Cross-Discipline Team Lead Review

Date	(electronic stamp)
From	Eileen Craig, MD
Subject	Cross-Discipline Team Lead and Division Director Review
NDA # and Supplement#	NDA 214012, SDN 899, S-018
Applicant	Novartis Pharmaceuticals
Date of Submission	August 13, 2025
PDUFA Goal Date	February 13, 2026
Proprietary Name	Leqvio
Established or Proper Name	inclisiran
Dosage Form(s)	Subcutaneous (SC) injection
Applicant Proposed Indication(s)/Population(s)	LEQVIO is indicated as an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH)/ new population of 12 to 17 years of age with HoFH
Applicant Proposed Dosing Regimen(s)	284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*LEQVIO is indicated as an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in pediatric patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH)/ new population of 12 to 17 years of age with HoFH*
Recommended Dosing Regimen(s) (if applicable)	*284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months*

Review Team

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1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

This Supplement-018 provides final efficacy and safety data from study CKJX839C12302 (referred to as ORION-13) and seeks to expand the indication to include pediatric patients aged 12 to less than 18 years with HoFH. Additional supportive safety data comes from (1) Supplement-017, with final efficacy and safety data from study CKJX839C12301 (referred to as ORION-16) which seeks to expand the indication to include pediatric patients aged 12 to less than 18 years with HeFH; (2) ORION-5 (CKJX839A12302/ MDCO-PCS-17-02), the completed trial in adults with HoFH; and (3) VICTORION-PEDS-OLE (CKJX839C12001B), an ongoing, open-label, single arm extension study in pediatric patients who have completed ORION-16 (adolescent HeFH study) or ORION-13 (adolescent HoFH study).

ORION-13 consists of a 1-year double-blind, parallel group period comparing inclisiran to placebo (randomized 2:1 ratio), followed by a 1-year open-label treatment period with all pediatric patients administered inclisiran to evaluate safety, tolerability, and efficacy of inclisiran in patients aged 12 to less than 18 years old with HoFH and elevated LDL-C (>130 mg/dL). Inclisiran sodium 300mg was administered subcutaneously via pre-filled syringe (PFS) on Days 1, 90, and 270 in part 1. The inclisiran formulation used in ORION-13 is identical to the commercial formulation presently used in adults. The primary endpoint was percent change in LDL-C from baseline to Day 330. HoFH was diagnosed by genetic confirmation and patients with LDLR null/null genotypes were excluded. Patients with LDLR null/null genotype have near or total absence of LDL receptor (LDLR) activity and typically do not respond to therapies, like statins and PCSK9 inhibitors, that act through the LDLR.

Efficacy: The effect of Leqvio (inclisiran) was evaluated in 13 patients aged 12 to less than 18 years with HoFH. The mean LDL-C at baseline was 272 mg/dL (range 154 to 451 mg/dL). In the double-blind period, all patients (9 in the inclisiran group and 4 in the placebo group) received all 3 scheduled doses of study drug with similar mean durations of exposure in both treatment groups (361 days in the inclisiran group and 364 days in the placebo group). In the open-label period, all patients received all 3 scheduled doses of inclisiran. At Day 330, pediatric patients treated with inclisiran had a mean change from baseline of -21.6% (95% confidence interval [CI]: -31.8%, -11.3%), compared with 11.7% (95% CI: -36.9%, 60.3%) for placebo. The mean difference between the inclisiran and placebo groups was -33.3% (95% CI: -79.8%, 13.3%). There was no missing data with respect to the primary endpoint. The mean absolute change in LDL-C from baseline at Day 330 was −63 mg/dL in the inclisiran group and 12 mg/dL in the placebo group, with a mean between-group difference of –75 mg/dL. The placebo-adjusted mean percent changes (95% CI) in ApoB, non-HDL-C, and total cholesterol were –23% (–50, 4), –33% (–87, 22) and –28% (–75, 19), respectively. A reduction in Lp(a) was not seen and small, variable effects were seen for triglycerides, HDL-C, and Apo A1. The main statistical issue was that the ORION-13 study was designed as a descriptive study and was not statistically powered to test any hypothesis. However, inclisiran did

show numerical improvement in the mean percent change in LDL-C from baseline to Day 330 compared to placebo. In addition, patients randomized to placebo demonstrated reduction in LDL-C over time after switching to inclisiran.

Safety:
In a 24-month, two-part study of 13 pediatric patients aged 12 years and older with HoFH, consisting of a 12-month randomized, double-blind, placebo-controlled part (Part 1/Year 1), followed by a 12-month open-label part (Part 2/Year 2), 9 patients received 284 mg of Leqvio administered subcutaneously during Part 1 and 13 patients continued treatment with LEQVIO during Part 2. There were no deaths, serious adverse events (SAEs), adverse events (AEs) leading to study drug discontinuation, or severe AEs. In the double-blind period, injection site reactions (ISRs) were reported in 2 (22%) patients treated with inclisiran. ISRs are a known adverse reaction of inclisiran. Other AEs that occurred more frequently in the inclisiran group include abdominal pain and pyrexia. No patients reported AEs of new onset or worsening of diabetes and there were no treatment-induced anti-drug antibody (ADA) responses. There were no clinically meaningful changes in safety laboratory data or vital signs. Safety concerns with Leqvio are monitorable, generally reversible with treatment discontinuation, and may be adequately addressed in labeling.

Overall benefit-risk assessment:
The Applicant has provided the substantial evidence of effectiveness required by law [see 21 CFR 314.126(a)(b)] to support approval in pediatric patients aged 12 to less than 18 years with HoFH through clinical data from a small number of pediatric patients with HoFH. This application also relies on the extrapolation of safety from adult and pediatric populations with HeFH. Given the rarity of the disease, its well-characterized natural history, the seriousness of the disease, the unmet medical need, and the persuasiveness of the results, these data are considered adequate for this population.
Percent change from baseline in LDL-C has served as the basis for traditional approval of other products intended to treat patients with HoFH. Leqvio (inclisiran) has an overall favorable benefit/risk profile in pediatric patients 12 years of age and older with HoFH. All review disciplines support approval.

