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 897, S-017
Applicant	Novartis Pharmaceuticals
Date of Submission	August 12, 2025
PDUFA Goal Date	February 12, 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 heterozygous familial hypercholesterolemia (HeFH)/ new population of 12 to 17 years of age with HeFH
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 heterozygous familial hypercholesterolemia (HeFH)/ new population of 12 to 17 years of age with HeFH*
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-017 provides final efficacy and safety data from study CKJX839C12301 (referred to as ORION-16) and seeks to expand the indication to include pediatric patients aged 12 to less than 18 years with heterozygous familial hypercholesterolemia (HeFH). Additional supportive safety data comes from (1) trials in adults with hypercholesterolemia, including HeFH (ORION-9, -10, and -11) that provided substantial evidence of effectiveness for the original application; and (2) 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-16 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 HeFH and elevated LDL-C. HeFH was diagnosed by genetic testing or clinical criteria. 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-16 is identical to the commercial formulation presently used in adults. One of the goals of ORION-16 was to fulfill postmarketing requirement (PMR) 4186-1: 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).

Efficacy: The effect of Leqvio (inclisiran) was evaluated in 141 patients aged 12 to less than 18 years with HeFH (93 patients received Leqvio; 48 received placebo). The mean age at baseline was 15 years (range: 12 to 17 years), 53% were female, 91% were White, 4% were Black or African American, 3% were Asian, and 3% were other races; 9% identified as Hispanic or Latino ethnicity. The mean LDL-C at baseline was 183 mg/dL; at baseline, 93% of patients were taking statins and 23% were on ezetimibe. The primary efficacy outcome measure was the percent change from baseline to Day 330 in LDL-C. The mean percent change in LDL-C from baseline to Day 330 was –27% in the inclisiran group and +1% in the placebo group, with a mean between-group difference (95% CI) of -29% (95% CI: −36%, −21%; $p < 0.0001$). The difference between the Leqvio and placebo groups in mean percent change in LDL-C from baseline at Day 270 (timepoint of last injection prior to primary endpoint) was -21% (95% CI: −29%, −12%). The placebo-adjusted mean percent changes (95% CI) in ApoB, non-HDL-C, and total cholesterol were –26% (–32, -20), –27% (–34, -20) and –19% (–25, -14), respectively. Small, variable effects were seen for lipoprotein a (Lp(a)), triglycerides, HDL-C, and Apo A1.

Safety:

Reference ID: 5740216

In a 24-month, two-part study of 141 pediatric patients aged 12 years and older with HeFH, 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), 93 patients received 284 mg of Leqvio administered subcutaneously during Part 1 and 139 patients received treatment with LEQVIO during Part 2. No pediatric patients died in ORION-16 or VICTORION-PEDS-OLE. There were few serious adverse events (SAEs) in the study and no clinically significant imbalances or patterns. In the double-blind period, injection site reactions (ISRs), mild in severity, were reported in 9% of patients treated with inclisiran compared to 2% with placebo. ISRs are a known adverse reaction of inclisiran. Other AEs that occurred more frequently in the inclisiran group include headache and upper respiratory tract infection. 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 HeFH. The clinical data from 141 pediatric patients with HeFH in study CKJX839C12301 (ORION-16) demonstrated a clinically meaningful LDL-C reduction treatment effect. The LDL-C-lowering data from the single randomized, placebo-controlled study in pediatric patients are supported by comparable LDL-C lowering in previously approved populations, including adults with HeFH and other forms of primary hypercholesterolemia.

Leqvio (inclisiran) has an overall favorable benefit/risk profile in pediatric patients 12 years of age and older with HeFH. All review disciplines support approval. 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 HeFH will provide an important therapeutic option for LDL-C reduction in this patient population. The safety profile of Leqvio in this study was generally consistent with the safety profile described in controlled and open-label trials involving adults with hypercholesterolemia, including HeFH.

