepatic-related AEs (hepatic enzyme increased, liver function test abnormal), malignancy-related AEs (Hodgkin's disease stage IV, plasma cell myeloma, prostate cancer, lung neoplasm malignant), coronavirus infection, cardiovascular-related AEs (coronary artery disease, ischemic stroke), and injection site rash/reaction. With the exception of injection site rash/reaction (0.2% in ORION-8, 0% in ORION-3), these findings are consistent with the enrolled population of older adults, with or at high risk for ASCVD, on maximally tolerated statin therapy. Further, no imbalances in the aforementioned AEs were reported in placebo-controlled data included in the original NDA submission.

In summary, the most frequent causes of death, SAEs, and drug discontinuation in the submitted open-label data were expected for the patient population and did not identify new safety concerns.

Adverse Events of Special Interest

Adverse events of special interest included in the Complete Response safety update were injection-site reactions and laboratory abnormalities. Refer to Dr. Craig's clinical review for details.

Injection site reactions

In open-label data (ORION-3/-8), the percentage of patients with a TEAE by MedDRA High Level Term at the injection site ranged from 4.9% (146/2990) to 13% (49/371). The most frequently reported PTs were *Injection site reaction*, *Injection site erythema*, *Injection site rash*, *Injection site pain*, *Injection site pruritus*, and *Injection site bruising*. Most ISRs were categorized as transient and mild; 14% of subjects in ORION-8 had a moderate ISR. The incidence of ISRs is generally similar to that reported in placebo-controlled data in the original NDA submission (8%); the higher incidence observed in ORION-3 may reflect longer treatment exposure (mean 35 to 44 months) and greater number of injections than that in other

trials.

Laboratory abnormalities

In the original NDA submission, there was no safety signal for hepatic adverse events or laboratory abnormalities. The incidence of hepatic-related TEAEs was similar between inclisiran and placebo (76 placebo vs. 70 inclisiran), whereas elevations in ALT, AST, alkaline phosphatase, and total bilirubin above baseline were similar in the two treatment arms. Trends in elevations above various thresholds were inconsistent, but no inclisiran patients experienced AST or ALT elevations above 10X, while one placebo patient experienced an AST elevation >10X ULN. No cases met the definition of Hy's Law.

In open-label data included in the Complete Response submission, very few subjects experienced AST or ALT elevations in ORION-5/-8 (2 subjects in ORION-5; 0.2% >3X ULN in ORION-8), and there were no imbalances in data from the placebo-controlled period of ORION-5 (0 inclisiran vs. 1 placebo). The incidence of ALT/AST elevations was higher in ORION-3 (1.1% experienced ALT >5X ULN, 1.3% experienced AST >3x ULN), but an association with inclisiran is not corroborated based on placebo-controlled data from phase 3 trials, open-label data from ORION-5/-8, and alternative etiologies in ORION-3 (concomitant medications, including statins).

In the original NDA submission, there was no evidence of myopathy with inclisiran. The incidence of elevations of creatinine kinase to various thresholds was similar between the two treatment arms, and the proportion of patients with at least one TEAE mapped to the SOC of *Musculoskeletal and connective tissue disorders* was similar between arms. There were no SAEs or severe AEs of rhabdomyolysis.

Across the 3 trials included in the Complete Response, 0% to 1.3% of subjects experienced an CK elevation >5X ULN and 0% to 0.3% experienced a CK elevation >10X ULN. Two subjects in ORION-3 experienced a CK elevation >20X ULN. Most elevations were transient, and an association with inclisiran was not supported based on alternative etiologies.

Treatment-Emergent Adverse Events

Table 1 below summarizes adverse events reported in placebo-controlled data, with a mean treatment exposure of 18 months, included in the original NDA submission.

Table 1: Adverse Reactions Occurring in Greater Than or Equal to 3% of Inclisiran-Treated Patients and More Frequently than with Placebo in ORION-9, ORION-10, ORION-11 – Safety Population¹

Adverse Reactions	Placebo (N = 1822) %	LEQVIO (N = 1833) %
Injection site reaction ²	1.8	8.2
Arthralgia	4.0	5.0
Urinary tract infection	3.6	4.4
Diarrhea	3.5	3.9
Bronchitis	2.7	4.3
Pain in extremity	2.6	3.3
Dyspnea	2.6	3.2

¹ Mean treatment exposure=18 months

² Includes related terms such as: injection site pain, erythema and rash

There were no significant differences in the relative incidence of TEAEs or SAEs with inclisiran compared to placebo when examined by sex, age, or race subgroups. The interpretation of AE subgroup data by race was limited by small sample size and small number of events for non-white patients. Refer to Dr. Chowdhury's analyses and discussion in the original clinical review for details.

Table 2 displays adverse events reported in open-label data, with mean treatment exposure of 27 months, included in the Complete Response NDA resubmission.

Table 2: Adverse Reactions Occurring in Inclisiran-Treated Patients in ORION-3, ORION-8, ORION-5 – Safety Population

Adverse Reactions	ORION-3¹ (N = 371) n (%)	ORION-8² (N = 2990) n (%)	ORION-5³ (N = 56) n (%)
Nasopharyngitis	68 (18.3)	71 (2.4)	3 (5.4)
Hypertension	56 (15.9)	133 (4.4)	2 (3.6)
Influenza	46 (12.4)		
Urinary tract infection	44 (11.9)	95 (3.2)	
Back pain	40 (10.8)	92 (3.1)	
Arthralgia	37 (10.0)	140 (4.7)	
Fatigue	31 (8.4)		
Diabetes mellitus	29 (7.8)	180 (6.0)	
Upper respiratory tract infection	29 (7.8)	73 (2.4)	
Pain in extremity	29 (7.8)		
Dizziness	29 (7.8)		
Angina pectoris	27 (7.3)	70 (2.3)	3 (5.4)
Myalgia	27 (7.3)		
Fall	27 (7.3)		
Headache	26 (7.0)		2 (3.6)
Dyspnoea	26 (7.0)		
Osteoarthritis	25 (6.7)	79 (2.6)	
Cough	24 (6.5)		
Nausea	22 (5.9)		
Diarrhoea	21 (5.7)		2 (3.6)
Non-cardiac chest pain	20 (5.4)		
Injection site reaction	19 (5.1)	76 (2.5)	
Influenza like illness	18 (4.9)		
Contusion	18 (4.9)		
Musculoskeletal pain	18 (4.9)		
Muscle spasms	17 (4.6)		

Cataract	17 (4.6)		
Gout	17 (4.6)		
COVID-19 ⁴		121 (4.0)	3 (5.4)
Respiratory tract infection viral			3 (5.4)
Aortic arteriosclerosis			2 (3.6)
Aortic valve stenosis			2 (3.6)
Pyrexia			2 (3.6)
Rhinorrhea			2 (3.6)
Anemia			2 (3.6)
Gastritis			2 (3.6)
Cystitis	11 (3.0)		
Gastroesophageal reflux disease	11 (3.0)		
Tendonitis	8 (2.2)		
Coronary artery disease		60 (2.0)	

1 Occurring in $\geq 5\%$ of subjects; mean treatment exposure=35 to 44 months; population=ASCVD, ASCVD risk equivalents

2 Occurring in $\geq 2\%$ of subjects; mean treatment exposure=25 months; population=ASCVD, ASCVD risk equivalents, HeFH, HoFH

3 Occurring in ≥ 2 subjects; mean treatment exposure=18 to 22 months; population=HoFH

4 Includes COVID-19, corona virus infection

Although TEAEs such as nasopharyngitis, hypertension, influenza, diabetes mellitus, back pain, upper respiratory tract infection, fall, dizziness, myalgia, and fatigue were reported with high frequency in open-label data, an imbalance in these TEAEs was not observed in placebo-controlled phase 3 data submitted with the initial NDA. Some reported AEs are common even outside of clinical trials (e.g., nasopharyngitis, back pain), some AEs are commonly associated with concomitant lipid-lowering therapy (e.g., myalgia), and some AEs are consistent with the enrolled population of older adults. Further, incidence of infections and conditions that present with advancing age (such as hypertension or diabetes mellitus) would be expected to be higher with a longer period of observation. Note that an analysis of vital sign data during the initial NDA review did not identify a signal for elevated blood pressure with inclisiran.

Immunogenicity

In the initial NDA review, the percentage of patients with confirmed ADA was 1.8% at baseline, and 4.9% with at least one confirmed positive at any other time point post-baseline. Among patients with treatment-induced ADA, defined as a positive ADA after initial treatment in a patient without pre-existing ADA, 1.7% were persistent, defined as two or more positive ADA samples separated by 16 weeks or longer or a single positive ADA at the final sampling time point or within 16 weeks of a negative final sample (consistent with definitions proposed by Shankar et al.¹).

¹ Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, et al. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. *AAPS J.* 2014;16(4): 658-673.

In data contained in the Complete Response resubmission, 0% (ORION-5), 1.5% (ORION-8), and 6.2% (ORION-3) of subjects developed treatment-induced ADA, of which 1.1% were persistent (ORION-3; data not available for ORION-8). No subject experienced an associated hypersensitivity event suspected to be related to inclisiran.

Summary of Safety

The safety profile of inclisiran in subjects with ASCVD or HeFH and elevated LDL-C is consistent with that previously identified during review of the initial NDA submission.

Injection-site reactions remained the most notable safety issue, occurring in 4.9% to 13% of subjects (8.2% during initial NDA review). No ISR was categorized as a serious or severe AE. In some cases, ISR led to study withdrawal but at low incidence (0% to 0.2%).

Adverse events associated with inclisiran use (placebo-controlled data) include arthralgia, urinary tract infections, diarrhea, and bronchitis. There were no new safety signals identified in open-label data. There were no laboratory trends of concern.

Treatment-emergent deaths and SAEs, with the exception of COVID-19-related deaths and SAEs, were similar to those reported during the initial NDA review cycle and occurred at similar incidence. Cardiovascular-, malignancy-, and infection-related were the most common. AEs that led to drug discontinuation included ISRs, stroke, COVID-19, and malignancy. With the exception of ISRs, causes of death, SAEs, and AEs leading to drug discontinuation are consistent with the trial population (older subjects with established ASCVD or risk equivalents).

The incidence of anti-drug antibodies was low, and there was no meaningful difference in mean changes in LDL-C or PCSK9 identified during the initial NDA review cycle.

8. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application during the original NDA review cycle nor during the Complete Response resubmission. The Division and the original Applicant (The Medicines Company) agreed on the components of the development program and the key design features of the clinical trials during development. The design of the development program and the approved initial indication for this application are consistent with those of the initial biologic license applications (BLAs) of the PCSK9 inhibitor monoclonal antibodies Praluent (alirocumab) and Repatha (evolocumab). These applications were discussed at meetings of the Endocrinologic and Metabolic Drugs Advisory Committee Meetings held on June 9 and 10, 2015, respectively.

No new efficacy or safety issues arose during review of this application.

9. Pediatrics

Safety and efficacy in pediatric patients have not been established. As a new active ingredient, the application is subject to Pediatric Research Equity Act (PREA) requirements. Under the initial Pediatric Study Plan (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 and clinical atherosclerotic cardiovascular disease and for pediatric

patients at high risk for cardiovascular disease and elevated LDL-C, birth to <8 years of age (or <6 years of age and on apheresis) with elevated cholesterol and HeFH. The rationale for the partial waiver is that “studies would be impossible or highly impracticable”.

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.

10. Other Relevant Regulatory Issues

Clinical Inspections

During the initial NDA review, the Office of Scientific Investigations (OSI) concluded that the clinical site inspections supported the validity of the data. Refer to the Clinical Inspection Summary authored by Dr. Cynthia Kleppinger for details. I concur with Dr. Kleppinger’s recommendation.

Financial Disclosures

No new financial disclosures were submitted with the Complete Response resubmission. During the initial NDA review, there were 10 covered clinical studies for this application, including 413 principal investigators, and no investigators with reportable financial interests.

Proprietary name

The Applicant’s proposed name Leqvio was found acceptable by the DMEPA reviewer, Dr. Ariane Conrad. I concur with her recommendation. Refer to her review for details.

11. Labeling

The majority of labeling negotiations occurred during the initial NDA review cycle. Refer to the clinical review by Dr. Eileen Craig and the Division Director Summary Review by Dr. John Sharretts for details of those changes.

This section summarizes major changes to the Applicant’s proposed labeling during negotiations between the Division of Diabetes, Lipid Disorders and Obesity (DDLO, the Division) and the Applicant during the Complete Response resubmission.