In conclusion, approval of 300 mg inclisiran sodium (equivalent to 284 mg inclisiran) administered by a healthcare professional at Day 1, Month 3, and every 6 months afterward in pediatric patients aged 12 to less than 18 years with HoFH will provide an important therapeutic option for LDL-C reduction in a patient population with a high unmet medical need. The safety profile of Leqvio in this study was generally consistent with the safety profile described in controlled and open-label trials involving adults and pediatric patients with HeFH.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HoFH Disorder o Rare genetic disorder (1 in 250,000 to 1 in 360,000 in US); estimated 900 to 1,300 affected individuals in the U.S. o Most common mutations: LDL-C receptor (90%), ApoB, PCSK9, LDLRAP1; mutations result in ineffective plasma clearance of LDL-C • Decreased expression or impaired function of the LDLR results in ineffective plasma clearance of LDL-C from the circulation o Persistent hypercholesterolemia >400-500 mg/dL beginning in childhood o Progressive and early heart disease including premature atherosclerosis, valvular stenosis, and supravalvular stenosis o Premature cardiovascular disease (CVD) and increased risk for CV events (myocardial infarction [MI] beginning 2nd decade) o Clinical manifestations include xanthomata and corneal arcus o Decreased life expectancy (20s to mid-40s) without aggressive treatment o Typically respond poorly to approved lipid-lowering therapies, because most therapies target the defective LDLR • Patients with HoFH are treated with aggressive lipid-lowering therapies to reduce CV risk, primarily based on extrapolation of evidence from LDL-C reduction in primary hypercholesterolemia • LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes in heterozygous familial hypercholesterolemia (HeFH) and non-familial hypercholesterolemia o Meta-analysis of statin trials reported a 22% reduction in 5- year incidence of major vascular events per 38.7 mg/dL (1 mmol/L) absolute reduction in LDL-C.[1] Unknown if this can be extrapolated to	HoFH is a rare genetic condition that results in persistent severe hypercholesterolemia, premature cardiovascular disease, and premature death. Patients with HoFH are treated with LDL-C-lowering therapies with the goal of reducing CV risk. However, patients with HoFH respond poorly to traditional LDL-C-lowering therapies as these treatments typically require a functional LDL-C receptor. There is a high unmet medical need in this population.

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the extreme levels of LDL-C that characterize individuals with HoFH. o CV outcomes trials of two approved PCSK9 inhibitors, alirocumab and evolocumab, demonstrated that reduction in LDL-C led to reduced risk of CV events.[2,3] o A CV outcomes trial with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering.[4] • Patients with HoFH are typically unable to achieve LDL-C goals and respond poorly to approved lipid-lowering therapies, since most therapies target the LDL-C receptor.	
Current Treatment Options	The goal of therapy is LDL-C reduction to reduce the risk of atherosclerosis, CV events, and CV death. • Published recommendations vary, but the LDL-C goal typically ranges from LDL-C <115 mg/dL in children/adolescents to LDL-C <70 to 55 mg/dL in adults or relative reduction of at least 50% from pretreatment baseline values.[5] Treatment options for HoFH • Statins (-14% to -30% LDL-C reduction in HoFH) o Crestor/rosuvastatin approved for patients aged 7 years and older o Lipitor/atorvastatin approved for patients aged 10 years and older • Ezetimibe (-21% to -27% LDL-C reduction in HoFH) approved for patients aged 10 years and older • Evolocumab (-31% LDL-C reduction in HoFH); approved for patients aged 10 years and older • Alirocumab (-36% LDL-C reduction in HoFH); not approved in pediatrics	The goal of therapy is to reduce LDL-C levels with the intent of reducing CV risk. Currently approved lipid-lowering therapies, whether approved for HoFH or used off-label, often do not adequately meet the need for LDL-C reduction in HoFH, particularly in pediatric patients.

[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
[4] Cannon, CP, Blazing, MA, Giugliano, RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.
[5] Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. European heart journal. 2023;44(25):2277-91.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Lomitapide (-40% LDL-C reduction in HoFH): approved for adults •Mipomersen is no longer marketed • Evinacumab-dgnb (-47% LDL-C reduction in HoFH); approved for patients aged 1 year and older • Apheresis: -30 to 50% reduction on average Outcomes trials are not feasible in HoFH because the condition is rare, but LDL-C lowering is expected to reduce the risk of CV events and death	
Benefit	• The efficacy of Leqvio was evaluated in 13 patients aged 12 to less than 18 years with HoFH. At baseline, 100% of patients were on statins, 85% on ezetimibe, and one (8%) patient, in the placebo group, was receiving LDL-apheresis. The mean LDL-C at baseline was 272 mg/dL (range 154 to 451 mg/dL). The mean percent change in LDL-C from baseline to Day 330 was –22% in the inclisiran group and +12% in the placebo group, with a mean between-group difference (95% CI) of –33% (–80, 13). • Reductions from baseline in other lipids (ApoB, total cholesterol, and HDL-C) were also observed during treatment with Leqvio.	Leqvio had a modest LDL-C reduction treatment effect in this difficult to treat patient population. LDL-C reduction in the intended population is expected to result in CV risk reduction.
Risk and Risk Management	• The most serious safety issues reported in the original application in adults were hypersensitivity reactions. Common adverse reactions in the original application (adults) included injection site reactions, arthralgia, and bronchitis. • In the application involving pediatric patients aged 12 to <18 years with HeFH, common adverse reactions included injection site reactions, headache, and upper respiratory tract infection. • In this application involving 13 pediatric patients aged 12 to <18 years, there were no deaths, SAEs, AEs leading to study drug discontinuation, or severe AEs. There were no clinically meaningful changes in safety laboratory data or vital signs.	The most concerning risk is hypersensitivity reactions, including anaphylaxis (seen in post approval clinical trials and postmarket setting) and angioedema. Leqvio is administered in a healthcare setting, and the risk is clinically monitorable. Risks associated with Leqvio are clinically manageable and can be adequately addressed through labeling. Safety postmarketing recommendations (PMRs) or enhanced pharmacovigilance are not necessary.