The final clinical study report for ORION-16 was submitted to IND 127589 on May 22, 2025, with cross-reference submitted to NDA 214012 on May 23, 2025, for the purpose of fulfilling PMR 4186-1. FDA confirms that Supplement 017 fulfills PMR 4186-1.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HeFH is a genetic condition, most often resulting from deficient or defective LDL-C receptor (LDLR) function, which results in elevated LDL-C beginning in childhood and an increased risk of premature atherosclerotic cardiovascular disease. • The general global population has an estimated overall pooled prevalence of ~1:300. • Diagnosis is either by phenotypic criteria (an elevated LDL-C level along with a family history of elevated LDL-C or premature coronary artery disease) or through genetic testing. • LDL-C reduction with statins and PCSK9 inhibitors in adults is associated with improved CV outcomes in HeFH and non-familial hypercholesterolemia. ○ Meta-analysis of statin trials reported a 22% reduction in 5-year incidence of major vascular events per ~40 mg/dL (1 mmol/L) absolute reduction in LDL-C.[1] ○ CV outcome trials in adults of the two approved PCSK9 inhibitors, alirocumab and evolocumab, demonstrated that reduction in LDL-C led to reduced risk of CV events.[2,3] ○ A CV outcome trial in adults with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering.[4]	HeFH is a genetic condition, typically affecting LDLR function, leading to elevated LDL-C levels and an increased risk of premature atherosclerotic cardiovascular disease. Individuals with HeFH typically respond well to statins and PCSK9 inhibitors, and therefore, can attenuate development of atherosclerosis and CVD. Patients with HeFH are treated with LDL-C-lowering therapies with the goal of reducing CV risk.
Current Treatment Options	Treatment options for pediatric patients with HeFH • Statins (-21 to -50% LDL-C) • Ezetimibe (-15% LDL-C) • Colesevelam (-13% LDL-C) • Evolocumab (-38% LDL-C)	Treatment consists of maintaining a healthy lifestyle (low-cholesterol diet, exercise, not smoking, etc.) and statin therapy, starting at around 8 years of age. Additional therapy beyond a statin is often necessary to achieve LDL-C goals.

[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.
[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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Alirocumab (-31% to -42% LDL-C)	
Benefit	• The efficacy of Leqvio was evaluated in 141 patients aged 12 to less than 18 years with HeFH. At baseline, 93% of patients were on statins and 23% on ezetimibe. The mean LDL-C at baseline was 183 mg/dL. The mean percent change in LDL-C from baseline to Day 330 was –27% in the inclisiran group and +1% in the placebo group, with a mean between-group difference (95% CI) of –29% (–36, -21); p<0.0001. • Reductions from baseline in other lipids (ApoB, total cholesterol, and non-HDL-C) were also observed during treatment with Leqvio.	Leqvio had a modest LDL-C reduction treatment effect in this pediatric patient population with HeFH on background LDL-C lowering therapy. Nevertheless, the data provides substantial evidence of effectiveness for inclisiran in pediatric patients aged 12 to 17 years with HeFH. 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, including angioedema and injection site reactions; in some cases, hypersensitivity reactions required treatment discontinuation. • 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, the most common adverse reactions included injection site reactions and headache. • There were no clinically meaningful changes in safety laboratory data or vital signs. • No patients developed antidrug antibodies in the double-blind period. • Although the data are limited in size and duration, there was no signal for adverse effects in growth and development.	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

Individuals with familial hypercholesterolemia (FH), an autosomal dominant genetic condition most often resulting from deficient or defective low density lipoprotein receptor (LDLR) function, have elevated total cholesterol and LDL-C beginning in childhood and an increased risk of premature ASCVD.[5] Since FH is a genetic condition, the prevalence among children is similar to the prevalence among younger adults. HeFH accounts for the majority of FH overall and historically was reported to have a prevalence of ~1:500 individuals in the general population.[6] More recent estimates, using larger studies and more systematic approaches, suggest that the general global population has an estimated overall pooled prevalence of 1:311 (95% CI, 1:250–1:397; similar between children [1:364] and adults [1:303]),[7,8] and affects males and females equally.[9] FH is a common genetic cause of premature coronary heart disease.