Prescribing Information

- *HIGHLIGHTS section:*
 - *Addition of the Established Pharmacologic Class (EPC) to Indications and Usage*
- *ADVERSE REACTIONS section:*
 - *Inclusion of additional information on immunogenicity in Section 6.2*
- *DESCRIPTION section:*
 - *Revised Applicant-proposed changes to the established pharmaceutical class.*

Other Labeling

The review team, with guidance from the Division of Medical Policy Programs and the Office of Prescription Drug Promotions, made changes to the Medication Guide and Instructions for Use consistent with the Prescribing Information and current practices.

12. Postmarketing

Postmarketing Risk Evaluation and Mitigation Strategies

A risk management plan, Elements to Assure Safe Use (ETASU), and Implementation System are not proposed by the Applicant and are not recommended by the clinical team.

Postmarketing Requirements and Commitments

Postmarketing Requirements

- 1) Conduct a two-part (double-blind inclisiran versus placebo [Year 1] followed by open-label with placebo-treated subjects switched to inclisiran [Year 2]), multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in children (aged 12 to <18 years) with heterozygous familial hypercholesterolemia (HeFH).

Study Completion: 06/2025
Final Report Submission: 12/2025

- 2) Conduct a two-part (double-blind inclisiran versus placebo [Year 1] followed by open-label with placebo-treated subjects switched to inclisiran [Year 2]), multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in children [aged 6-7 (if on plasma apheresis) or 8 to <12 years] with heterozygous familial hypercholesterolemia (HeFH).

Draft Protocol Submission: 12/2023
Final Protocol Submission: 06/2024
Study Completion: 06/2027
Final Report Submission: 12/2027

- 3) Conduct a worldwide, single-arm, 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.

Final Protocol Submission: 03/2022
Interim Report Submission: 03/2022
03/2023
03/2024
03/2025
03/2026
03/2027
03/2028
03/2029
03/2030

Study Completion: 12/2030
Final Study Report: 07/2031

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: 08/2022

Final Report Submission: 10/2022

- 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. Reevaluate and tighten the purity and impurity content specification for finished product, based on additional batch release and stability data to be available from commercial scale Sandoz GmbH drug product batches, manufactured using at least 10 batches of active substance.

Study Completion: 07/2023

Final Report Submission: 08/2023

- 3) Reevaluate and tighten the purity and impurity content specification for finished product, based on additional batch release and stability data to be available from commercial scale Sandoz GmbH drug product batches, manufactured using at least 10 batches of active substance.

Final Report Submission: 11/2023

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/

LAURA B HIGGINBOTHAM
12/22/2021 11:28:02 AM

JOHN M SHARRETTTS
12/22/2021 11:36:15 AM

LISA B YANOFF
12/22/2021 01:07:35 PM
i concur with the conclusions of this review.

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	John M. Sharretts, M.D.
Subject	Division Director Summary Review
NDA/BLA # and Supplement #	NDA 214012
Applicant	Novartis Pharmaceuticals Corporation.
Date of Submission	December 23, 2019
PDUFA Goal Date	December 23, 2020
Proprietary Name	LEQVIO
Established or Proper Name	Inclisiran (formerly ALN-PCSSC)
Dosage Form(s)	Subcutaneous injection
Applicant Proposed Indication(s)/Population(s)	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
Action or Recommended Action:	Complete Response
Approved/Recommended Indication(s)/Population(s) (if applicable)	<i>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)</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review - Efficacy	Eileen Craig, M.D.
Medical Officer Review - Safety	Iffat Chowdhury, M.D.
Statistical Review	Jennifer Clark, Ph.D.
Pharmacology Toxicology Review	Elena Braithwaite, Ph.D.
OPQ Review – Technical Lead	Muthukumar Ramaswamy, Ph.D.
OPQ Review – Drug Substance	Daniel Jansen, Ph.D.
OPQ Review – Drug Product	Theodore Carver, Ph.D.
OPQ Review – Manufacturing	Kumar Janoria, Ph.D.
Microbiology Review	Avital Shimanovich, Ph.D.
OBP Review	Mayumi Takahashi, Ph.D.
Clinical Pharmacology Review	Sang Chung, Ph.D., Justin Earp, Ph.D.
DPMH	Christos Mastroyannis, M.D.

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
QT-IRT	Ferdouse Begum, Ph.D.
OPDP	Ankur Kalola, PharmD.
OSI	Cynthia Kleppinger, M.D.
OSE/DMEPA	Melina Fanari, R.Ph. Ariane O. Conrad, PharmD., BCACP, CDCES
OCD/CSS	Joshua Hunt, PharmD., M.P.H.

OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OBP=Office of Biotechnology Products
 DPMH=Division of Pediatrics and Maternal Health
 QT-IRT=Interdisciplinary Review Team for Cardiac Safety Studies
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 OCD=Office of the Center Director
 CSS=Controlled Substances Staff

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

The applicant, Novartis Pharmaceuticals Corporation, submitted a New Drug Application (NDA) for inclisiran, supported primarily by three randomized, double-blind, placebo-controlled, 18-month trials in patients with heterozygous familial hypercholesterolemia (HeFH), established atherosclerotic cardiovascular disease (ASCVD), and ASCVD risk equivalents who were on maximally tolerated statin therapy.

Consistent with current published guidelines, recent approvals of LDL-lowering agents have limited the initial indication to the two higher CV risk populations (HeFH and ASCVD), as an adjunct to diet and maximally tolerated statin therapy in those patients who require additional lowering of LDL-C. Given the availability of therapies with proven outcomes benefit for lower-risk populations, the indications have been broadened only after the successful completion of cardiovascular outcomes trials (CVOTs) demonstrating clinical benefit.

The phase 3 trials submitted with this application, ORION-9, ORION-10, and ORION-11, evaluated the effects of inclisiran on LDL-C levels and other lipid parameters. The study populations included patients with relevant comorbidities, such as increased age, diabetes, hypertension, and renal impairment.

The data demonstrated a clinically meaningful, statistically significant, and durable LDL-C reduction with inclisiran. Consistent effects were observed across various subpopulations defined by demographics and baseline disease characteristics.

The submitted data represent substantial evidence of effectiveness consisting of adequate and well-controlled trials to support an indication for LDL-C lowering in high-risk populations (ASCVD and HeFH). The primary endpoint and observed treatment effect were clinically meaningful, and the analyses were statistically robust. The indication could potentially be expanded to lower risk populations in the future if the ongoing CVOT demonstrates favorable effects on clinical endpoints.

The benefit-risk consideration is favorable, as safety issues are monitorable and generally reversible. Injection-site reactions (ISRs) were the most notable safety issue in clinical trials, occurring in 8.2% of patients in the inclisiran arm and 1.8% on placebo. No ISR was categorized as a serious or severe adverse event (AE). Other AEs that occurred more frequently with inclisiran than placebo included arthralgia, urinary tract infections, diarrhea, and bronchitis.

Adverse events of special interest included common safety issues with nucleotide therapies (hepatic and renal events, hypersensitivity reaction) and events associated with other lipid-lowering therapies (myopathy, new-onset diabetes, neurologic events, neurocognitive events, and psychiatric events). There were no imbalances in adverse events or laboratory trends of concern.

The incidence of anti-drug antibodies (ADA) was low, and there was no meaningful difference in mean changes in LDL-C or PCSK9 or the pattern of individual responses among patients with confirmed positive ADA compared to patients with negative ADA.

The Office of Pharmaceutical Quality (OPQ) recommends withholding approval because of deficiencies related to the (b) (4) drug product manufacturing site. I concur with the recommendation.

Otherwise, reviewers from all other review disciplines support approval. Within OPQ, these include the drug substance, drug product, and microbiology reviewers. The Office of Biotechnology reviewer supports approval but recommends a postmarketing commitment to reassess assay sensitivity for detection of anti-drug antibodies and reanalysis of clinical samples. The Pharmacology/Toxicology reviewer concluded that the nonclinical data are adequate within the scope of the review, as did the clinical pharmacology reviewers regarding the pharmacokinetic, pharmacodynamic, and pharmacometric data. The Office of Scientific Investigations site inspections support the validity of the clinical data. Consult reviews, including the QT-Integrated Review Team and Controlled Substance Staff, found no deficiencies that would preclude approval.

In summary, the applicant submitted data demonstrating substantial evidence of effectiveness to support the revised indication, 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. Weighing the magnitude of inclisiran's LDL-C lowering effects against the relatively small incidence of adverse reactions and their non-serious nature, the benefit-risk consideration is favorable. Safety issues were mostly minor or self-limited and may be addressed in labeling.

I support a complete response action, because of deficiencies at the (b) (4) manufacturing site. Aside from the manufacturing deficiencies, the application would be approvable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Analysis of Condition</p>	<ul style="list-style-type: none"> • Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the US and worldwide. • Hypercholesterolemia is a major modifiable risk factor for the development of ASCVD, and LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes. <ul style="list-style-type: none"> ○ A meta-analysis of statin trials demonstrated that an absolute reduction of 39 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). • Current treatment guidelines emphasize reducing the risk of ASCVD through lipid lowering, considering individual risk for a CV event. <ul style="list-style-type: none"> ○ Primary prevention: Reduction of the risk for developing ASCVD in patients without established disease ○ Secondary prevention: Reduction of the risk for additional CV events in patients with established ASCVD • 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 monoclonal antibody proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are considered as second-line, add-on therapies to a background of maximally tolerated statin therapy in patients at highest CV risk, including high-risk secondary prevention patients and patients with Heterozygous Familial Hypercholesterolemia (HeFH) who may benefit from additional LDL-C reduction. 	<p>LDL-C reduction with therapies targeting upregulation of the LDL-C receptor is the cornerstone of preventive treatment for ASCVD.</p> <p>Statin are considered first-line, standard-of-care therapy for lowering LDL-C with the goal of reducing CV risk.</p> <p>Current guidelines emphasize an individualized approach that considers the risk for a CV event.</p> <p>There is unmet medical need among high-risk patients with HeFH or established CVD with elevated LDL-C levels despite maximally tolerated statin therapy, with or without adjunctive therapies, such as ezetimibe or PCSK9 inhibitors.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	<ul style="list-style-type: none"> • High-intensity statins reduce LDL-C by $\geq 50\%$. • Moderate-intensity statins reduce LDL-C by 30% to 49%. • PCSK9 inhibitors lower LDL-C by 45% to 60% and have proven CV benefit, but their use is limited by expense and lack of coverage. • Ezetimibe lowers LDL-C by 18% to 20% as monotherapy and 12% to 15% as add-on to moderate- or high-intensity statin. • Bempedoic acid lowers LDL-C by about 18-19% as an adjunct to maximally tolerated statin but was approved after the most recent guideline update. A CV outcome trial is ongoing. • 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 statin. • 	<p>Statin and PCSK9 inhibitors reduce LDL-C and have proven outcome benefit.</p> <p>Guidelines recommend additional LDL-C lowering in very-high-risk patients on high-intensity (or maximally tolerated) statin therapy who have persistent LDL-C elevation above targets for their risk category.</p>
Benefit	<ul style="list-style-type: none"> • In patients with HeFH or established ASCVD on maximally tolerated statin therapy, inclisiran lowered LDL-C by 48% to 52% from baseline to Day 510 compared to placebo. • LDL-C lowering is a surrogate endpoint for risk reduction of CVD that has served as the basis for conventional approval of other products. • Changes in secondary endpoints were supportive of the primary endpoint. • The treatment effect was relatively stable over the 18-month trials. • There were no major statistical issues identified in the clinical trials, and the efficacy findings were robust because of the large treatment effect and small amount of missing data. • A cardiovascular outcomes trial to evaluate the benefit of inclisiran as an adjunct to statin therapy is ongoing. 	<p>The clinical trials submitted represent substantial evidence of effectiveness of effectiveness consisting of adequate and well-controlled trials for LDL-C lowering in high-risk populations.</p> <p>The phase 3 trials demonstrated a clinically meaningful, statistically robust, and durable LDL-C reduction with inclisiran in high-risk patients who required additional lowering of LDL-C.</p> <p>Given the 15% relative risk reduction in major adverse cardiovascular events observed with PCSK9 inhibitor monoclonal antibodies, one might expect comparable risk reduction from inclisiran; the absolute risk reduction would be a function of the underlying cardiovascular risk in the population.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none"> • The major safety issue was ISRs, which occurred more frequently with inclisiran (8.2% of patients) than placebo (1.8%). • Other adverse events occurring more frequently in patients assigned to inclisiran included arthralgia, urinary tract infections, diarrhea, and bronchitis. None of these adverse events caused irreversible harm. • There was a numerically small numerical imbalance in cardiovascular deaths, 13 deaths on inclisiran and 9 on placebo, but there was no overall imbalance in deaths between treatment arms, and fewer patients in the inclisiran arm experienced cardiovascular serious adverse events compared to placebo. • The incidence of anti-drug antibodies (ADA) was low, and there was no evidence of reduced efficacy in patients with positive ADA. 	<p>Injection site reactions were mild to moderate in severity. The risk for ISR is monitorable and can be adequately addressed in labeling.</p> <p>Other safety issues may be addressed in labeling and do not alter the overall favorable benefit-risk consideration.</p>

2. Background

Inclisiran (proposed trade name Leqvio) is a double-stranded short interfering ribonucleic acid (siRNA) that inhibits hepatic production of proprotein convertase subtilisin/kexin type 9 (PCSK9), resulting in decreased circulating low-density lipoprotein cholesterol (LDL-C) levels. Reduction in intrahepatic PCSK9 levels leads to increased recycling and expression of the LDL-C receptor (LDLR) on the hepatocyte cell surface, which in turn increases LDL-C uptake, thus reducing circulating LDL-C.