2. Background

Analysis of Condition

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder caused by, in the majority of cases, mutations in which both low-density lipoprotein cholesterol (LDL-C) receptor (LDLR) alleles are defective. The diagnosis may be made using clinical criteria or genetic testing. The United States of America (US) prevalence of HoFH had been estimated in the literature, using a definition based on clinical phenotype, as ~1 in 1,000,000 persons. However, using more sophisticated genetic cascade testing analyses, the worldwide prevalence may be higher, ranging from 1 in 170,000 to 1 in 320,000.[6,7,8,9,10] The prevalence of HoFH in the US is now estimated between 1/250,000 to 1/360,000[11]; thus, as many as 1,300 individuals in the US may be affected. Untreated individuals have very high concentrations of LDL-C, often in the range of 650 to 1000 mg/dL, cutaneous and tendinous xanthomata, corneal arcus, premature coronary artery disease, and aortic stenosis. Individuals with HoFH are at increased risk for premature cardiovascular (CV) disease and death due to the early onset and prolonged duration of elevated lipid values.

HoFH is caused by, in greater than 90% of the cases, mutations in which both LDLR alleles are defective.[12] Mutations in other genes, such as gain of function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9), which regulates expression of the LDLR, APOB, which encodes apolipoprotein B-100, or LDLRAP1, affecting LDL receptor adaptor protein-1 (LDLRAP1) encoding, may cause a similar phenotype with varying severity.[13] Many

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[6] Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new in- sights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35: 2146-2157.

[7] Nordestgaard BG, Chapman MJ, Humphries SE, et al. A European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478–3490.

[8] de Ferranti SD, Rodday AM, Mendelson MM, Wong JB, Leslie LK, Sheldrick RC. Prevalence of Familial Hypercholesterolemia in the 1999 to 2012 United States National Health and Nutrition Examination Surveys (NHANES). Circulation. 2016;133(11):1067-72.

[9] Beheshti SO, Madsen CM, Varbo A, Nordestgaard BG. Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. Journal of the American College of Cardiology. 2020;75(20):2553-66.

[10] Hu P, Dharmayat KI, Stevens CAT, Sharabiani MTA, Jones RS, Watts GF, et al. Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis. Circulation. 2020;141(22):1742-59.

[11] Cuchel M, Lee PC, Hudgins LC, Duell PB, Ahmad Z, Baum SJ, et al. Contemporary Homozygous Familial Hypercholesterolemia in the United States: Insights From the CASCADE FH Registry. J Am Heart Assoc. 2023;12(9):e029175.

[12] Cuchel M, Bruckert E, Ginsberg H, Raal F, Santos R, Hegele R, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European heart journal. 2014;35(32):2146-57.

[13] Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 223(2), 262–268 (2012).

individuals with HoFH may be compound heterozygotes with different mutations on each of the LDL receptor alleles.[14]

When patients with HoFH come to medical attention because of a classic clinical phenotype, untreated individuals typically have very high concentrations of LDL-C, often in the range of 650 to 1000 mg/dL, cutaneous and tendinous xanthomata, corneal arcus, and premature coronary artery disease and aortic stenosis. HoFH may be diagnosed by clinical criteria or confirmed via genetic testing. At academic centers, HoFH patients are often characterized by their degree of residual LDLR activity using ex vivo assays. Patients who are LDLR-negative (<2% of LDL receptor function in cultured fibroblasts) tend to have higher levels of LDL-C and a worse prognosis than those who are LDLR-defective (2 to 25% residual LDLR activity). Untreated LDLR-negative patients rarely survive beyond the second decade of life. Those who are LDLR-defective have a better prognosis, but still often develop clinically significant atherosclerotic vascular disease by the age of 30 years without treatment.[13]

Unlike hypercholesterolemia and dyslipidemia in the general population, in which multiple genetic and environmental factors contribute to its pathophysiology, the HoFH phenotype is essentially a monogenic disorder of deranged LDL metabolism. Thus, lowering LDL-C is an appropriate therapeutic goal in this orphan population, and LDL-C lowering as the target of therapy was supported in 2012 during meetings of the Endocrinologic and Metabolic Drugs Advisory Committee that preceded the approval of lomitapide and mipomersen for HoFH. It is unknown, however, whether the often-quoted quantitative relationship between cardiovascular risk and LDL-C reduction (i.e., ~22% reduction in major vascular events per 40 mg/dL reduction in LDL-C, based on clinical trials of statins) can be extrapolated to the extreme levels of LDL-C that characterize individuals with HoFH.

Current Treatment Options

The goal of treatment is LDL-C lowering to reduce the risk of atherosclerotic cardiovascular disease (ASCVD), CV events, and death. High-dose statin therapy, lomitapide, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapies, evinacumab-dgnb, and lipid apheresis are the main treatment options for HoFH. Despite many effective lipid-lowering therapies available for primary hypercholesterolemia, treatment options in HoFH are limited due to the lack of a functional LDL-C receptor (the primary target of statins and PCSK9 inhibitors); hepatotoxicity and tolerability issues (lomitapide, mipomersen [no longer marketed in the US]); and cost, availability, and patient burden (lipid apheresis). Patients with HoFH typically have severe hypercholesterolemia (LDL-C ≥190 mg/dL) even after treatment with multiple lipid-lowering agents.

[14] Goldstein J, Hobbs H, Brown, M. 2001. Familial hypercholesterolemia. In The metabolic and molecular bases of inherited disease. C. Scriver, A. Beaudet, W. Sly, and D. Valle, editors. McGraw-Hill. New York, New York, USA. 2863–2913.

Treatment guidelines vary, but target LDL-C generally ranges from LDL-C <115 mg/dL in children/adolescents to LDL-C <70 to 55 mg/dL in adults or relative reduction of at least 50% from pretreatment baseline values.[15]

In patients 5 years of age and older, treatment of HoFH typically involves lipid-modifying medical therapy as well as extracorporeal removal of plasma LDL via LDL apheresis, typically once every 1 to 2 weeks. Since HoFH is a condition caused by either absent or deficient LDL receptor function resulting in reduced LDL-C clearance from plasma, therapies such as PCSK9 inhibitors and statins, which do not improve the function of individual LDL receptors but rather upregulate native (dysfunctional) LDL receptors, are not particularly effective. LDL apheresis is FDA approved and indicated if the LDL-C is >500 mg/dl in patients with HoFH, >300 mg/dl in HeFH patients without coronary artery disease (CAD), or >200 mg/dl in HeFH patients with CAD despite 6 months of treatment with maximal drug and dietary therapy.[16] The reduction in LDL-C with apheresis is transient (~2 weeks), as LDL cholesterol begins to reaccumulate after each session. While LDL apheresis significantly lowers LDL-C and is considered the standard of care for patients with HoFH, the limitations include limited availability, high cost, procedure duration, and the need to maintain adequate vascular access.[17]

The following drugs are currently approved for the reduction of elevated LDL-C specifically for patients with HoFH: simvastatin, atorvastatin, rosuvastatin, ezetimibe, simvastatin/ezetimibe, atorvastatin/ezetimibe, lomitapide, mipomersen, evolocumab, alirocumab, and evinacumab-dgnb. The drugs that have an FDA approved indication for pediatric patients with HoFH includes atorvastatin, rosuvastatin, ezetimibe, evolocumab, and evinacumab-dgnb.