FH is caused by variants in genes encoding proteins involved in the clearance of LDL particles. LDL receptor (LDLR) is the most commonly affected gene. 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 also be the cause of FH.[10] A genetic basis for the disease is not found in all patients and may be due to mutations in unidentified genes or from polygenic causes.[11] Diagnosis is either by phenotypic criteria (an elevated LDL-C level along with a family history of elevated LDL-C or premature coronary artery disease) or through genetic testing or cascade screening of families using a combined phenotypic and genotypic strategy. Several diagnostic tools are available, such as the WHO Criteria/Dutch Lipid Clinical Network Criteria,[12] the UK Simon Broome Register Diagnostic

[5] Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers 2017;3:17093-17093.

[6] Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. J Clin Invest. 2003;111:1795-1803.

[7] Nordestgaard BG, Chapman MJ, Humphries SE, et al. 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;34:3478-3490a

[8] Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation 2020;141:1742-1759.

[9] Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ open. 2017;7(9):e016461.

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

[11] McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. J Am Heart Assoc. 2019;8(24):e013225.

[12] World Health Organization. Familial Hypercholesterolaemia (FH): Report of a second WHO consultation. 1998. Available at: whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf.

Criteria,[13] the US Make Early Diagnosis to Prevent Early Death (MEDPED) criteria,[14] and the National Lipid Association expert panel recommendations.[15] These tools incorporate clinical features and medical history and do not rely solely on genotyping (the Dutch Lipid Clinic Network and the Simon Broome criteria incorporate genetic test results into their algorithm). Although these diagnostic tools differ from each other and have differing cut-off values of the LDL-C level necessary for diagnosis, their predictive values are similar.[16]

Untreated LDL-C levels in individuals with HeFH are significantly elevated compared to those without FH, and these individuals are at increased risk for CVD. Individuals with HeFH, unlike HoFH, typically respond well to statins and, therefore, can attenuate development of atherosclerosis and prevent coronary heart disease (CHD).[17] Treatment consists of maintaining a healthy lifestyle (low-cholesterol diet, exercise, not smoking, etc.) and statin therapy, starting at 8 years of age.[18] Identifying FH early in childhood allows for interventions to reduce LDLC to start early in life and thus has a larger impact on reducing the increased risk for CVD.[19,20] Despite available therapies, guideline-recommended LDL cholesterol levels are not achieved in many pediatric patients with familial hypercholesterolemia.[21,22]

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[13] Risk of fatal coronary heart disease in familial hypercholesterolaemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ (Clinical research ed). 1991;303(6807):893-6

[14] Williams RR, Hunt SC, Schumacher MC, Hegele RA, Leppert MF, Ludwig EH, Hopkins PN. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol. 1993;72:171–176.

[15] Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, Daniels SR, Gidding SS, de Ferranti SD, Ito MK, McGowan MP, Moriarty PM, Cromwell WC, Ross JL, Ziajka PE. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S1–S8.

[16] European Association for Cardiovascular Prevention Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D, ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J. 2011;32:1769–1818.

[17] Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, Heeringa J, Witteman JC, Lansberg PJ, Kastelein JJ, Sijbrands EJ. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008;337:a2423.

[18] Grundy SM, Stone NJ, Bailey AL, 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. Circulation 2019;139(25):e1082-e1143

[19] Wiegman A, Gidding SS, Watts GF, et al. European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36:2425-2437.

[20] Luirink IK, Wiegman A, Kusters DM, et al. 20-Year follow-up of statins in children with familial hypercholesterolemia. N Engl J Med 2019; 381: 1547-56.

[21] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-188.

[22] Ramaswami U, Futema M, Bogsrud MP, et al. Comparison of the characteristics at diagnosis and treatment of children with heterozygous familial hypercholesterolaemia (FH) from eight European countries. Atherosclerosis 2020;292:178-187.