The proposed product is provided in 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, and then every 6 months.

The applicant proposes an indication as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce LDL-C.

Analysis of Condition

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease (CVD), the leading cause of death and disability worldwide. Hypercholesterolemia is a major modifiable risk factor for the development of atherosclerosis and CVD.

Many large-scale, randomized cardiovascular outcomes trials (CVOTs) have shown that reducing low-density lipoprotein cholesterol (LDL-C) levels with statins reduces the risk of CVD. A meta-analysis¹ of statin trials concluded that lowering LDL-C by 1 mmol/L (39 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 approximately 22%, and that statin regimens using higher doses or more-potent agents – resulting in greater reductions in LDL-C – reduce the risk of vascular events more than less-intensive statin regimens in high-risk patients. More recently, CVOTs of the two approved monoclonal antibody PCSK9 inhibitors, alirocumab² and evolocumab,³ demonstrated that reducing LDL-C levels with these agents led to a reduction in risk of CV events.

Moderate-intensity and high-intensity statins reduce LDL-C by 30% to 49% and $\geq 50\%$, respectively. PCSK9 inhibitors lower LDL-C by an additional 50% to 70%. Ezetimibe lowers LDL-C by 15% to 20%. Other drug categories, such as fibrates or niacin, are not considered mainstays of LDL-C lowering therapy because of mild LDL-lowering ability and clinical trial

¹ 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.

² Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. *N Engl J Med*. 2018; 379: 2097-107.

³ 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.

data that show no benefit in reducing CV morbidity or mortality among patients already treated with a statin.

Current treatment guidelines⁴ emphasize reducing the risk of atherosclerotic cardiovascular disease (ASCVD) through lipid management, considering an individual 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 risk category. Low-intensity statins are not recommended for any population.

Ezetimibe and 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 may benefit from additional LDL-C reduction.

Recent approvals of novel LDL-lowering therapies, in the absence of outcomes data and in the context of available therapy, have been influenced by the magnitude of LDL-C lowering, mechanism of action, and evidence for off-target toxicity. FDA approved the monoclonal antibody PCSK9 inhibitors in 2015 prior to the completion of their CVOTs, but the initial indications were restricted to a higher CV-risk population, as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CVD, who require additional lowering of LDL-C. The indication was broadened after the successful completion of their CVOTs, which demonstrated reassuring long-term safety data in addition to demonstrating CV benefit.

Brief Regulatory History

The original Sponsor, The Medicines Company, submitted IND 127589 on January 21, 2016.

An end-of-phase 2 meeting was held April 6, 2017 to reach alignment on key aspects of the proposed phase 3 program. Clinical recommendations included:

- Requirement for subjects to be on maximally tolerated statin therapy in non-HeFH trials, with the majority on high-intensity statin therapy.
- Inclusive eligibility criteria, including patients with a history of hemorrhagic stroke, stable heart failure, and renal insufficiency.
- A safety database comprising at least 1500 patients exposed to inclisiran for approximately 18 months, in order to include the safety data from at least 4 injections.
- Comments on population: although the eligibility criteria for ORION-11 included a history of ASCVD-risk equivalents, the Division advised the sponsor that the initial indication (b) (4) would likely be similar to that granted for the PCSK9 monoclonal antibodies unless there were favorable results from a CVOT. (b) (4)

⁴ Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2018.

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

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

On December 23, 2019, the original applicant, The Medicines Company, submitted the NDA.

On April 1, 2020, the applicant notified FDA of transfer of ownership to Novartis Pharmaceuticals Corporation, as The Medicines Company became a wholly owned subsidiary of Novartis.

There is an ongoing randomized, placebo-controlled trial (Study CTSU-MDCO-PCS-17-01) to evaluate the effects of inclisiran on CV outcomes in patients with ASCVD. The trial, also known as HPS-4/TIMI 65/ORION-4 (NCT03705234), is being conducted at approximately 180 clinical sites in the UK and the US, and is expected to enroll approximately 15,000 participants aged 55 years or older with atherosclerotic cardiovascular disease randomized to inclisiran sodium 300 mg or matching placebo in a 1:1 ratio for a planned median duration of about 5 years. The estimated primary completion date is December 2024, with results expected by 2025.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends a complete response action because the Office of Process Manufacturing Assessment (OPMA) inspection recommendation is to “withhold approval” because of deficiencies related to the (b) (4) drug product manufacturing site. Refer to the OPQ Integrated Quality Assessment authored by the application technical lead, Dr. Muthukumar Ramaswamy, for details. I concur with Dr. Ramaswamy’s recommendation.

The major issues addressed within the chemistry, manufacturing, and controls (CMC) reviews are summarized below.

Inclisiran is a small interfering RNA (siRNA) duplex that contains a 21-nucleotide long sense strand linked to a triantennary acetyl galactosamine (GalNAc) on the 3’ end and a 23-nucleotide long anti-sense strand. Modifications at the 2’ ribose moiety and a phosphodiester backbone confer stability and protect the siRNA from nucleases. The molecular formula is C₅₂₉H₆₆₄F₁₂N₁₇₆Na₄₃O₃₁₆P₄₃S₆, and the molecular weight of the salt form is 17,284.75 g/mol. Inclisiran sodium is a white to pale white powder that is freely soluble in water.

The drug substance reviewer, Dr. Daniel Jensen, 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, and that the specifications are consistent with batches used in clinical, nonclinical, and registration stability studies. He concluded that the retest period is (b) (4) months when stored (b) (4)

Refer to Dr. Jensen’s review for details.

The drug product, Leqvio (inclisiran) injection, 189 mg/mL is a clear, colorless to pale

yellow sterile solution provided as a single-use 1.5 mL pre-filled syringe containing 284 mg inclisiran (equivalent to 300 mg inclisiran sodium). The product is formulated in water for injection as a preservative-free solution with a target pH of 7. (b) (4)

(b) (4). The product should be stored at 20°C to 25°C (68°F to 77°F) (b) (4) with excursions permitted between 15°C and 30°C (59°F and 86°F).

The drug product reviewer, Dr. Ted Carver, concluded that the product composition, specification, excipient information, analytical methods, container closure system, compatibility information, and stability data are adequate to support the quality of the product. Dr. Carver additionally granted the applicant categorical exclusion from submitting an environmental assessment and concluded that the carton and container labeling meet all regulatory requirements. Refer to Dr. Carver's review for additional information.

The microbiology reviewer, Dr. Avital Shimanovich, concluded that the proposed microbiological controls are adequate to support the NDA. Refer to her Section 6 of this review and her review for details.

The manufacturing process involves (b) (4)

(b) (4) The process reviewer, Dr. Kumar Janoria, concluded that the proposed drug product manufacturing process controls are adequate to support the NDA.

Dr. Janoria also reviewed facility compliance information for the drug product and drug substance manufacturing and testing facilities. He concluded that two manufacturing facilities (b) (4) were acceptable but identified deficiencies at the drug product manufacturing facility (b) (4) located at (b) (4).

FDA inspected the (b) (4) facility in (b) (4) and issued a 6-item Form 483 (inspection observations). The facility review team recommended a pre-approval inspection to verify the corrective actions and confirm the required (b) (4). Because of travel restrictions related to the COVID-19 pandemic, a 704(a)(4) records review was initiated in lieu of a pre-approval inspection (PAI). The records review identified several deficiencies related to (b) (4).

(b) (4) The review team concluded that the deficiencies would require either a PAI or adequate facility responses addressing the conditions before the application could be approved. As a result, the facility assessment recommendation is inadequate.

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

Office of Biotechnology Products – Immunogenicity Assay Validation

The Office of Biotechnology Products (OBP) reviewer, Dr. Mayumi Takahashi, evaluated the assay used to assess anti-drug antibodies and recommends a postmarketing commitment from the applicant to repeat validation of the assay sensitivity and other parameters using purified positive controls. I concur with Dr. Takahashi's recommendations. Refer to her review for details of the deficiencies and recommendations summarized here.

The applicant developed and used an ELISA method to detect anti-inclisiran-reactive immunoglobulin G (IgG) and IgM antibodies in sera. Dr. Takahashi concluded that two positive controls prepared with unpurified rabbit anti-KLH-TTRSC serum were not adequate to ensure the sensitivity, specificity, and selectivity of the assay, but she agreed that the other validation parameters, including the cut-points assessed with affinity purified rabbit serum, were evaluated appropriately.

To resolve the deficiencies, Dr. Takahashi recommends that the applicant reassess the assay sensitivity using an affinity-purified antiserum, and that all existing clinical samples should be re-analyzed using the appropriately validated assay. The applicant has agreed to two postmarketing commitments, one to address assay sensitivity as recommended, and the second to re-analyze the clinical samples.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Elena Braithwaite, concluded that the nonclinical data submitted by the applicant are adequate, and she recommends approval. I concur with her recommendations and have summarized key findings in her review relevant to approvability and labeling. Refer to Dr. Braithwaite's review for details.

Primary pharmacology studies in which inclisiran was administered subcutaneously resulted in a decrease in the expression of plasma PCSK9 in transgenic mice expressing human PCSK9 and cynomolgus monkeys, and these decreases correlated with sustained decreases in LDL-C and total cholesterol levels in monkeys. In safety pharmacology studies in monkeys, inclisiran did not have an adverse impact on neurological, respiratory or cardiovascular function.

Inclisiran was well-tolerated in repeat-dose studies up to 29-weeks in duration in rats and 40-weeks in duration in monkeys. Non-adverse histopathological findings, such as vacuolization or basophilic granules, were observed in the liver (target organ), kidney (organ of elimination), and lymph nodes. These findings were generally exposure-related and were partially reversible in most cases. Previous immunohistochemical analysis with other siRNA products has shown that these findings reflect non-adverse accumulation of the siRNA in tissue. Subcutaneous injection-site reactions occurred in rats increased in severity with duration of use and concentration. Delayed or absent IgM immune response to keyhole limpet hemocyanin (KLH) antigen and reduced IgG 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) and 300 mg/kg/28-days (19-fold the recommended clinical dose), respectively.

No new or exacerbated toxicity was observed with inclisiran administered in combination with atorvastatin for 85 days. Inclisiran did not have an adverse impact on reproduction or development in rats and rabbits. The no observed adverse effect levels (NOAELs) in the pivotal rat and monkey studies were 250 mg/kg/28 days (8-fold the recommended clinical dose) and 300 mg/kg/28 days (19-fold the recommended clinical dose), respectively.

Inclisiran tested negatively for genotoxicity in a standard battery tests and did not promote neoplastic transformations in TgRasH2 mice or Sprague Dawley rats. On July 16, 2020, the Executive Carcinogenicity Assessment Committee concluded that the carcinogenicity studies performed in mice and rats were adequate and negative for drug-related neoplasms.

Dr. Braithwaite concluded that the nonclinical data support approval. She provided labeling recommendations for Sections 8.1 (Pregnancy), 8.2 (Lactation), and 13 (Nonclinical Toxicology) of the Prescribing Information. I concur with her conclusions and recommendations.

5. Clinical Pharmacology

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) reviewed the clinical pharmacology data and recommends approval. I concur with the recommendation. Refer to the OCP review authored by Dr. Sang Chung and Dr. Justin Earp for details.

Data supporting effectiveness came from results of the Phase 3 trials (ORION-9, ORION-10, and ORION-11) with supplemental clinical information from four Phase 1 and three Phase 2 trials. The observed placebo-adjusted LDL-C percentage changes from baseline to Day 510 (primary end point) were -50%, -58% and -54%, in ORION-9, ORION-10, and ORION-11, respectively. Clinical effectiveness is discussed in greater detail in Section 7 of this review.