Leqvio (inclisiran)

Inclisiran is a double-stranded small interfering ribonucleic acid (siRNA), conjugated on the sense strand with triantennary N-Acetylgalactosamine (GalNAc) to facilitate uptake by hepatocytes. In hepatocytes, inclisiran utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9. This increases LDL-C receptor recycling and expression on the hepatocyte cell surface, which increases LDL-C uptake and lowers LDL-C levels in the circulation.

Leqvio (inclisiran) was approved in the United States of America (US) on December 22, 2021, 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). Leqvio is currently indicated as “as an adjunct to diet and exercise to reduce low-density

[15] Cuchel M, Raal FJ, Hegele RA, Al-Rasadi K, Arca M, Averna M, et al. 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. European heart journal. 2023;44(25):2277-91.

[16] Page MM, et al. Lipoprotein apheresis and new therapies for severe familial hypercholesterolemia in adults and children. Best Pract. Res. Clin. Endocrinol. Metab. 2014;28:387-403.

[17] Thompson GR. Lipoprotein apheresis. Curr Opin Lipidol. 2010;21: 487–491.

lipoprotein cholesterol (LDL-C) in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH)."[18] Inclisiran is administered subcutaneously as a single injection initially, again at 3 months, and then every 6 months.

Regulatory History

Leqvio received Orphan Drug Designation for the treatment of HoFH on January 22, 2018 (DRU-2017-6180). FDA issued a Written Request (WR), dated November 1, 2019, to obtain pediatric information on inclisiran. The Applicant accepted the WR on December 4, 2019. Leqvio is being evaluated in pediatric patients with HoFH (b) (4) .[19]

- CKJX839C12302 (referred to as ORION-13) in pediatric patients aged 12 to less than 18 years

(b) (4)

Leqvio is also being evaluated in pediatric patients with HeFH (b) (4) .

- CKJX839C12301 (referred to as ORION-16) in pediatric patients aged 12 to less than 18 years

(b) (4)

ORION-16 and ORION-13 have been completed, (b) (4) .

- November 22, 2024: Type C meeting to discuss the planned sNDA for treating pediatric patients (12 to <18 years) with HeFH and HoFH. FDA noted that separate supplements are needed for the pediatric HeFH and HoFH indications. FDA agreed that ORION-5 (completed trial in adults with HoFH) and VICTORION-PEDS-OLE (open-label extension study in pediatric patients who have completed ORION-16 or ORION-13) can be submitted as supplemental safety information. The 90-day safety update will include data from VICTORION-PEDS-OLE (data lock-point of January 2, 2025). FDA requested the following to be included: protocols, Statistical Analysis Plans (SAPs), Clinical Trial Material, General Data and Analyses, and items such as Statement of Good Clinical Practice and Applicability of Foreign Data.
- April 30, 2025: Type B pre-sNDA Meeting to discuss the study data to support the pediatric indications for HeFH and HoFH. FDA commented that the data appeared adequate to support review of the proposed pediatric indications and appeared likely to meet the requirements for a priority review designation. FDA requested that pre-filled syringe (PFS)/device-related adverse event (AE) data including use errors and device

[18] NDA 214012 LEQVIO, revised 07/2025, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6fc0afca-4513-4c35-b594-6544aee29a44

[19] (b) (4)

malfunction in clinical studies for the >12 years of age group and postmarketing device data be included in the sNDAs for pediatric patients with HeFH and HoFH.

3. Product Quality

The drug substance and drug product used in ORION-13 was the same as used in the original NDA submission. For this indication, the currently marketed product will be used. There are no unresolved product quality issues.

4. Nonclinical Pharmacology/Toxicology

No new pharmacology or toxicology data were submitted for this application.

5. Clinical Pharmacology

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) and Division of Pharmacometrics (OCP/DPM) have reviewed clinical pharmacology data from NDA 214012 Supplement 018 and found the data acceptable. OCP/DCEP and DPM recommend approval of this supplement for pediatric patients aged 12 years and older with HoFH.

Dosage: The proposed dosage for pediatric patients aged 12 years and older is the same as the approved dosage for adults, and the observed and predicted inclisiran exposures in pediatric patients aged 12 years and older are comparable to those in adults. Because of the temporal disconnect between the pharmacokinetics (PK) of inclisiran and the prolonged pharmacodynamic (PD) effect, the value of PK comparison with adults to support inclisiran dosing in adolescent patients with HeFH is somewhat limited. Inclisiran is not approved for the HoFH indication in adults; therefore, there is no basis for PK comparison of inclisiran exposure between pediatric patients with HoFH and adults.

Hepatic Impairment (same as the current label): No dose adjustment is necessary in patients with mild to moderate hepatic impairment. Leqvio has not been studied in patients with severe hepatic impairment.

Renal Impairment (same as the current label): No dose adjustments are necessary for patients with mild, moderate, or severe renal impairment. Leqvio has not been studied in patients with end stage renal disease.

Immunogenicity: The immunogenicity of inclisiran was evaluated in pediatric patients with HeFH in study ORION-16 and was found to be comparable to that observed in adults. Specifically, 5.8% of patients developed ADA as compared to 4.6% reported in adults. All ADA positive samples had low titers with no apparent impact on safety or pharmacodynamics (i.e., LDL-C reduction). The immunogenicity of inclisiran was evaluated in pediatric patients with HoFH in Study ORION-13 and was found to be comparable to that observed in adults. In Study

ORION-13, there were no persistent or transient treatment-induced ADA responses reported. A single patient who received inclisiran (1 out of 9 in the inclisiran group) throughout the study had a positive ADA result at the pre-dose timepoint on Day 1 and at the subsequent assessments with low titers.