Current Treatment Options

United States of America (U.S.) and European Union (E.U.) guidelines recommend consideration of pharmacologic treatment for pediatric patients ≥8 years of age with elevated LDL-C. US pediatric guidelines[23,24] recommend considering pharmacologic intervention after initial treatment with lifestyle modification has failed in patients ≥8 years of age with LDL-C that is:

- ≥130 mg/dL for the highest risk (e.g., diabetes mellitus)
- ≥160 mg/dL for intermediate risk (≥2 other CHD risk factors, family history of premature coronary artery disease [CAD])
- ≥190 mg/dL for the lowest risk (no cardiovascular risk factors)

Treatment guidelines from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)[25] recommend starting a heart-healthy diet early in life and consideration of statin treatment at 6 to 10 years of age. The 2018 American Heart Association/American College of Cardiology (AHA/ACC) guideline recommends an LDL-C <110 mg/dL as an acceptable lipid value, borderline as 110 to 129 mg/dL, and ≥130 mg/dL as an abnormal lipid value in pediatric patients.[26] The goal in children with HeFH >10 years of age is an LDL-C <130 mg/dL and at 8 to 10 years a ≥50% reduction of LDL-C.

Statins are the standard of care for the treatment of HeFH in children and adolescents and have been shown to reduce LDL-C from 20 to 50% in pediatric patients and to reduce the risk of cardiovascular events in adults. Available therapies, as add-on treatment to statins, for the treatment of HeFH in pediatric patients include ezetimibe, colesevelam, and evolocumab.

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

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[23] McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and pediatrics: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115:1948-1967.

[24] Daniels SR, Greer FR. Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198-208.

[25] ESC Scientific Document Group, 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 111–188, https://doi.org/10.1093/eurheartj/ehz455

[26] Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr, Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a Report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. J Am Coll Cardiol. 2019;73:3168–3209.

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 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 lipoprotein cholesterol (LDL-C) in adults with hypercholesterolemia, including heterozygous familial hypercholesterolemia (HeFH)."[27] Inclisiran is administered subcutaneously as a single injection initially, again at 3 months, and then every 6 months.

Regulatory History

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 HeFH (b) (4) :[28]
CKJX839C12301 (referred to as ORION-16) in pediatric patients aged 12 to less than 18 years (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 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-16 was the same as used in the original

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

[28] (b) (4)

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 017 and found the data acceptable. OCP/DCEP and DPM recommend approval of this supplement for pediatric patients aged 12 years and older with HeFH.

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.

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).

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

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: 5729456).

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: 5736172).

The efficacy, safety, and tolerability of inclisiran in pediatric patients with HeFH were studied in a randomized, multicenter, international, phase 3 study in pediatric patients aged 12 to <18 years (ORION-16). The study had two parts: Part 1 (Year 1) was a 12-month double-blind, parallel group period, in which patients were randomized in a 2:1 ratio to receive either inclisiran sodium 300 mg or placebo; Part 2 (Year 2) was a 12-month single-arm open-label follow-up period, in which all patients received inclisiran.

The primary efficacy endpoint was percent change in LDL-C from baseline to Day 330 (Year 1). The multiplicity-adjusted key secondary efficacy endpoints were:

- Time-adjusted percent change in LDL-C from baseline after Day 90 and up to Day 330 (Year 1), defined as the average of percent changes from baseline to Day 150, 270, and 330.
- Absolute change in LDL-C from baseline to Day 330 (Year 1)
- Percent change in apolipoprotein B (Apo B) from baseline to Day 330 (Year 1)
- Percent change in lipoprotein (a) (Lp(a)) from baseline to Day 330 (Year 1)
- Percent change in non-high density lipoprotein cholesterol (non-HDL-C) from baseline to Day 330 (Year 1)
- Percent change in total cholesterol from baseline to Day 330 (Year 1)

A hierarchical testing strategy was applied to control the family-wise type I error rate at a two-sided significance level of alpha = 0.05. The key secondary endpoints were tested in the order listed above. There was no multiplicity adjustment for other endpoints.

Patient Disposition

A total of 141 patients were randomized into the study, 93 to the inclisiran group and 48 to the placebo group; 98% in the inclisiran group and 100% in the placebo group completed the double-blind study treatment and study. One patient discontinued treatment because the subject/guardian changed their mind about participating in the study. The second patient discontinued treatment due to an adverse event. All patients who completed the double-blind study period entered and completed the open-label study period. One patient in the inclisiran group discontinued study treatment during the open-label period while continuing in the study. The reason for discontinuation from study treatment was a concern about weight gain, which according to the

Investigator's judgment was related to other causes, including concomitant treatments the patient was taking. No patient discontinued the study during the open-label period.