Inclisiran pharmacokinetics (PK) were dose proportional in the range from 25 mg to 800 mg administered subcutaneously in the single ascending dose (SAD) study. The time (T_{max}) to reach maximum plasma concentration (C_{max}) was approximately 4 hours following a 300 mg subcutaneous (SC) injection.

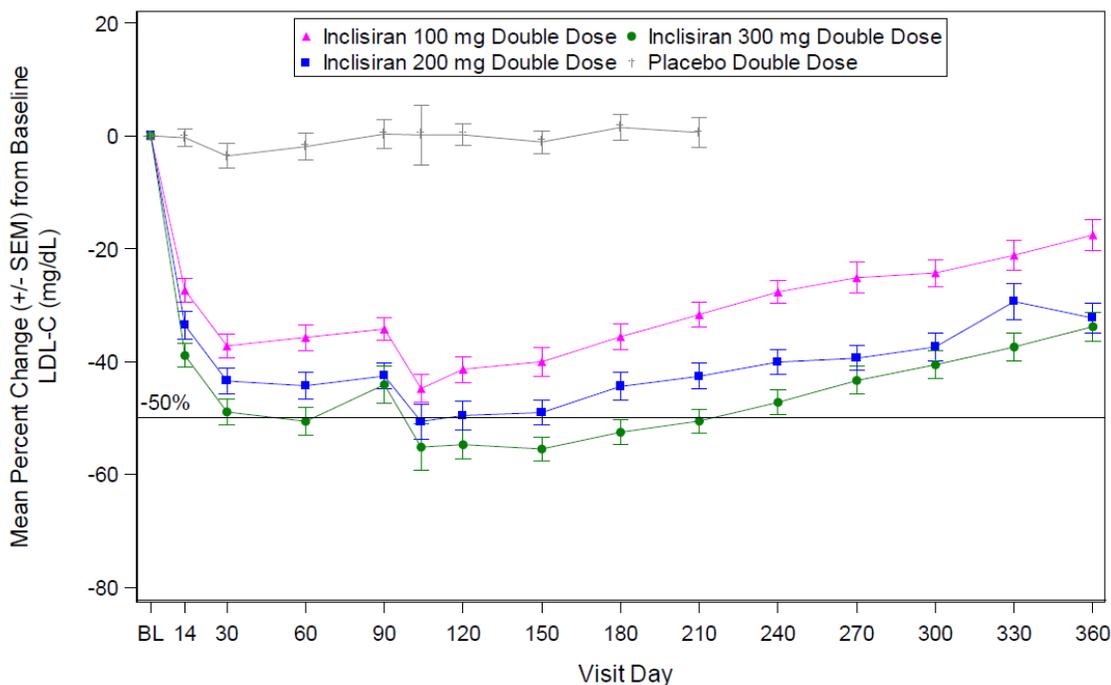
Inclisiran is approximately 87% bound to plasma proteins at 0.5 g/mL, the mean C_{max} following 300 mg SC injection. It is neither a substrate for nor an inhibitor or inducer of major cytochrome P450 (CYP) enzymes or transporters, and it is metabolized by exonucleases. The apparent terminal half-life is approximately 7 hours following a 300-mg dose. Approximately 17% (range 9% to 31%) of the dose is eliminated unchanged in urine. Refer to Dr. Chung's review for details of PK and Absorption, Distribution, Metabolism and Elimination (ADME).

The proposed dose for marketing is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, and then every 6 months. If a planned dose is missed by less than 3 months, the dose may be administered, with subsequent dosing maintained according to the patient's original schedule. If a planned dose is missed by more than 3 months, the patient must start a new dosing schedule.

There is a significant temporal dissociation between PK exposure and pharmacodynamics (PD) with inclisiran. Inclisiran concentrations are not detectable approximately 24 to 48 hours following most single doses, whereas the PD changes last for months. Figure 1 summarizes the LDL percent change from baseline following two doses of inclisiran administered at Day 0 and Day 30.

A conventional exposure-response relationship was not applicable to support the proposed dosing frequency evaluated in phase 3 trials. Instead, the applicant used a population PD model with abbreviated PK. Simulation results presented at the end-of-phase 2 meeting were considered by the clinical pharmacology team to be acceptable to support the proposed maintenance dose. Simulation results also support labeling recommendations for missed doses. Refer to the pharmacometrics section of the clinical pharmacology review authored by Dr. Earp for details of the modeling and simulation.

Figure 1: Percent Change from Baseline LDL-C by Dose Group Over Time Following Double Dose (Baseline and Day 30), Study ALN-PCSSC-001 (ORION-1) – MITT Population



Abbreviations: LDL-C=low-density lipoprotein cholesterol, BL=baseline, SEM=standard error of the mean, MITT=modified intent-to-treat

Source: Clinical Study Report (CSR), Study ALN-PCSSC-001 (ORION-1), Figure 5.3.2.2

There was an increase in inclisiran exposure in patients with severe renal impairment (2.5-fold) and moderate hepatic impairment (2.1-fold), but changes in PD markers, including PCSK9 and LDL-C, were comparable to those with normal renal or hepatic function. 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. No dose adjustment is needed in patients with mild or moderate hepatic impairment. Inclisiran was not studied in patients with severe hepatic impairment. No dose adjustments are needed for other demographics such as

age, body weight, sex, and race. Dosing recommendations for impaired renal and hepatic function will be included in labeling. Refer to the clinical pharmacology review for details.

The to-be-marketed drug product (formulation and device) was used in the phase 3 trials. No bridging between the to-be-marketed and clinical trial formulations was needed.

QT Interval Evaluation

The effect of inclisiran was evaluated in a thorough QT 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 a 900-mg single dose (administered as 3 subcutaneous injections), which covers the worst-case exposure scenario (renal impairment). 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. For details, refer to the QT Integrated Review Team (IRT) consult review authored by Dr. Ferdouse Begum. I concur with the IRT recommendation.

Controlled Substance Evaluation

Following review of the non-clinical pharmacology and summarized adverse event data, the Controlled Substance Staff concluded that inclisiran lacks meaningful abuse-related CNS activity and does not require inclusion of Section 9 (Drug Abuse and Dependence) in labeling. Refer to the consult review by Dr. Joshua Hunt for details.

6. Clinical Microbiology

The microbiology reviewer, Dr. Avital Shimanovich, reviewed the microbiological controls used in the drug product manufacturing process, including (b) (4), sterility specifications, container closure integrity, endotoxin, (b) (4), media fill studies, hold times, and post-approval stability commitment. Her review concluded that the proposed microbiological controls are adequate to support the NDA, and I concur with her recommendation.

7. Clinical/Statistical-Efficacy

The clinical effectiveness of inclisiran was evaluated in three similarly designed, randomized, double-blind, placebo-controlled trials, ORION-9 (NCT03397121), ORION-10 (NCT03399370), and ORION-11 (NCT3400800). The clinical reviewer, Dr. Eileen Craig, and the statistical reviewer, Dr. Jennifer Clark, both concluded that the submitted data constitute substantial evidence of effectiveness to support approval, and I concur with their recommendations. This section of the review will focus on the major issues in the application regarding approvability and labeling. For details and additional analyses, refer to the clinical review, authored by Dr. Craig and Dr. Iffat Chowdhury (who reviewed the safety data) and the statistical review authored by Dr. Clark.

The three phase 3 trials evaluated the efficacy and safety of inclisiran sodium 300 mg in high CV-risk patients on maximally tolerated statins who required additional lowering of LDL-C. ORION-9 enrolled patients with Heterozygous Familial Hypercholesterolemia (HeFH), ORION-10 enrolled patients with established atherosclerotic cardiovascular disease (ASCVD),

and ORION-11 enrolled patients with either ASCVD or ASCVD risk equivalents. Definitions of these populations were reasonable and consistent with current clinical practice. At the end-of-phase 2 meeting, the division had clarified that [REDACTED] (b) (4)

[REDACTED], and that sufficient patients with established ASCVD or HeFH should be included in phase 3 trials. Current guidelines do not recommend for additional LDL-C lowering on top of statins for primary prevention aside from familial hypercholesterolemia. Efficacy analyses in this review are limited to patients with HeFH and ASCVD.

The trials were nearly identical in design, differing primarily in their study populations. Each was a randomized, double-blind, placebo-controlled trial of patients with elevated LDL-C (≥ 70 mg/dL or ≥ 100 mg/dL, depending on the risk category) despite maximally tolerated LDL-C lowering therapies, including statins. The purpose of the trials was to evaluate the efficacy, safety, and tolerability of four subcutaneous inclisiran injections administered over a period of 18 months. Screening occurred approximately 2 weeks prior to randomization. Patients were randomized 1:1 to either inclisiran sodium 300 mg or placebo, stratified by country and current use of statins or other lipid-modifying therapies. The study schedule included four blinded injections on Day 1, Day 90, Day 270, and Day 450, endpoint assessments at Day 510, and an end-of-study (EOS) visit 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. ORION-10 had only US sites, ORION-11 had only sites in Europe and South Africa. ORION-9 enrolled patients in the US, Canada, Europe, and South Africa.

Pharmacodynamic assessments scheduled at various visits included fasting LDL-C levels and other standard lipid profile parameters, high sensitivity C-reactive protein (hsCRP), and PCSK9. All subjects were offered pharmacogenetic analyses, unless underlying causal mutations of HeFH were previously documented by a validated specialized laboratory. The Analysis Populations for the trials were defined as follows: The Intent-to-Treat (ITT) Population comprised all subjects randomized into the study and was used for analysis of the primary and secondary endpoints; the Full Analysis Set (FAS) comprised all subjects randomized into the study, who received at least one dose of study medication and had at least one post-treatment lipid data measured. The Modified Intent-to-Treat (mITT) Population comprised randomized subjects who received at least one dose of study medication and had non-missing values at both the baseline and Day-510 study visits; the Safety Population consisted of all subjects who received at least one dose of investigational product.

The primary endpoint was the percentage change in LDL-C from baseline to Day 510. The “co-primary” endpoint was the time-adjusted percentage change in LDL-C from baseline after Day 90 and up to Day 540 (see below for detail on the co-primary testing scheme). The analysis of the primary percent-change endpoint used an analysis of covariance model (ANCOVA) that included fixed effects for treatment group and baseline LDL-C. Missing values were imputed for LDL-C using a modified control-based multiple imputation. Imputations were combined using Rubin’s rule. The model assumed that all missing data for placebo patients were missing at random (MAR). Missing data were also assumed MAR at Day 510 for inclisiran patients who completed the study, received all for doses of study

medication, and had available data at Day 540, whereas data were assumed missing not at random (MNAR) for all other inclisiran patients with missing data.

The time-adjusted LDL-C “co-primary” endpoint used a mixed-effects model for repeated measures (MMRM) with fixed effects for treatment, visit (Days 90, 150, 270, 330, 450, and 510), baseline, and an interaction between treatment and visit. Missing data for the time-adjusted endpoint were imputed using a control-based pattern mixed-model (PMM), such that missing values after study discontinuation were assumed MNAR, whereas missing intermittent values were imputed using an MAR assumption.

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, and percentage change from baseline to Day 510 in PCSK9, total cholesterol, ApoB, and non-HDL-C. Statistical methodologies for change-from-baseline and time-averaged change-from-baseline were similar to the methods used for the primary and “co-primary” endpoints, respectively.

The applicant used a sequential testing procedure to control the Type I error rate. The percentage change at Day 510 was tested first at a 2-sided level of $\alpha=0.05$. If the analysis rejected the null hypothesis, the time-adjusted endpoint could then be tested, also at a 2-sided level of $\alpha=0.05$. The Hochberg procedure was used to control alpha for key secondary endpoints. In her review, Dr. Clark noted that a sequential testing procedure is not a typical approach to control type I error for co-primary endpoints, as sequential methods are usually reserved for testing endpoints in a hierarchy where one is ranked above the other, not when endpoints are considered equal. In the applicant’s arrangement, the method could theoretically reject the null hypothesis for the primary LDL-C change from baseline but fail to reject the null hypothesis for the “co-primary” time-adjusted endpoint, whereas the converse could not possibly occur. Granted, the first scenario was highly unlikely given that the two endpoints were highly correlated, with the Day 510 LDL-C value constituting a component of the time-averaged endpoint.