Refer to the review by Tian Zhou, PhD, Li Li, PhD, Xiaolei Pan, PhD, and Justin Earp, PhD for additional details (in DARRTS dated January 20, 2026; Reference ID: 5729788).

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Review Strategy
Mengjie Zheng, PhD was the primary statistical reviewer and Feng Li, PhD was the secondary statistical reviewer for this submission. They concluded that there were no major statistical issues identified during the review. They recommend approval for the requested indication. Refer to their review for details on the statistical analysis and assessment of this application (in DARRTS dated January 16, 2026; Reference ID: 5729565).

Michael Nguyen, MD was the primary clinical reviewer for this submission. Refer to his thorough review for details on the clinical assessment of efficacy for this application (in DARRTS dated January 29, 2026; Reference ID: Reference ID: 5736175).

Study Design: ORION-13 consists of a 1-year double-blind, parallel group period comparing inclisiran to placebo (randomized 2:1 ratio), followed by a 1-year open-label treatment period with all pediatric patients administered inclisiran to evaluate safety, tolerability, and efficacy of inclisiran in patients aged 12 to less than 18 years old with HoFH and elevated LDL-C (>130 mg/dL). Inclisiran sodium 300mg was administered subcutaneously via pre-filled syringe (PFS) on Days 1, 90, and 270 in part 1. The inclisiran formulation used in ORION-13 is identical to the commercial formulation presently used in adults. The primary endpoint was percent change in LDL-C from baseline to Day 330. HoFH was diagnosed by genetic confirmation and patients with LDLR null/null genotypes were excluded. Patients with LDLR null/null genotype have near or total absence of LDL receptor (LDLR) activity and typically do not respond to therapies, like statins and PCSK9 inhibitors, that act through the LDLR.

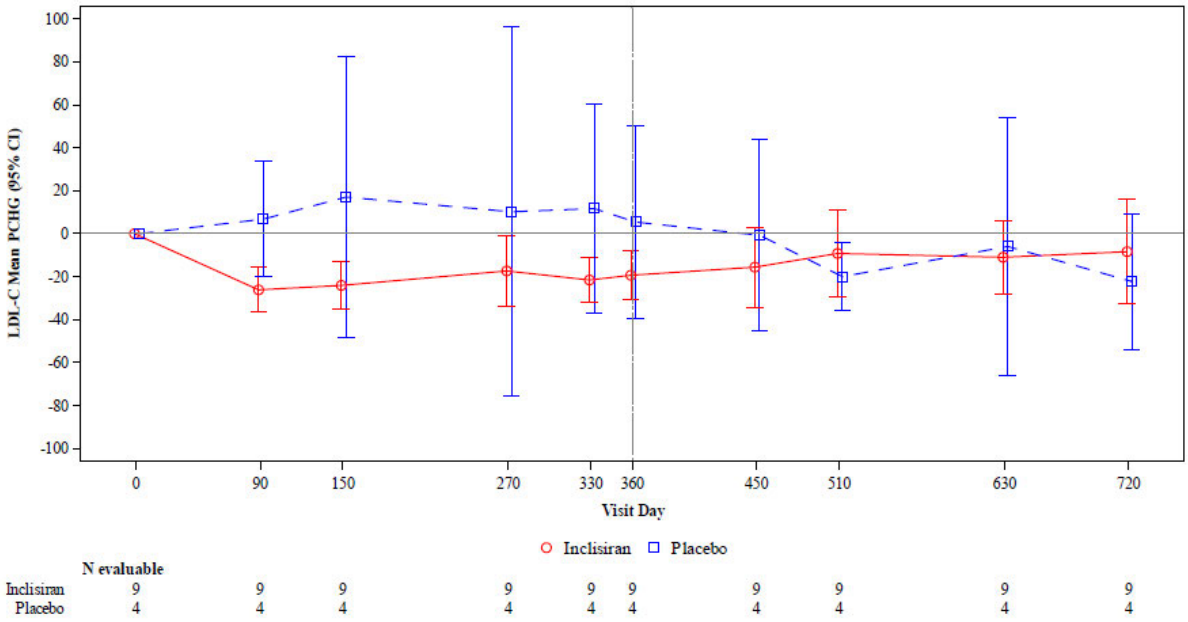
Demographics: The effect of Leqvio (inclisiran) was evaluated in 13 patients aged 12 to less than 18 years with HoFH. Nine (69%) females and four males were enrolled in the program. Eleven (85%) patients were White, and the remaining 2 patients (15%) patients were Asian, 1 in each treatment group. One patient (8%), in the inclisiran group, was of Hispanic or Latino ethnicity. One patient was from the United States (US), 2 patients were from Canada, and the remainder came France, Greece, Lebanon, Malaysia, Netherlands, and Turkey. At baseline, 100% of patients were on statins, 85% on ezetimibe, and one (8%) patient, in the placebo group, was receiving LDL-apheresis. The mean LDL-C at baseline was 272 mg/dL (range 154 to 451 mg/dL)

(265 mg/dL [SD 116] in the inclisiran group and 288 mg/dL [SD 115] in the placebo group). The mean age was 15 years (range 12 to 17 years), the mean weight was 54 kg (range 40 to 93 kg), and the mean body mass index (BMI) was 21 kg/m^2. No patients had a medical history of pre-diabetes, type 1 or type 2 diabetes, hypertension, coronary heart disease, cerebrovascular disease, peripheral artery disease, or chronic heart failure. One (8%) patient in the inclisiran group met the fasting plasma glucose (FPG) laboratory criteria for pre-diabetes.