Baseline Demographics

The baseline demographic characteristics were similar between the treatment groups. Approximately 53% of the randomized patients were female, the mean age was 15 years (range: 12 to 18 years), the majority (91%) of patients were White, and approximately 11% were Hispanic or Latino. The mean baseline LDL-C was 183 mg/dL (SD 48.7) (183.5 (SD 50.1) in the inclisiran group and 182.4 (SD 46.2) in the placebo group). Overall, 93% of patients received statin treatment, 97% in the inclisiran group and 85% in the placebo group. The statistical reviewer adjusted for this additional statin use covariate in analyzing the primary efficacy endpoint of percent change from baseline in LDL-C which yielded a consistent result with the primary analysis. About 25% reported use of other lipid-lowering treatments, mostly ezetimibe. Most patients (96%) had a genetic diagnosis of HeFH.

Efficacy Endpoint Results

Primary: At Day 330, patients treated with inclisiran achieved least squares (LS) mean change from baseline of -27.1% (95% CI: -32.0%, -22.2%), compared with 1.4% (95% CI: - 4.0%, 6.8%) for placebo. The LS mean difference between the inclisiran and placebo groups was -28.5% (95% CI: -35.8%, -21.3%; p<0.0001).

Dr. Zheng states that there were few intercurrent events and the amount of missing data was limited. Additionally, the primary efficacy result was robust across different sensitivity analyses including analysis of covariance (ANCOVA) adjusting for baseline concomitant lipid-modifying therapies, baseline age group, region, and a treatment-by-region interaction, and mixed-effects model for repeated measures (MMRM) method with a control-based method to impute missing data.

Table 1. Key Secondary Efficacy Endpoints

Inclisiran N=93 **LS Mean CHG (95% CI)**	**Placebo N=48** **LS Mean CHG (95% CI)**	**LS Mean Difference from Placebo (95% CI)**	**p-value**
LDL Cholesterol-Time adjusted percent change from baseline after Day 90 and up to Day 330[1]			
-26.0 (-30.1, -22.0)	3.3 (-2.4, 8.9)	-29.3 (-36.2, -22.4)	<0.0001
LDL Cholesterol – Absolute change (mg/dL) from baseline to Day 330[2]			
-50.5 (-59.2, -41.9)	-0.5 (-10.5, 9.4)	-50.0 (-63.2, -36.8)	<0.0001
Apo B – Percent change from baseline to Day 330[2]			
-21.5 (-25.6, -17.3)	4.2 (-0.1, 8.6)	-25.7 (-31.7, -19.7)	<0.0001
Lp (a) – Percent change from baseline to Day 330[2]			
-5.0 (-14.2, 4.1)	1.1 (-5.5, 7.8)	-6.2 (-17.5, 5.1)	0.2838
Non-HDL-C – Percent change from baseline to Day 330[2]			
-25.0 (-29.7, -20.4)	1.8 (-3.3, 6.8)	-26.8 (-33.6, -20.0)	<0.0001[3]
Total Cholesterol – Percent change from baseline to Day 330[2]			

-18.7 (-22.5, -15.0)	0.5 (-3.5, 4.4)	-19.2 (-24.6, -13.8)	<0.0001[3]

Source: Clinical Study Report and Statistical Reviewer
[1]A control-based method was used for missing data imputation to generate 100 total imputed datasets. A MMRM was performed on each of the 100 datasets by including fixed effects for treatment, visit (Day 150, 270, and 330), interaction between treatment and visit, and baseline LDL-C and baseline age group as a covariate. A linear combination of the estimated means after Day 90 and up to Day 330 was used to compare treatment groups. Treatment effects from the 100 analyses were combined using Rubin's rule.
[2]A placebo washout model was used for missing data imputation to generate 100 total imputed datasets. ANCOVA, assuming unequal variance for treatment group, was performed on each of the 100 datasets by including fixed effects for baseline LDL-C and baseline age group as a covariate. Treatment effects from the 100 analyses were combined using Rubin's rule.
[3]Given the hierarchical nature of testing for the key secondary endpoints and the non-significant result for Lp(a) using the primary analysis method, the analyses for non-HDL-C and total cholesterol should be considered exploratory.
Abbreviations: CHG, change; CI, confidence interval; LS, least square; LDL-C, Low density lipoprotein cholesterol; Apolipoprotein B, Apo B; lipoprotein (a), Lp (a); MMRM, mixed model repeated measure; non-high density lipoprotein cholesterol, non-HDL-C; ANCOVA, analysis of covariance.