The primary endpoints used a reflexive LDL-C approach, whereby calculated LDL-C was used, unless calculated LDL-C was less than 40 mg/dL, calculated LDL-C was missing, or triglycerides were greater than 400 mg/dL, in which case direct LDL-C was used (when it was available). Because direct LDL-C measurement using ultracentrifugation was done only at baseline and at Day 510, calculated LDL-C was used for most values contributing to the time-averaged LDL-C endpoint, regardless of LDL-C or triglyceride levels. Calculated LDL-C used the Friedewald equation ($LDL=TC-[HDL+TG/5]$), which is commonly used in clinical practice and is considered reliable within <0.5 mg/dL of direct LDL-C, except in patients with low LDL-C or elevated triglycerides.

The placebo-adjusted mean change from baseline to study endpoint in LDL-C is the regulatory standard to support approval of LDL-C lowering therapies. FDA has not used the time-adjusted endpoint to support approval of LDL-C lowering therapies.

Results

Disposition

Disposition was similar across the three phase 3 trials. For details of the individual trials, refer to the clinical review by Dr. Craig. Overall, 3422 of 3660 (93.5%) patients completed the trials, including 94.3% (1728/1833) of patients in the inclisiran arm. The most frequently cited reasons for discontinuing the study were withdrawal of consent (3.0% of placebo patients and 2.0% of inclisiran patients), death (1.5% in both arms), and lost to follow-up (1.6% placebo and 0.9% inclisiran).

Demographics and Baseline Characteristics

Demographics and baseline characteristics were generally balanced between arms across the phase 3 program, but there were notable differences in the populations of each individual trial. In ORION-9 (HeFH), patients were younger, a higher proportion were women, fewer patients had diabetes, and baseline LDL-C was higher despite a slightly higher percentage taking high-intensity statins and a higher percentage taking ezetimibe. Women were under-represented in the ASCVD populations. Non-white and Hispanic/Latino patients were substantially under-represented in all studies relative to the US population with two exceptions: In ORION-10, conducted entirely in the US, the percentages of Black of African American (13%) patients and Hispanic/Latino patients (14%) were only modestly lower than the estimated percentages in the US overall population.

ORION-9 enrolled 482 patients (240 assigned placebo and 242 inclisiran) with HeFH diagnosed by either genotyping or clinical criteria. The mean age at baseline was 55 years (range: 21 to 80 years), 22% were ≥ 65 years old, 53% were women, 94% were White, 3% were Black, 3% were Asian, and 3% identified as Hispanic or Latino ethnicity. Approximately 10% of patients had diabetes at baseline. Mean baseline LDL-C was 153 mg/dL. At randomization, 90% of patients were receiving statin therapy – including 74% who were on high-intensity statin therapy (most commonly atorvastatin and rosuvastatin) – and 52% of patients were receiving ezetimibe. Approximately 14% of patients were enrolled in the US.

ORION-10 enrolled 1561 patients (780 assigned placebo and 781 inclisiran) with ASCVD. The mean age was 66 years (range: 35 to 90 years), 60% were ≥ 65 years old, 31% were women, 86% were White, 13% were Black, <1% were Asian, and 14% identified as Hispanic or Latino ethnicity. Approximately 45% of patients had diabetes at baseline. The mean baseline LDL-C was 105 mg/dL. At randomization, 89% of patients were receiving statin therapy and 69% were receiving high-intensity statin therapy. All patients were enrolled at US clinical sites.

ORION-11 enrolled 1617 patients (807 assigned placebo and 810 inclisiran) with ASCVD (87%) or ASCVD risk equivalents (13%). The mean age was 65 years, 55% were ≥ 65 years old, 28% were women, 98% were White, 1.2% were Black, <0.5% were Asian, and <1% identified as Hispanic or Latino. Approximately 35% had diabetes at baseline. Mean LDL-C was 105 mg/dL. At randomization, 95% of patient were receiving statin therapy and 78% were receiving high-intensity statin therapy. No patients were enrolled in the US.

Efficacy – Primary Endpoint

The primary efficacy outcome measure in each of the three Phase 3 trials was the percent change from baseline to Day 510 in LDL-C. The placebo adjusted mean percentage changes in LDL-C from baseline to Day 510 ranged from -48% to -52%. Refer to Table 1 for details.

Table 1: Percentage Change in LDL-C from Baseline to Day 510 (Washout Imputation*) in ORION-9, ORION-10, and ORION-11 – ITT Population

Trial	Arm (N)	LS Mean (95% CI)	LS Mean Difference (95% CI) From Placebo
ORION-9	Placebo (N=240)	8.2 (4.3, 12.2)	-47.9 (-53.5, -42.3; p<0.0001)
	Inclisiran (N=242)	-39.7 (-43.7, -35.6)	
ORION-10	Placebo (N=780)	1.0 (-1.5, 3.4)	-52.2 (-55.7, -48.8; p<0.0001)
	Inclisiran (N=781)	-51.3 (-53.8, -48.8)	
ORION-11	Placebo (N=807)	4.0 (1.8,6.3)	-49.9 (-53.1, -46.6; p<0.0001)
	Inclisiran (N=810)	-45.8 (-48.2, -43.5)	

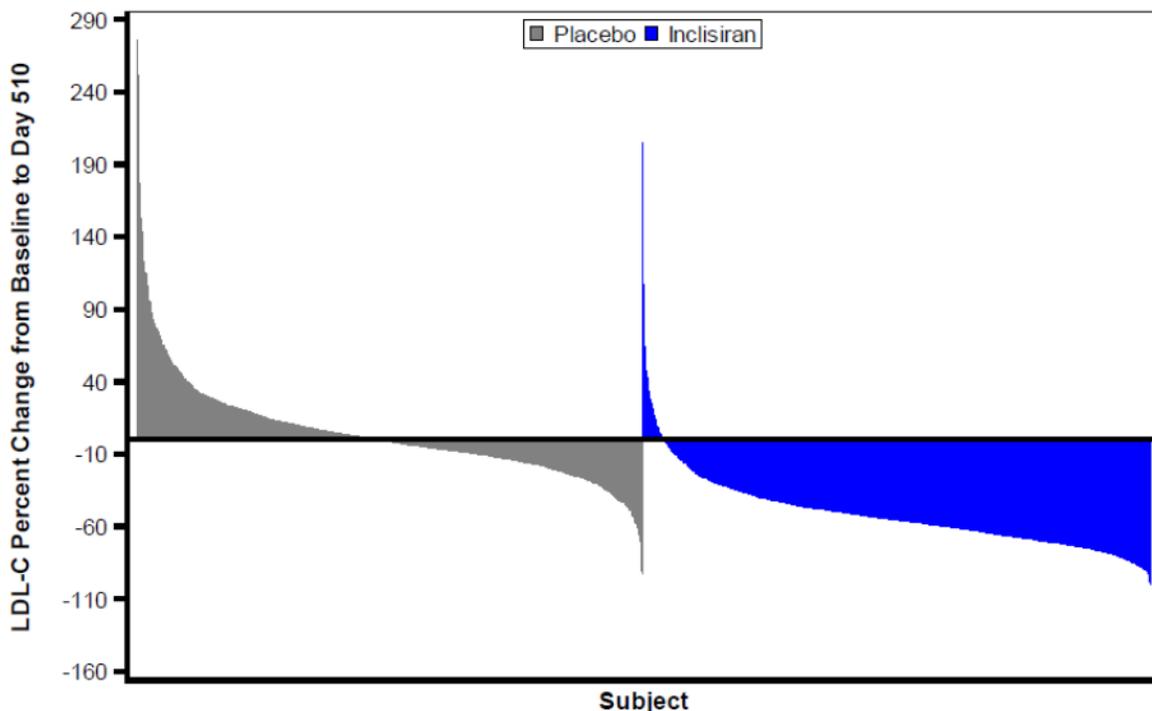
*Missing data were imputed using a modified, control-based, multiple imputation to account for treatment adherence. The model assumed missing Day 510 at random for inclisiran patients if they received all 4 doses and had data observed at Day 540. Percent change from baseline in LDL-C was analyzed using analysis of covariance (ANCOVA) with fixed effect for treatment group and baseline LDL-C as a covariate.
Abbreviations: CI=confidence interval; ITT=Intent-to-Treat; LDL-C=low-density lipoprotein cholesterol; LS=least squares; N=number of patients

Source: Modified from Applicant Integrated Summary of Effectiveness (ISE), Table 12, p. 46/118

Dr. Clark confirmed the applicant's analyses. In the statistical review, Dr. Clark noted that small differences between her analyses and the applicant's results within 1% were due to minor differences in the multiple imputation patterns. Dr. Clark concluded that the findings were statistically robust given the low amount of missing data and the consistently large treatment effects. Tipping point analyses conducted by the applicant failed to reject the null hypothesis only under implausible scenarios.

Waterfall plots of the data illustrate the large treatment difference between groups. Figure 2 summarizes pooled LDL-C changes from baseline to Day 510 for the three phase 3 studies by treatment arm. The vast majority of patients assigned to inclisiran experienced large reductions in LDL-C from baseline, whereas the placebo patient changes from baseline show a distribution, centered around near-zero (no change overall).

Figure 2: Waterfall Plot of Percent Change in LDL-C from Baseline to Day 510 in ORION-9, ORION-10 and ORION-11 Pooled -- Patients with Available LDL-C data in ITT Population



Source: Applicant ISE, Figure 14.2.3.1.1.1.

Because the primary endpoints achieved statistical significance, the applicant was able to test the “co-primary” endpoint, the time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 540, per the prespecified method. The differences between the placebo and inclisiran groups in the time-adjusted percent change in LDL-C from baseline were:

- -44.3% (95% CI: -48.5, -40.1; $p < 0.0001$) in ORION-9
- -53.8% (95% CI: -56.2, -51.3; $p < 0.0001$) in ORION-10
- -49.2% (95% CI: -51.6, -46.8; $p < 0.0001$) in ORION-11

Dr. Clark confirmed the applicant’s analyses in her review.

(b) (4)
 While Dr. Craig acknowledged that the time-adjusted value provided an estimate of LDL-C changes over time, and that the data were consistent with the Day-510 primary endpoint, she noted that FDA has not previously used a time-adjusted endpoint as a regulatory standard for approval, (b) (4)

(b) (4)
 She also pointed out limitations of the analysis, including a lack of data prior to Day 90. In her review, Dr. Clark stated that it is unclear (b) (4)

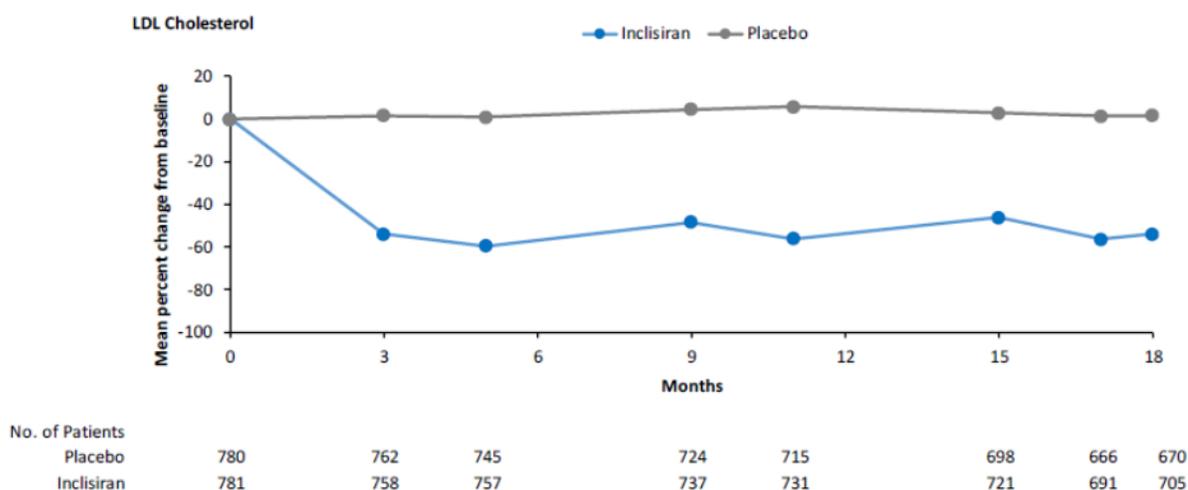
(b) (4)
 In her view, the Day-510 primary endpoint

demonstrates the durability of the treatment effect, whereas the time-adjusted endpoint provides a hypothesis test to quantify the consistency of the effect over time.

Both reviewers agreed that a figure in labeling for demonstrating the mean percent change over the duration of each trial could also demonstrate the consistency of the treatment effect, that such a plot would be interpretable given the small amount of missing data, (b) (4)

Similar figures demonstrating LDL-C over time are included in labeling of other approved LDL-C products. Figure 2 depicts the LDL-C change from baseline over time in ORION-10 and is representative.