Efficacy: In the double-blind period, all patients (9 in the inclisiran group and 4 in the placebo group) received all 3 scheduled doses of study drug with similar mean durations of exposure in both treatment groups (361 days in the inclisiran group and 364 days in the placebo group). In the open-label period, all patients received all 3 scheduled doses of inclisiran. At Day 330, pediatric patients treated with inclisiran had a mean change from baseline of -21.6% (95% confidence interval [CI]: -31.8%, -11.3%), compared with 11.7% (95% CI: -36.9%, 60.3%) for placebo. The mean difference between the inclisiran and placebo groups was -33.3% (95% CI: -79.8%, 13.3%). There was no missing data with respect to the primary endpoint. The mean absolute change in LDL-C from baseline at Day 330 was −63 mg/dL in the inclisiran group and 12 mg/dL in the placebo group, with a mean between-group difference of –75 mg/dL. The placebo-adjusted mean percent changes (95% CI) in ApoB, non-HDL-C, and total cholesterol were –23% (–50, 4), –33% (–87, 22) and –28% (–75, 19), respectively. A reduction in Lp(a) was not seen and small, variable effects were seen for triglycerides, HDL-C, and Apo A1. The main statistical issue was that the ORION-13 study was designed as a descriptive study and was not statistically powered to test any hypothesis. However, inclisiran did show numerical improvement in the mean percent change in LDL-C from baseline to Day 330 compared to placebo. In addition, patients randomized to placebo demonstrated reduction in LDL-C over time after switching to inclisiran.

Mean percent changes in LDL-C by visit are shown in the figure below. As detailed in Dr. Zheng's review, the mean percent change in LDL-C from baseline to Day 720 was -13% (95% CI: -30%, 5%) overall, -8% (95% CI: -33%, 16%) in the inclisiran-inclisiran group, and -22% (95% CI: -56%, 9%) in the placebo-inclisiran group. Dr. Zheng points out that in the inclisiran-inclisiran group, mean reductions in LDL-C achieved during the double-blind period diminished over the open-label period; noting that 2 pediatric patients had large increases of +27% and +47% at Day 720. In the placebo-inclisiran group, reductions in LDL-C were observed by the first assessment following the switch from placebo to inclisiran at Day 450, with some further decrease at Day 510 that was sustained through Day 720.

Figure 1. Mean Percent Change from Baseline in LDL-C by Visit, ORION-13



Source: FDA Statistical Reviewer

The statistical reviewer performed subgroup analyses for the primary efficacy endpoint: percent change in LDL-C from baseline to Day 330. Due to the small overall sample size, the subgroup analyses by sex, race, age groups, ethnicity, and region are limited. However, all subgroups on inclisiran demonstrated a reduction in LDL-C of 20 to 24%, with the exception of the subgroup by sex (female [n=7], -25%; males [n=2], -9%).

Conclusions on the Substantial Evidence of Effectiveness

HoFH is a rare and life-threating disease, and the observed LDL-C lowering in these 13 pediatric patients was deemed acceptable. The Applicant has provided the substantial evidence of effectiveness required by law [see 21 CFR 314.126(a)(b)] to support approval in pediatric patients aged 12 to less than 18 years with HoFH through clinical data from a small number of pediatric patients with HoFH. This application also relies on the extrapolation of safety from adult and pediatric populations with HeFH.

8. Safety

Michael Nguyen, MD was the primary clinical reviewer for safety for this submission. Refer to his thorough review for details on the clinical assessment of safety for this application (in DARRTS dated 29, 2026; Reference ID: Reference ID: 5736175).

Exposure:

- Part 1 (Double-blind period): All inclisiran and placebo treated pediatric patients received all 3 scheduled doses of study drug, with similar mean durations of exposure in both treatment groups (361 days in the inclisiran group and 364 days in the placebo group).
- Part 2 (Open-label period): All inclisiran and placebo treated pediatric patients received all 3 scheduled doses of study drug (inclisiran) with mean durations of exposure of 358.5 days.

In ORION-13, there were no deaths, serious adverse events (SAEs), adverse events (AEs) leading to study drug discontinuation, or severe AEs. In the double-blind period, injection site reactions (ISRs) were reported in 2 (22%) patients treated with inclisiran. ISRs are a known adverse reaction of inclisiran. Other AEs that occurred more frequently in the inclisiran group include abdominal pain and pyrexia. There were no cardiac, hepatic, renal, musculoskeletal, neurological, or psychiatric events in either treatment group, and no patients reported AEs of new onset or worsening of diabetes. There were no clinically meaningful changes in safety laboratory data for hematology, chemistry (including liver enzymes, creatine kinase [CK)] fasting plasma glucose [FPG], and HbA1c) in either group. One patient in the inclisiran group had a decreased estimated glomerular filtration rate (eGFR) value of 87 mL/min/1.73m^2 during part 1 although the baseline eGFR value was 91 mL/min/1.73m^2 and the post-baseline was 91 to 113 mL/min/1.73m^2. No patients developed treatment-induced anti-drug antibodies (ADA). There were no clinically meaningful changes in vital signs, including blood pressure and heart rate. Although limited by the small sample size and older age of the pediatric patients, there were no adverse effects seen in the inclisiran group regarding growth (height, weight, BMI), pubertal development (Tanner staging), or hormonal status (estradiol in females, testosterone in males, luteinizing hormone [LH], follicle-stimulating hormone [FSH], dehydroepiandrosterone sulfate [DHEAS], and cortisol).

The safety data in the open-label portion were consistent with that from the double-blind portion; no new safety signals were noted.

Given the small size of the ORION-13 study, the safety data in pediatric patients aged 12 years and older with HoFH also relies on the safety data in pediatric patients aged 12 years and older with HeFH (ORION-16) as well as the safety profile of inclisiran in adults with hypercholesterolemia. Safety issues seen with adults include serious hypersensitivity events (e.g., angioedema) and common adverse reactions such as injection site reactions, arthralgia, and bronchitis.

Hypersensitivity

Anaphylaxis was added to the Contraindications, Warnings & Precautions, and Postmarketing Experience sections of the prescribing information (PI) based an adverse reaction seen in the ongoing VICTORION-2 PREVENT CVOT in adults with established ASCVD and a review of cases in the postmarket database identified through FDA Adverse Event Reporting System (FAERS). DPV-I identified seven cases sourced from FAERS of anaphylaxis in patients using inclisiran reported from January 11, 2024, to November 17, 2025. The evidence supporting an association between anaphylaxis with inclisiran use includes a plausible temporal relationship for all cases that reported time to onset of anaphylaxis symptoms (n=6). Most cases (n=4) specified at least one corrective treatment (e.g., epinephrine, corticosteroid, intravenous fluid) for anaphylaxis. The cases were assessed as having a probable (n=2) or possible (n=5) causal

association between inclisiran use and anaphylaxis. All seven cases had a serious outcome, with three patients requiring hospitalization and two patients requiring epinephrine administration to treat the anaphylactic reaction. DPV-I provided an update to the previous Pharmacovigilance and Epidemiology Review analyzing inclisiran and hypersensitivity (in DARRTS dated March 14, 2024). The previous review identified two cases with evidence supporting an association between anaphylaxis with inclisiran use (1 case probable and 1 case possible). Cumulatively, nine cases of anaphylaxis in patients using inclisiran have been identified from FAERS. For additional information, refer to the review by H Longanacre, Safety Evaluator DPV-I (in DARRTS dated January 12, 2026; Reference ID: 5726189).