Subgroup Analyses

Subgroup analyses were performed for the primary efficacy endpoint, percent change in LDL-C from baseline to Day 330. Dr. Zheng states that the race subgroups of "Asian", "Black or African American", and "Multiple" had no patients in the placebo group, the ethnicity subgroups of "Hispanic or Latino" and "Not reported" had too few patients and the model-based analyses could not be performed. The point estimates along with 95% confidence intervals for the primary endpoint favor inclisiran across analyzed subgroups defined by sex and region. Shrinkage estimates of subgroup treatment effects, derived using a Bayesian hierarchical model based on summary sample estimates, were consistent with the frequentist means and intervals.

Conclusions on the Substantial Evidence of Effectiveness

The FDA review team concludes that the Applicant has demonstrated substantial evidence of effectiveness for inclisiran for LDL-C lowering in patients with HeFH aged 12 to <18 years. The primary efficacy result is robust across different sensitivity analyses and the point estimates along with 95% confidence intervals for the primary endpoint favor inclisiran across subgroups defined by sex, region, and age. The LDL-C lowering effect with inclisiran was accompanied by relevant improvements in other lipids, including ApoB, total cholesterol, and non-HDL-C. HeFH is a life-threating disease, and the observed LDL-C lowering in these pediatric patients was deemed acceptable and clinically meaningful. The design and statistical analysis of ORION-16 are aligned with the FDA Written Request.

The FDA 2019 guidance on effectiveness[29] provides 3 paths to meeting the substantial evidence standard:

1. based on two adequate and well-controlled clinical investigations
2. based on one adequate and well-controlled clinical investigation plus confirmatory evidence

[29] FDA Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products*

3. *for a new population* or a different dose, regimen, or dosage form, *based on reliance of FDA's previous finding of effectiveness of an approved drug when scientifically justified* and legally permissible [italics added]

This sNDA meets the effectiveness standard via the third pathway, which does not require additional adequate and well-controlled clinical trials. The guidance states that "Ordinarily, this will be because other types of evidence provide a way to apply the known effectiveness to a new population...For example, the effectiveness of a drug for pediatric use can sometimes be based on FDA's previous finding of effectiveness of the drug in adults, together with scientific evidence that justifies such reliance." In this sNDA, the scientific evidence from 141 pediatric patients provides justification that the known effectiveness of inclisiran in adults is consistent with and supportive of patients aged 12 to <18 years with HeFH.

4. 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 January 29, 2026; Reference ID: 5736172). As detailed in Dr. Nguyen's review, the safety review focused on the target population of pediatric patients aged 12 to 17 years using data from the ORION-16 study and supportive data from the open label extension study, VICTORION-PEDS-OLE. The safety of inclisiran in adults has been previously established in a clinical development program consisting of three 18-month phase 3 trials (ORION-9, ORION-10, ORION-11) with 1,833 adults with ASCVD, ASCVD risk equivalents, and/or HeFH who were on background of maximally tolerated statin therapy, combined with two extension studies (ORION-3 and ORION-8) that provided long-term safety data up to >6 years of exposure. The dose, dose regimen, and formulation of inclisiran in the pediatric population are the same as the approved adult population. The key pediatric safety issues evaluated include injection site reactions, growth and pubertal development (sex hormones and Tanner staging), hypersensitivity reactions, new onset or worsening diabetes, musculoskeletal and muscle-related events, neuropsychiatric events, and liver, hepatic, renal and cardiac adverse events.