Figure 3: Observed Mean Percent Change from Baseline in LDL-C Over 18 Months in Patients with ASCVD on Maximally Tolerated Statin Assigned to Inclisiran or Placebo in ORION-10 – ITT Population



Reflexive LDL-C measurements used as per protocol.
Source: Applicant’s ORION-10 submission, Figures 4 and 14.2.1.3

(b) (4)
The time-adjusted endpoint represents a “closely related” endpoint that conveys essentially the same information as the Day-510 primary endpoint. Furthermore, the time-averaged endpoint has additional limitations to interpretation, such as lack of sampling during the expected period of greatest change and peak pharmacodynamic effect (the 30 days post-dose), less rigorous methodology used for assessment of LDL-C levels in patients with very low LDL-C or elevated triglycerides, and use of a single point estimate to describe an integrated value over time.

Secondary endpoint results for absolute change in LDL demonstrated similarly large treatment effects as percent change. (b) (4)

Refer to Dr. Craig’s review for additional details of these endpoints.

Percentage change in PCSK9 is relevant to the clinical pharmacology section of labeling but is not used in clinical practice to assess efficacy. Refer to the clinical review, the clinical

pharmacology section of this review, and the clinical pharmacology review for additional details.

Key secondary endpoints that are relevant to clinical practice include percent change in non-HDL-C, total cholesterol, and Apo-B from baseline to Day 510. The applicant is seeking labeling claims based on these pre-specified secondary endpoints, and both Dr. Craig and Dr. Clark agreed that these are appropriate for inclusion in labeling, consistent with data included in labeling for most other LDL-C lowering agents, such as statins, ezetimibe, and the PCSK9 monoclonal antibody inhibitors.

In the phase 3 trials, total cholesterol reduction ranged from -30 to -33%, Apo-B reduction ranged from -36 to -43%, and non-HDL-C reduction ranged from -42 to -47% compared to placebo. The results of these endpoints were statistically robust, clinically meaningful, and supportive of the effect on LDL-C. LDL-C is a major component of total cholesterol and non-HDL-C, and apolipoprotein B is the primary apolipoprotein expressed on LDL particles.

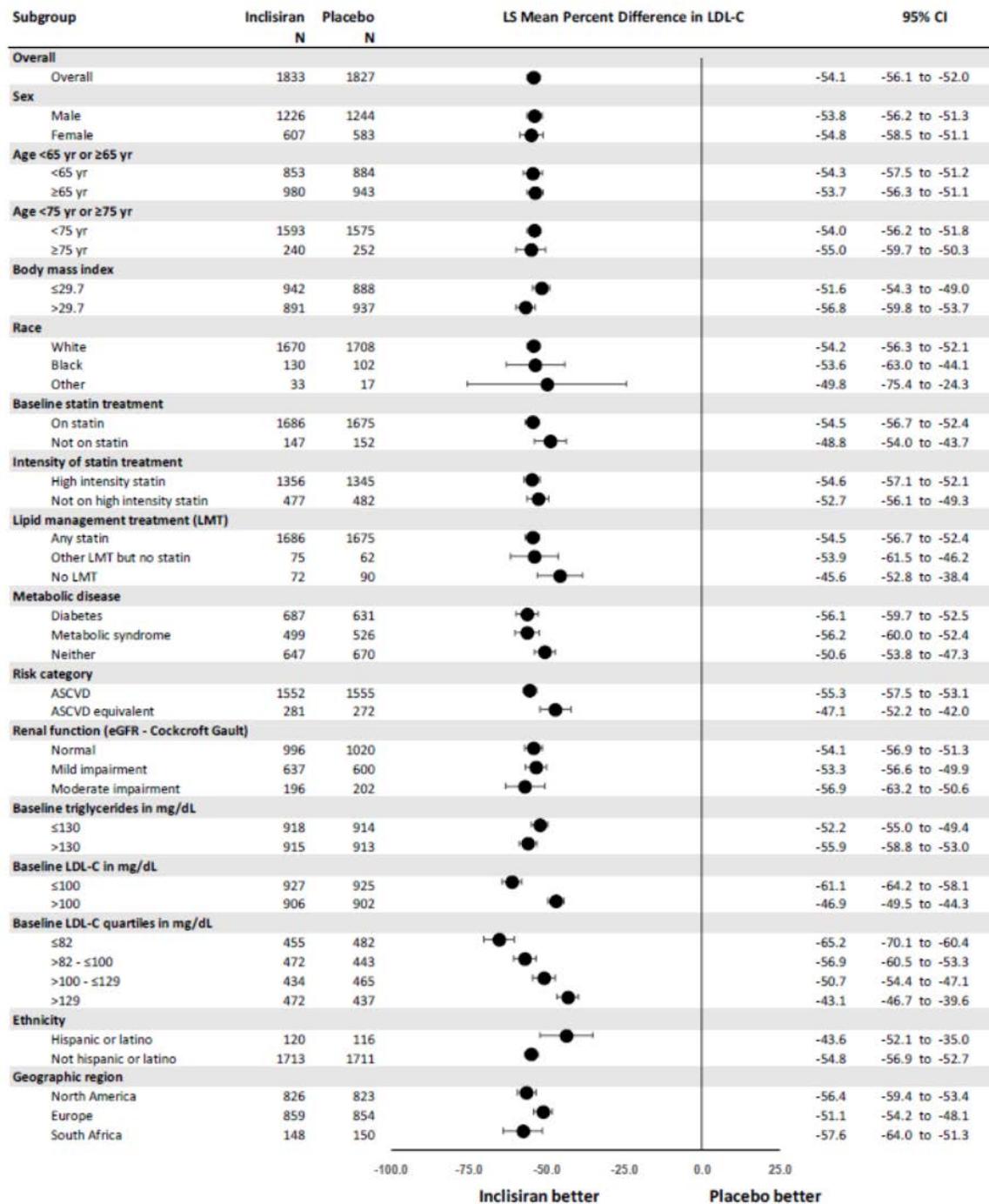
Across the phase 3 trials, triglyceride reduction ranged from -9 to -12%, and HDL-C increase ranged from +3 to +6% compared to placebo. The clinical significance of the modest changes in TG and HDL-C is unclear; (b) (4). Lp(a) reduction ranged from -19 to -32%, compared with placebo. Although epidemiological studies suggest that Lp(a) levels are independently associated with development of ASCVD, the clinical implications of reduction of Lp(a), independent of changes in other lipid parameters, is unclear. (b) (4)

(b) (4). Refer to Dr. Craig's review for additional details of these endpoints.

Subgroup Analyses

Estimates of the treatment effect of percent change in LDL-C at Day 510 appeared similar for subgroups and consistent with the primary endpoint results for each study. Figure 3 summarizes treatment effects in the pooled study population by various subgroups, such as age, sex, race, and baseline disease and treatment characteristics. Dr. Clark conducted shrinkage estimates to further evaluate variability in smaller subgroups and concluded that the sample and shrinkage estimates were generally consistent both with each other and with the primary estimates of the treatment effect.

Figure 4: Forest Plot of Treatment Differences in Percentage Change from Baseline in LDL-C at Day 510 in ORION-9, ORION-10, and ORION-11 Pooled Data by Subgroup – ITT Population

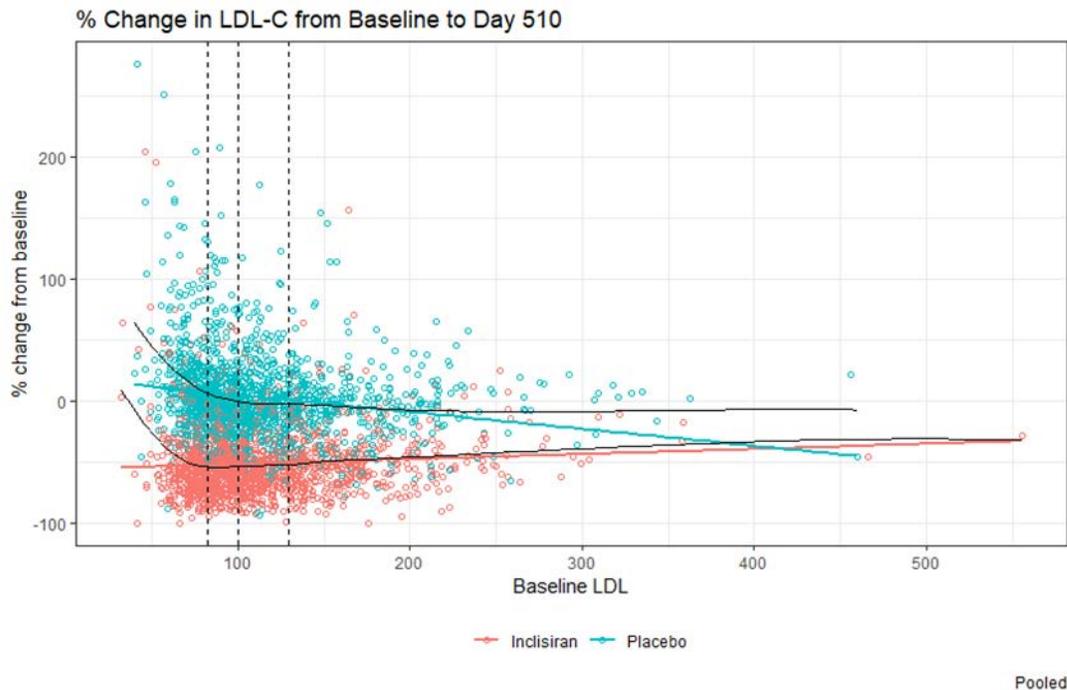


Source: Applicant ISE, Figure 6, p. 77/118.

There were trends in all three studies suggesting that patients with baseline LDL-C in the lowest quartiles had a greater treatment effect than patients in the higher quartiles. To evaluate this apparent trend, Dr. Clark created plots of percent change in LDL-C versus baseline LDL-C level and drew nonparametric curves to characterize the change in treatment effect with

change in baseline LDL-C. These plots suggest that patients with very low LDL-C levels at baseline ($<<100$ mg/dL) had greater LDL-C reduction than patients in other quartiles. The effect was not seen in ORION-9, but this trial of patients with HeFH had fewer patients with very low LDL-C levels at baseline. In ORION-10 and ORION-11, the trend of increased percent change in LDL-C in patients with very low baseline LDL-C was also evident in the placebo arm of the trials, suggesting that the effect is not necessarily treatment-related. The curves were flat across the second to fourth quartiles in plots of all individual studies (refer to Dr. Clark’s review) and in a pooled analysis depicted in Figure 5.

Figure 5: Percentage Change from Baseline LDL-C by Baseline Absolute LDL-C Level in ORION-9, ORION-10, and ORION-11 Pooled Data – ITT Population



Abbreviations: LDL-C=low-density lipoprotein cholesterol, ITT=intent-to-treat
Source: FDA Statistical Reviewer

The significance of the observed trend among patients with low baseline LDL-C is unclear. It is possible that these patients, those whose LDL-C response to statins – which upregulate the LDLR – is more robust, are more responsive to this same mechanism of action with inclisiran. The effect could represent improved adherence to background lipid-lowering therapies in both treatment arms. Alternatively, the trends may represent heterogeneity in the population. In ORION-9, a trial of HeFH patients – all of whom carry an allele for defective LDLR – the response curve was flat across the entire range of baseline LDL-C, whereas the trend was evident among patients in ORION-10 and ORION-11, who comprised a mixed population of non-familial and familial hypercholesterolemia. Thus, patients with low LDL-C at baseline (biallelic functional LDLR) may represent a different population in terms of LDL-C response to inclisiran than those with higher LDL-C at baseline (carriers of defective LDLR).

Summary of Efficacy

LDL-C lowering is a valid surrogate endpoint for risk reduction of CVD and has served as the basis for conventional approval of drug and biologic products. LDL-C lowering has been consistently proven to reduce the risk of atherosclerotic cardiovascular disease in large randomized controlled trials of statins and PCSK9 monoclonal antibody inhibitors. In the absence of cardiovascular outcomes data, decisions to approve novel LDL-lowering therapies are influenced by the direction and magnitude of changes in LDL-C, the mechanism of action of the novel agent, effects on other lipid parameters and markers of cardiometabolic risk, and any evidence for off-target toxicity.