Device Issues

The Applicant was asked to provide information on medical device AEs in all trials and postmarketing device-related AE data from the approved NDA 214012 Leqvio pre-filled syringe PFS as part of the planned safety data for the sNDA for adolescents with HeFH and sNDA for adolescents with HoFH. The most recent postmarket assessment was submitted in the Periodic Safety Update Report (PSUR) covering the reporting interval of January 1, 2024, until December 31, 2024, submitted to the FDA NDA 214012 on March 6, 2025. In the postmarketing product update, per the latest PSUR (March 2025), device-related AEs for the PFS have been reported (e.g., device malfunction, difficult to use, etc.). DDLO consulted the Division of Mitigation Assessment and Medication Error Surveillance (DMAMES) to provide an assessment of device-related concerns associated with the currently marketed Leqvio prefilled syringes as device issues could result in dose omission, delayed therapy, or potentially multiple needle exposures in the pediatric population if healthcare providers encounter administration difficulties due to clogged needles and need to re-inject the product with a new syringe. DMAMES' comprehensive review of FAERS data and the 2024 PSUR did not identify any new safety concerns beyond those already characterized. While device-related issues with the Leqvio prefilled syringe continue to occur, they appear to be reported infrequently and the current Instructions for Use provide adequate guidance for proper administration and use error mitigation, and no changes to the labeling appear necessary at this time (see DMAMES review by M. Siahpoushan, Y. Maslov, and Z. Oleszczuk in DARRTS dated November 5, 2025; Reference ID: 5690024).

Conclusion on the Safety Profile

The safety evaluation in these 13 pediatric patients with HoFH aged 12 to <18 years provides reassurance that the safety profile in this population is similar to that already labelled for adults with hypercholesterolemia, including HeFH. Overall, the safety profile of inclisiran includes a contraindication for serious hypersensitivity reactions (which did not occur in any of the 13 pediatric patients with HoFH), while labelled adverse reactions (most notably injection site reactions) are mostly mild and self-limited.

Regarding safety in this sNDA, recommended regulatory actions include edits to Sections 6 and 8.4 on Pediatric Use that states that the safety profile of Leqvio in pediatric patients with HoFH aged 12 to 17 years was similar to the safety profile in adults. In addition, the term 'anaphylaxis' was added to Section 4 Contraindications based on an adverse reaction seen in the ongoing VICTORION-2 PREVENT CVOT in adults with established ASCVD and a review of cases in the postmarket database. Section 5 Warnings and Precautions was added with a new Hypersensitivity section.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application. The design of the pediatric study, specifically the primary endpoint, was consistent with other development programs for HoFH. Percent change in LDL-C has previously served as the basis for traditional approval in this population. Efficacy data were convincing and clinically meaningful, and safety concerns would not preclude a favorable benefit-risk consideration in the intended population.

10. Pediatrics

Efficacy and Safety in Pediatric Patients
The application provides substantial evidence of effectiveness to support an indication for pediatric patients with HoFH aged 12 to <17 years. Refer to the *Efficacy* and *Safety* sections of this review.

Other Pediatric Issues
Leqvio received Orphan Drug Designation for the treatment of HoFH on January 22, 2018 (DRU-2017-6180); therefore, the application is exempt from the requirements of the Pediatric Research Equity Act (PREA). FDA issued a Written Request (WR), dated November 1, 2019, to obtain pediatric information on inclisiran for HeFH and HoFH. The Applicant accepted the WR on December 4, 2019. Leqvio is being evaluated in pediatric patients with HoFH (b) (4)

11. Other Relevant Regulatory Issues

Clinical Inspections
Two clinical site inspections were requested for this application.

- Site #6601: Dr. Wiegman (Amsterdam, Netherlands)
  At this site for Study ORION-16, 19 pediatric patients were screened, randomized, and enrolled. All 19 pediatric patients completed the study. Records for all 19 enrolled patients were reviewed. At this site for Study ORION-13, 2 pediatric patients were screened, randomized, and enrolled. Two patients completed the study. Records for both enrolled patients were reviewed.
- Site #7001: Dr. Bergeron (Quebec, Canada)
  At this site for Study ORION-16, 9 pediatric patients were screened, and 8 patients were enrolled. All 8 patients completed the study. Records for all 8 enrolled patients were reviewed. At this site for Study ORION-13, 2 pediatric patients were screened, randomized, and enrolled. Two patients completed the study. Records for both enrolled patients were reviewed.

Based on the inspection results of these two clinical investigators (CIs), no significant regulatory violations were identified. The clinical data generated by these CIs are verifiable and appear acceptable in support of the respective indications. The studies appear to have been conducted adequately. For additional information, refer to the review by Drs. Kim, Lu, and Sellers (in DARRTS dated January 16, 2026; Reference ID: 5729880).

Financial Disclosures
The Applicant confirms that no clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. No disclosable financial information was reported by any of the clinical investigators participating in ORION-13.

Statement of Good Clinical Practice (GCP)
The Applicant confirms that the studies were designed, implemented, and reported in accordance with the ICH Harmonization Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the declaration of Helsinki. Furthermore, all non-IND foreign sites participating in ORION-13 conformed to the requirements of 21 CFR 312.120.

Rationale for assuring the applicability of foreign data to the US population
Thirteen pediatric patients were enrolled from 8 different countries, including 1 (8%) male pediatric patient from the United States and 3 (23%) pediatric patients from North America (2 patients were from Canada). The Applicant asserts, and FDA agrees, that the pharmacokinetic (PK) and pharmacodynamic (PD) data in healthy volunteers and participants showed that there are no relevant intrinsic or extrinsic factors to influence inclisiran PK or PD. Japanese, Chinese and Non-Asian participants showed similar PK and PD, and no ethnicity-related dose adjustments are required. Age, sex, race, and creatinine clearance were found not to significantly influence inclisiran PK or PD in adults. In addition, baseline demographics and disease characteristics, as well as baseline lipid modifying therapies from the pediatric patients in North America and globally were similar. The review team agrees that the results from ORION-13 are applicable to the US population.