Exposure

ORION-16 had excellent study completion rates with nearly all pediatric patients completing all planned study doses. The mean duration of exposure in the double-blinded period was similar in both study arms (358 days in the inclisiran group and 363 days in the placebo group). Pediatric patients in ORION-16 were exposed to inclisiran for approximately 1 to 2 years, depending on the study arm (inclisiran-inclisiran versus placebo-inclisiran).

Adverse Events

In Part 1 (double-blind period), there were no deaths, 4 serious adverse events (SAEs), and one adverse event (AE) leading to study drug discontinuation. Upon review, none of the SAEs were believed to related to study drug. The AE leading to discontinuation occurred in a patient receiving inclisiran who experienced an injection site reaction (ISR), vertigo (mild in severity), and nausea on the day of the second study drug injection (Day 90) which resolved within 4 days.

In the double-blind period, ISRs, mild in severity, were reported in 9% of patients treated with inclisiran compared to 2% with placebo. ISRs are a known adverse reaction of inclisiran. Other AEs that occurred more frequently in the inclisiran group include headache and upper respiratory tract infection. A total of 5 (5%) patients had syncopal events compared to none in the placebo group. None of the events of syncope were severe, serious, recurrent, or were associated with administration by injection. In Part 1, no patients reported AEs of new onset or worsening of diabetes and there were no treatment-induced anti-drug antibody (ADA) responses. In Part 2, there was one patient in the inclisiran-inclisiran group with a family history of type 1 diabetes who was diagnosed with type 1 diabetes. There were no clinically meaningful changes in safety laboratory data, including estradiol, testosterone, LH, FSH, DHEA-S, or cortisol. There were no clinically meaningful changes in body mass index (BMI), height, weight, or Tanner stage. Safety concerns with Leqvio are monitorable, generally reversible with treatment discontinuation, and may be adequately addressed in labeling.

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 studies 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 141 pediatric patients with HeFH 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. 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 HeFH aged 12 to 17 years was similar to the safety profile in adults, with the exception of a higher incidence of headaches in the pediatric population. 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.

5. 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 HeFH. 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.

6. Pediatrics

Efficacy and Safety in Pediatric Patients

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

Other Pediatric Issues

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 HeFH (b) (4).

7. 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-16.

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-16 conformed to the requirements of 21 CFR 312.120.

Rationale for assuring the applicability of foreign data to the US population
There was a total of 141 pediatric patients enrolled in ORION-16, 8 (6%) patients from the US and 16 (11%) participants from North America. The baseline demographics of patients in the ORION-16 study from the US and globally were found to be generally similar. 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, and race were found not to significantly influence inclisiran PK or PD in adults. The review team agrees that the results from ORION-16 are applicable to the US population.

8. 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 HeFH. 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. 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 HeFH 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 HeFH 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 141 pediatric patients with HeFH. This indication is also supported by evidence from an adequate and well-controlled study in adults with HeFH. The safety profile reported in pediatric patients aged 12 years and older

with HeFH was consistent with adult patients with hypercholesterolemia, with the exception of headache. 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 added for the pediatric patients aged 12 years and older with HeFH 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 is an exploratory endpoint and was not controlled for multiplicity.
  - A description of the clinical data, to include baseline demographics and effectiveness information, that was collected through the ORION-16 pediatric study was included in this section. Removed reference to (b) (4) .
  - In the figure describing the percent change in LDL-C over time, the y-axis extended to (b) (4) %. We requested updating the figure, so the y-axis extends to -100%. The statistical team requested including 1 additional patient's Day 360 data so that n=91 at Day 360 for the inclisiran arm. This patient had laboratory measurements taken 1 day after dosing, but this patient was in the inclisiran group and received placebo at the Day 360 visit. The Applicant agreed with the change to the y-axis but declined to add this additional subject who was technically no longer in Part 1 as per the statistical analysis plan; the statistical team agreed with not including this subject as requested previously.
- 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).

9. 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)
ORION-16 fulfills the PMR 4186-1: 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).

No new PMRs or PMCs were considered for this application.

10. 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 03:09:27 PM

JOHN M SHARRETTS
02/04/2026 05:34:56 PM
I concur with the review and conclusions.