ORION-9, ORION-10, and ORION-11 evaluated the effects of inclisiran on LDL-C in patients with HeFH or ASCVD on maximally tolerated statin therapy who required additional lowering of LDL-C. The study population included relevant comorbidities such as increased age, renal impairment, hepatic impairment, hypertension, and diabetes.

The data from these trials demonstrated a clinically meaningful, statistically robust, and durable LDL-C reduction with inclisiran. Effects on total cholesterol, non-HDL-C and apo-B endpoints are supportive. Consistent effects were observed across various subpopulations defined by demographic and baseline disease characteristics.

Dr. Craig concluded that the clinical trials submitted represent substantial evidence of effectiveness consisting of adequate and well-controlled trials for LDL-C lowering in high-risk populations. She recommends limiting the indication initially, given the availability of therapies with proven CV benefit in lower-risk patients. The indication could potentially be expanded if the ongoing CVOT demonstrates favorable effects on clinical endpoints. Dr. Craig supports approval, and I concur with her recommendation.

Dr. Clark concluded that there were no major statistical issues that would impact or change the overall conclusions, and that redundancy of endpoints constituted a minor issue that may be resolved with judicious selection of data to include in labeling. She also concluded that the results were statistically robust, considering the large treatment effect and small amount of missing data. Dr. Clark supports approval, and I concur with her recommendation.

8. Safety

Dr. Iffat Chowdhury was the clinical safety reviewer. In the clinical review she co-authored with Dr. Craig, Dr. Chowdhury concluded that there were few safety issues that individually and collectively did not outweigh the observed efficacy in the intended population. The most notable safety issues were injection-site reactions (ISRs) and small shifts suggesting worsening glycemia (normal to pre-diabetes, pre-diabetes to diabetes) with inclisiran compared to placebo. Dr. Chowdhury supports approval, and I agree with her recommendation. This review focuses on those issues that affect approvability and labeling. For details of the safety evaluation, refer to the clinical review.

Safety Database

The overall safety population of the development program, defined in all trials as patients who received at least one dose of investigational product, consisted of 4332 patients, including 2452 patients exposed to any dose of inclisiran. Of these patients, approximately 2118 patients were exposed to the phase 3 dose (inclisiran 300 mg subcutaneously), including 1833 patients in the three randomized, controlled Phase 3 trials supporting efficacy, ORION-9, ORION-10, and ORION-11, and constituting the Safety Pool.

The Safety Pool was the major source of safety data supporting the application. ORION-9, ORION-10, and ORION-11 were similarly designed, randomized, placebo-controlled, 18-month trials that differed primarily in the population enrolled (HeFH, ASCVD, and ASCVD or ASCVD risk equivalents, respectively). All three trials had the same primary endpoint, randomization ratio (1:1), and followed the same schedule of events for visits and data collection. Patients were required to be on maximally tolerated statin at baseline in all three trials. Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.1.

Demographics and baseline characteristics were similar between treatment arms among patients in the Safety Pool. The mean age was 64 years, 68% of subjects were male, and 92% were white. Approximately 85% of patients had established ASCVD at baseline, 36% of patients had diabetes, 80% had hypertension, and most were on statins at baseline. Refer to the efficacy section of this review and the clinical review for details of the population.

In the Safety Pool, 92.8% (1691/1822) of placebo-treated patients and 94.4% (1731/1833) of inclisiran-treated patients completed the study. The most common reason for discontinuation in both arms was relocation. Only 0.7% of inclisiran and 0.3% of placebo patients discontinued because of an AE.

General Safety Issues

Deaths, Serious Adverse Events, Withdrawals Due to Adverse Events

The incidence of death was 1.5% in both arms (27/1822 in the placebo group and 27/1833 in the inclisiran-treated group). The most common cause of death in both arms by MedDRA System with inclisiran was within the MedDRA System Organ Class (SOC) of *Cardiac disorders*, as expected for a trial of patients with or at high risk for CVD. There was a small numerical imbalance in cardiovascular deaths, with 9 deaths (0.5%) in the placebo group versus 13 deaths (0.7%) in the inclisiran group.

A higher proportion of patients in the placebo arm (23.0%) reported at least one serious adverse event (SAE) compared to patients in the inclisiran arm (20.4%), including 9.4% with SAEs in the *Cardiac disorders* SOC among placebo patients versus 8.0% among inclisiran patients. Following Cardiac disorders, the most frequent causes of SAEs were in the *Infections and infestations* (3.6% placebo versus 3.9% inclisiran) and *Nervous system disorders* (2.7% placebo versus 2.4% inclisiran) SOCs.

Three of the four most common SAEs by MedDRA Preferred Term (PT) -- *Coronary artery disease*, *Acute myocardial infarction*, and *Unstable angina* – favored inclisiran (i.e. a higher proportion of patients with events in the placebo group), while the fourth, *Angina pectoris*, was similar between treatment groups (20 placebo versus 21 inclisiran).

Despite a small imbalance in cardiovascular death favoring placebo, the trends in cardiovascular SAEs favoring inclisiran, while not definitive, were reassuring. There is an ongoing cardiovascular outcomes trial to assess the effect of inclisiran on major adverse cardiovascular events.

The incidence of treatment-emergent adverse events (TEAEs) leading to withdrawal of study treatment was 1.9% (35/1822) in the placebo arm and 2.5% (45/1833) in the inclisiran arm. The most frequently reported reasons for withdrawal of study drug were in the *Neoplasms benign, malignant and unspecified* SOC, with 10 patients (0.5%) in the placebo group and 13 patients (0.7%) in the inclisiran group. Most reported neoplasms in both arms occurred in one patient, with the exception of prostate cancer, which occurred in four inclisiran patients versus two placebo patients. These findings are consistent with the population.

The most common PTs reported as the reason for withdrawal of treatment were injection-site reactions, cited by 3 patients (0.2%) in the inclisiran group and none in placebo.

In summary, deaths were similar in frequency in the two treatment arms, SAEs occurred at a higher frequency among placebo patients, whereas AEs leading to withdrawal were more frequent among inclisiran. The most frequent causes of death and SAEs were expected for the patient population. Trends in cardiovascular SAEs favored inclisiran.

Adverse Events of Special Interest

Adverse events of special interest encompassed common safety issues observed with related therapies, such as nucleotides, injectables, and other LDL-C lowering products, in addition to issues identified in nonclinical studies and concerns related to very low cholesterol levels. This review focuses on injection-site reactions, hypersensitivity, and new-onset diabetes. Refer to the clinical review for details of the other issues, which are described only briefly in this review because they did not impact approvability or labeling.

Injection site reactions

In the Safety Pool, the percentage of patients with TEAE by MedDRA High Level Term at the injection site was 8.2% (150/1833) for the inclisiran treatment arm versus 1.8% (33/1822) for the placebo treatment arm. The most frequently reported PTs were *Injection site reaction*, *Injection site pain*, *Injection site erythema*, and *Injection site rash*, all greater with inclisiran than with placebo. These ISRs were categorized as mild (86%) or moderate (14%). There were no severe or serious ISRs, although four inclisiran-treated patients withdrew from study drug secondary to non-serious TEAEs at the injection site as compared to no withdrawals in the placebo arm attributed to ISRs.

There were numerical differences in the occurrence of TEAEs at the injection site by gender and age among patients on inclisiran. The incidence of ISRs was 6.5% in male patients

compared to 11.6% in female patients, and 6.6% in patients ≥ 65 years of age versus 10.0% in patients < 65 years of age. The incidence of ISRs was higher among patients in the inclisiran arm with a medical history of allergy (identified using the MedDRA High-Level Group Term *Allergic conditions*) compared to patients without such a history.

Hypersensitivity

There was no meaningful difference in the number (137) or percentage (7.5%) of patients with TEAEs related to hypersensitivity in the placebo arm compared with 136 patients (7.4%) in the inclisiran arm using the Standard MedDRA Query (SMQ) *Hypersensitivity* (broad). Although numerically small imbalances among individual PTs were in some cases more frequent with inclisiran, such as *Asthma* (0.8% placebo patients versus 1.1% inclisiran) and *Seasonal allergy* (0.4% versus 0.7%), other PTs were more frequent with placebo, such as *Rash* (1.2% versus 0.9%) and *Pruritus* (0.7% versus 0.3%). There was no discernable pattern to events that were more frequent in either group, thus the small imbalances appear to be due to chance.

The incidence of serious hypersensitivity reactions such as anaphylaxis, angioedema, and severe cutaneous adverse reaction was low overall and similar between arms. The MedDRA SMQ *Anaphylactic reaction* (narrow) identified three patients with three events on placebo compared to no patients on inclisiran. The MedDRA SMQ *Angioedema* (narrow) resulted in 12 patients with 12 events on inclisiran and 10 patients with 11 events on placebo. The MedDRA SMQ *Severe cutaneous adverse reaction* (narrow) identified two patients on inclisiran and one patient on placebo. Refer to the clinical review for details of these analyses.

In summary, there was no observed imbalance in hypersensitivity events overall or severe hypersensitivity reactions. (b) (4)

New-Onset Diabetes Mellitus

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 as: (1) at least one post-baseline HbA1C $\geq 6.5\%$, (2) two consecutive values of fasting plasma glucose ≥ 126 mg/dL, (3) initiation of a new concomitant medication for control of plasma glucose, or (4) diabetic TEAEs identified by SMQ.

The overall incidence of new-onset diabetes was similar in the two treatment arms, with 92/1138 (8.1%) placebo patients and 87/1088 (8.0%) inclisiran patients meeting the definition. Among patients with normal fasting glucose at baseline (< 100 mg/dL), the incidence of new-onset diabetes was slightly higher in placebo patients compared to inclisiran patients (4.7% versus 4.3%). Among patients with impaired fasting glucose at baseline, the incidence was slightly higher among inclisiran patients (14.6%) versus placebo (13.8%). Time to new-onset diabetes was similar between arms among the patients who developed diabetes, with a mean of 43 weeks in the placebo group and 45 weeks in the inclisiran group.

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, a difference that would generally not be considered clinically meaningful. The difference was largely accounted for by greater decrease in fasting glucose in placebo patients with diabetes compared to inclisiran patients with diabetes (-18.5 mg/dL versus -10.1 mg/dL, respectively). The mean change from Baseline in HbA1c was 0.0% on placebo compared to +0.1% on inclisiran.

Plasma glucose shift tables revealed that slightly more patients on inclisiran experienced a worsening in 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%), and more patients with impaired fasting glucose shifted to diabetes on inclisiran (9.2%) than on placebo (8.0%). The significance of these laboratory changes is unclear, because the trial did not control for initiation or adjustment of diabetes medications.

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 consistently greater incidence of worsening glycemia (normal to pre-diabetes, pre-diabetes to diabetes) with inclisiran compared to placebo, but confounding by initiation or adjustment of glucose-lowering medications cannot be excluded. Given the small differences of unclear significance, the review team concluded that inclusion of these data in labeling is not warranted. I concur with their recommendation.

Other

There was no safety signal for hepatic adverse events or laboratory abnormalities. The incidence of hepatic-related TEAEs was similar between inclisiran and placebo (76 placebo vs 70 inclisiran), whereas elevations in ALT, AST, alkaline phosphatase, and total bilirubin above baseline were similar in the two treatment arms. Trends in elevations above various threshold were inconsistent, but no inclisiran patients experienced AST or ALT elevations above 10X, while one placebo patient experienced an AST elevation >10X ULN. No cases met the definition of Hy's Law definition.

There was no signal of renal toxicity. Investigation of TEAEs associated with renal safety using SMQs were balanced between arms. The incidence of patients with clinically significant changes in creatinine was also similar between arms. Median change from baseline in creatinine was similar between arms, and shift tables demonstrated no meaningful differences.

There was no evidence of myopathy with inclisiran. The incidence of elevations of creatinine kinase to various thresholds was similar between the two treatment arms, and the proportion of patients with at least one TEAE mapped to the SOC of *Musculoskeletal and connective tissue disorders* was similar between arms. There were no SAEs or severe AEs of rhabdomyolysis.

There were no signals of neurologic, neurocognitive, or psychiatric toxicity. 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. There were no differences in neurologic events between arms. There were no meaningful

differences between arms in the incidence of neurocognitive events, and no differences in psychiatric disorders.

Treatment-Emergent Adverse Events.

Adverse events occurring in $\geq 3\%$ of patients and greater than placebo are summarized in Table 2, which is adapted from draft labeling. Aside from the previously discussed imbalance in ISRs, the clinical significance of small imbalances in common AEs, such as arthralgia and bronchitis, is unclear.