12. Labeling

Labeling recommendations encompass recommendations from Melinda Wilson, Associate Director for Labeling for DDLO.

Prescribing Information
The following summarizes changes to proposed labeling and highlights areas of disagreement with the applicant.

- INDICATIONS AND USAGE:
  - Indication added for use in pediatric patients 12 years and older with HoFH. We agreed with the Applicant's proposed wording of the indication.
- DOSAGE AND ADMINISTRATION:
  - The dosage for this younger population is the same as in adults. Revisions were made in this section to include the pediatric population as described in the indication.

- CONTRAINDICATIONS:
  - Anaphylaxis was added based an adverse reaction seen in the ongoing VICTORION-2 PREVENT CVOT in adults with established ASCVD and a review of cases in the postmarket database identified through FDA Adverse Event Reporting System (FAERS).
- WARNINGS AND PRECAUTIONS:
  - This section was added to provide for a new Warning and Precaution (5.1) for Hypersensitivity Reactions based on the anaphylaxis cases noted above. Language was added that described that hypersensitivity reactions, including anaphylaxis and angioedema, have been reported in patients treated with LEQVIO.
- ADVERSE REACTIONS:
  - A brief summary of the pediatric study in HoFH was added to this section along with noting that the safety profile reported in pediatric patients was consistent with adult patients.
  - Clarified the population from which safety information was obtained (e.g. adults versus pediatric patients) throughout this section.
  - We recommend using consistent terminology throughout the labeling, where appropriate. Because clinical trials represent a specific subset of clinical studies that are controlled, prospective investigations designed to evaluate interventions, we recommend using the term "trials" throughout the labeling (unless specifically addressed in statue or regulation or not applicable), to accurately contextualize data from such interventions.
  - Anaphylaxis and pruritus were added to 6.2 Postmarketing Experience
- USE IN SPECIFIC POPULATIONS:
  - Pediatric Use: Added that the safety and effectiveness of LEQVIO as an adjunct to diet and other LDL-C-lowering therapies for the treatment of HoFH have been established in pediatric patients aged 12 years and older. Use of LEQVIO for this indication is based on data from a 12-month, randomized, placebo-controlled, double-blind study in 13 pediatric patients with HoFH. The safety and effectiveness of LEQVIO have not been established in pediatric patients with HeFH or HoFH younger than 12 years of age. The safety and effectiveness of LEQVIO has not been established in pediatric patients with other types of hypercholesterolemia.
  - The term 'study', rather than 'trial', was allowed in this section. The guidance for industry: *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019) refer to clinical study data in the labeling. In addition, the Best Pharmaceuticals for Children Act (BPCA)and the Pediatric Research Equity Act (PREA) refer to "study requirements". Thus, we agree to maintain the use of the term, "studies" in this section.
- CLINICAL PHARMACOLOGY:
  - New information was included for the pediatric patients aged 12 years and older with HoFH for sections 12.3 and 12.6.
- CLINICAL STUDIES:
  - New subheadings were added for adult and pediatric indications.
  - We requested for all figures in this section describing the percent change in LDL-C, add in dose markers in the figure for when the drug was administered. The

applicant also expanded the x axis to include 1 month intervals (versus 2 month intervals previously reported).
    - We requested that for the adult trials, information be added on the mean percent change in LDL-C from baseline at Day 450 (timepoint of last injection prior to primary endpoint) to be consistent with labeling of other LDL-C lowering therapies that describe effectiveness at the time of injection (not at some time after injection). The Applicant declined the change and provided their rationale. While our preference remains for the primary endpoint to be at the time just prior to the injection (i.e., Day 450), we agree that the visual depiction of the percentage change in LDL-C at each timepoint shown in section 14 of the PI provides an acceptable descriptive summary of inclisiran's effect over time, especially as the Day 450 timepoint was not controlled for multiplicity and is an exploratory endpoint.
    - A description of the clinical data, to include baseline demographics and effectiveness information, that was collected through the ORION-13 pediatric study was included in this section. The statistical reviewer requested that the 95% confidence intervals be recalculated based on t-distribution assuming unequal variance.
    - We requested that the Applicant include a figure (Mean Percent Change from Baseline in LDL-C Over 24 Months in Pediatric Patients aged 12 Years and Older with HoFH) to describe LDL-C changes during the double-blind and OLE period for the HoFH study. Include dose markers in the figure for when the drug was administered. The Applicant requested that for consistency in trial presentation for the HeFH clinical trial results and the adult trials, that the results information in the section for HoFH reflect the 12-month double-blind portion of the study in both narrative and in Figure. We accepted this request.
- PATIENT COUNSELING INFORMATION
    - To be consistent with the newly added Warnings and Precautions section, we added a subsection on hypersensitivity.

Other Labeling

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) evaluated the proposed Leqvio Prescribing Information and instructions for use [S-017 (pediatric HeFH) and S-018 (pediatric HoFH) efficacy supplements] for areas of vulnerability that may lead to medication errors. Their evaluation did not identify areas of vulnerability that may lead to medication errors (see review S. Vee and D. Birkemeier in DARRTS dated November 20, 2025; Reference ID: 5698855).

The Office of Prescription Drug Promotion (OPDP) reviewed the labeling and provided comments that were incorporated into the PI (see the review by Ankur Kalola, Regulatory Review Officer, OPDP, in DARRTS dated January 22, 2026; Reference ID: 5732331).

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A REMS was not under consideration for this application. In the original submission and in this submission, it was determined that a REMS was not required to ensure safe use of the product. The benefit-risk profile for inclisiran is favorable in the intended populations and the identified risks may be adequately mitigated with labeling.

Postmarketing Requirements (PMRs) and Commitments (PMCs)
No new PMRs or PMCs were considered for this application.

14. Recommended Comments to the Applicant

This section is not applicable as the regulatory action recommendation is for approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EILEEN M CRAIG
02/04/2026 03:25:58 PM

JOHN M SHARRETTS
02/04/2026 05:35:33 PM
I concur with the review and conclusions.