Table 2: Adverse Reactions Occurring in Greater Than or Equal to 3% of Inclisiran-Treated Patients and More Frequently than with Placebo in ORION-9, ORION-10, ORION-11 – Safety Population

Adverse Reactions	Placebo (N = 1822) %	LEQVIO (N = 1833) %
Injection site reaction†	1.8	8.2
Arthralgia	4.0	5.0
Urinary tract infection	3.6	4.4
Diarrhea	3.5	3.9
Bronchitis	2.7	4.3
Pain in extremity	2.6	3.3
Dyspnea	2.6	3.2

†includes related terms such as: injection site pain, erythema and rash

Source: Draft Prescribing Information, Leqvio (inclisiran)

There were no significant differences in the relative incidence of TEAEs or SAEs with inclisiran compared to placebo when examined by sex, age, or race subgroups. The interpretation of AE subgroup data by race is limited by small sample size and small number of events for non-white patients. Refer to Dr. Chowdhury’s analyses and discussion in the clinical review for details.

Other General Safety Topics

Liver, muscle, and glycemic parameters were discussed previously. There were no clinically meaningful differences in any other laboratory parameters and no consistent or clinically meaningful differences or trends in vital signs. The incidence of patients with ECG abnormalities reported as adverse events was similar in the two treatment arms.

Immunogenicity

Anti-inclisiran binding antibodies occurred at a low frequency among patients in the Safety Pool. Assessment of anti-drug antibodies 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. 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. Because there were no observed adverse events or loss of effect associated with positive ADA, and because the frequency and titer of pre- and post-treatment ADA positive samples was similar, further characterization (i.e. neutralizing

antibodies) was not conducted. The OBP reviewer concluded that this approach was acceptable.

The three phase 3 trials included approximately 9100 anti-drug antibody (ADA) assays from 1830 patients. The percentage of patients with confirmed ADA was 1.8% at baseline, and 4.9% with at least one confirmed positive at any other time point post-baseline.

Among patients with treatment-induced ADA, defined as a positive ADA after initial treatment in a patient without pre-existing ADA, 1.7% were persistent, defined as two or more positive ADA samples separated by 16 weeks or longer or a single positive ADA at the final sampling time point or within 16 weeks of a negative final sample (consistent with definitions proposed by Shankar et al.⁵).

There were no differences in mean change from baseline in PCSK9 or LDL-C levels among patients with confirmed positive ADA compared to patients without ADA, or in patients with higher maximum titers versus lower maximum titers. There was also no difference in the patterns of individual patient responses between patients with confirmed, transient and confirmed, persistent ADA. Refer to Dr. Chowdhury's discussion of the immunogenicity data in the clinical review for details. The applicant had defined persistent ADA as any confirmed ADA at the patient's last sample and transient ADA response as a negative post-treatment ADA sample occurring after a positive ADA sample and a negative ADA at the last sample analyzed. In response to an information request, the applicant repeated these analyses using the Shankar⁵ definitions of negative, transient, and persistent ADA response and obtained similar results.

The OBP team recommended repeating assay validation parameters to determine assay sensitivity using affinity-purified positive control and then re-analyzing all clinical samples with the appropriately validated assay as a postmarketing commitment. Refer to the Immunogenicity Assay sub-section of Section 2 (Product Quality) of this review for details.

Summary of Safety

Injection-site reactions were the most notable safety issue observed in phase 3 trials, occurring in 8.2% of patients in the inclisiran arm as compared to 1.8% on placebo. No ISR was categorized as a serious or severe AE. Four patients in the inclisiran group withdrew from treatment due to non-serious ISRs.

Other adverse events that occurred more frequently with inclisiran than placebo included arthralgia, urinary tract infections, diarrhea, and bronchitis.

Although there was no overall imbalance in deaths between treatment arms, there was a numerically small numerical imbalance in cardiovascular deaths of unclear significance, with 13 deaths on inclisiran and 9 on placebo. Fewer patients in the inclisiran arm (20%)

⁵ Shankar G, Arkin S, Cocea L, Devanarayan V, Kirshner S, et al. Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. *AAPS J.* 2014;16(4): 658-673.

experienced serious adverse events (versus 23% placebo), and imbalances in cardiovascular SAEs favored inclisiran (more events occurred in patients assigned to placebo).

Adverse events of special interest included common safety issues with nucleotide therapies (hepatic and renal events, hypersensitivity reaction) and events associated with other lipid lowering therapies (myopathy, new-onset diabetes, neurologic events, neurocognitive events, and psychiatric events). There were no imbalances in adverse events or laboratory trends of concern.

The incidence of anti-drug antibodies was low, and there was no meaningful difference in mean changes in LDL-C or PCSK9 or the pattern of individual responses among patients with confirmed positive ADA compared to patients with negative ADA.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application. The Division and the original Applicant (The Medicines Company) agreed on the components of the development program and the key design features of the clinical trials during development. The design of the development program and the approved initial indication for this application are consistent with those of the initial biologic license applications (BLAs) of the PCSK9 inhibitor monoclonal antibodies Praluent (alirocumab) and Repatha (evolocumab). These applications were discussed at meetings of the Endocrinologic and Metabolic Drugs Advisory Committee Meetings held on June 9 and 10, 2015, respectively.

No new efficacy or safety issue arose during review of this application.

10. Pediatrics

Safety and efficacy in pediatric patients have not been established. As a new active ingredient, the application is subject to Pediatric Research Equity Act requirements. Under the initial Pediatric Study Plan (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 and clinical atherosclerotic cardiovascular disease and for pediatric patients at high risk for cardiovascular disease and elevated LDL-C, birth to <8 years of age (or <6 years of age and on apheresis) with elevated cholesterol and HeFH. The rationale for the partial waiver is that “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.

11. Other Relevant Regulatory Issues

Clinical Inspections

The Office of Scientific Investigations (OSI) concluded that the clinical site inspections support the validity of the data. Refer to the Clinical Inspection Summary authored by Dr. Cynthia Kleppinger for details. I concur with Dr. Kleppinger’s recommendation.

The inspection consisted of two domestic clinical investigator sites, one foreign clinical investigator site, and the sponsor. Planned foreign onsite inspections could not be completed because of the COVID-19 global pandemic. OSI conducted remote assessment of source records for Dr. Elane Van Nieuwenhuizen's site in South Africa and concluded that there was adequate adherence to regulations and the investigational plan at the site. OSI was unable to conduct an inspection of the site for Dr. Anna Sidorowicz-Bialynicka in Poland as planned because of local restrictions on access to source records. Inspections of domestic sites for Dr. Ahmad A. Aslam in Tomball, TX and Dr. Kishor M. Bora in Owensboro, KY revealed no objectionable conditions at either site, and only minor non-compliance issues at the latter. Inspection of the sponsor, Novartis Pharmaceuticals Corporation in East Hanover, NJ revealed adequate adherence to the regulations and the investigational plan and no objectionable conditions.

Dr. Kleppinger concluded that the remote regulatory assessment of one foreign site, combined with the domestic inspectional findings support validity of data as reported by the sponsor.

Financial Disclosures

There were 10 covered clinical studies for this application, including 413 principal investigators, and no investigators with reportable financial interests.

Proprietary name

The previous applicant, the Medicines Company submitted the proposed proprietary name (b) (4) on December 26, 2019, and the Division of Medication Error Prevention and Analysis (DMEPA) found the name acceptable. Refer to the consult review by Dr. Melina Fanari. Following the transfer of ownership, the new applicant, Novartis, submitted a request to withdraw the proposed name (b) (4) and submitted the name Leqvio for review on June 10, 2020. The DMEPA reviewer, Dr. Ariane Conrad, found the proposed name acceptable. I concur with her recommendation. Refer to her review for details.

12. Labeling

This section summarizes major changes to the applicant's proposed labeling during negotiations between the Division of Diabetes, Lipid Disorders and Obesity (DDLO, the Division) and the applicant.

Prescribing Information

- ***INDICATIONS AND USAGE section:***
 - *Narrowed the intended population as an adjunct to diet and maximally tolerated statin therapy in patient with HeFH or clinical ASCVD who require additional lowering of LDL-C. This language is consistent with other recent approvals of LDL-C lowering therapies prior to completion of an outcomes trial. The applicant had initially proposed an indication for patients with primary hyperlipidemia to reduce LDL-C.*
 - *Removed a statement proposed by the applicant stating (b) (4)*

- *Added a Limitation of use stating that the effect of inclisiran on cardiovascular morbidity and mortality has not been determined.*
- **DOSAGE AND ADMINISTRATION** section:
 - *Revised for consistency with current labeling practice.*
 - *Removed a statement proposed by the applicant stating [REDACTED] (b) (4)*
 - *Added guidance on monitoring LDL-C levels to assess efficacy.*
- **Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS** sections:
 - *There are no Boxed Warnings, Contraindications, or Warnings/Precautions.*
- **ADVERSE EVENTS** section:
 - *Revised trial description*
 - *Revised adverse reactions table [REDACTED] (b) (4) events occurring at higher frequency than placebo. Combined related terms.*
 - *Removed [REDACTED] (b) (4)*
 - *Removed [REDACTED] (b) (4)*
 - *Revised immunogenicity information*
- **DRUG INTERACTIONS** section:
 - *Removed information about [REDACTED] (b) (4)*
- **USE IN SPECIFIC POPULATIONS** section:
 - *Revised nonclinical data in consultation with Pharmacology/Toxicology team.*
 - *The Division of Pediatrics and Maternal health provided recommendations to conform with the Pregnancy and Lactation Labeling Rule (PLLR) in a consult review Authored by Dr. Christos Mastroyannis. The major recommendations are summarized here:*
 - *Recommend discontinuing during pregnancy for most patients, in whom the chronic benefits on atherosclerosis would not outweigh potential risks of cholesterol lowering based on mechanism of action.*
 - *Statement that it is not known if the drug is present in human milk, but risk to newborns is unlikely because of poor oral bioavailability observed in nonclinical studies.*
 - *Removed [REDACTED] (b) (4)*
- **DESCRIPTION** section:
 - *Revised applicant-proposed changes to the established pharmaceutical class.*
- **NONCLINICAL TOXICOLOGY** section:
 - *Revised in consultation with Pharmacology/Toxicology team for consistency with current labeling practice.*
- **CLINICAL PHARMACOLOGY** section:
 - *Revised in consultation with clinical pharmacology team for consistency with current labeling practice.*
 - *Revised [REDACTED] (b) (4) recommendations as described above.*

- *CLINICAL STUDIES section:*

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-
-
-
-

(b) (4)

Other Labeling

The review team, with guidance from the Division of Medical Policy Programs and the Office of Prescription Drug Promotions, made changes to the Medication Guide and Instructions for Use, consistent with the Prescribing Information and current practices:

13. Postmarketing

Postmarketing Risk Evaluation and Mitigation Strategies

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

Postmarketing Requirements and Commitments

Postmarketing Requirements

- 1) Conduct a two-part (double-blind inclisiran versus placebo [Year 1] followed by open-label with placebo-treated subjects switched to inclisiran [Year 2]), multicenter study to evaluate safety, tolerability, and efficacy of inclisiran in children (aged 12 to <18 years) with heterozygous familial hypercholesterolemia (HeFH).

Draft Protocol Submission: Already submitted
Final Protocol Submission: Final protocol approved 7/2020
Study/Trial Completion: 06/2025
Final Report Submission: 12/2025

- 2) Conduct a two-part (double-blind inclisiran versus placebo [Year 1] followed by open-label with placebo-treated subjects switched to inclisiran [Year 2]), multicenter study to

evaluate safety, tolerability, and efficacy of inclisiran in children [aged 6-7 (if on plasma apheresis) or 8 to <12 years] with heterozygous familial hypercholesterolemia (HeFH).

Draft Protocol Submission: No later than 12/2022
Final Protocol Submission: 06/2023
Study/Trial Completion: 06/2026
Final Report Submission: 12/2026

- 3) Conduct a worldwide, single-arm, 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. (b) (4)

Draft Protocol Submission: June 2021
Final Protocol Submission: December 2021
Interim Study Report: December 2022
December 2023
December 2024
December 2025
December 2026
December 2027
December 2028
December 2029
December 2030
December 2031
December 2032

Study Completion: December 2032
Final Study Report: June 2033

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: 04/2022
Final Report Submission: 06/2022

- 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: 03/2023

Final Report Submission: 04/2023

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/

JOHN M SHARRETTS
12/18/2020 08:25:33 AM

ELLIS F UNGER
12/18/2020 09:23:57 AM

I agree with the assessment of Dr. Sharretts, and this document will also serve as the decisional memorandum from the Office of Cardiology, Hematology, Endocrinology, and Nephrology.