CLINICAL REVIEW

Application Type	sBLA
Application Number(s)	BLA 125559 S-039 (IND 105574)
Priority or Standard	Standard
Submit Date(s)	05/10/2023
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Division/Office	DDLO
Reviewer Name(s)	Craig Hales, MD
Review Completion Date	02/09/2024
Established/Proper Name	Alirocumab
(Proposed) Trade Name	Praluent
Applicant	Regeneron Pharmaceuticals, Inc.
Dosage Form(s)	SC
Applicant Proposed Dosing Regimen(s)	The proposed pediatric dose regimens can be administered with the currently approved PRALUENT® DAI Prefilled Pen (DAI-PFP). • The recommended dosage of PRALUENT for subjects with a body weight (BW) less than 50 kg is 150 mg once every 4 weeks (Q4W) administered subcutaneously. • The recommended dosage of PRALUENT for subjects with a BW of 50 kg or more is 300 mg once Q4W administered subcutaneously. • If the LDL-C response is inadequate, the dosage may be adjusted for subjects with a BW less than 50 kg to 75 mg subcutaneously once every 2 weeks (Q2W) or for subjects with a BW of 50 kg or more to 150 mg subcutaneously once Q2W.
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and other LDL-C-lowering therapies in pediatric subjects aged 8 to 17 years with HeFH to reduce LDL-C.
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C/ pediatric patients with HeFH, 8 years and older

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BW	Body weight
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	subject package insert
PREA	Pediatric Research Equity Act
PRO	subject reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Praluent® (alirocumab) is a human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 binds to the low-density lipoprotein (LDL) receptors (LDLR) on the surface of hepatocytes to promote LDLR degradation within the liver. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLRs available to clear LDL, thereby lowering LDL-C levels.

In 2015, alirocumab/Praluent, 75 mg and 150 mg every 2 weeks subcutaneous (SC) dose, was approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of LDL-C. Alirocumab, 300 mg once monthly, was subsequently approved in 2017.

In 2019, alirocumab/Praluent was approved in adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and unstable angina based on the results of a cardiovascular outcomes trial in which approximately 9450 patients were exposed to Praluent or placebo for 2 ½ years. Given the positive demonstration of CV risk reduction, the original indication for the treatment of hyperlipidemia in adults with HeFH or ASCVD was broadened to include adults with primary hyperlipidemia as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), to reduce LDL-C.

In 2021, alirocumab/Praluent was approved for the treatment of adults with homozygous familial hypercholesterolemia (HoFH).

In this application, the Applicant submits data to support their proposed indication for alirocumab as an adjunct to diet and other lipid-lowering therapies in pediatric patients aged 8 to 17 years with HeFH to reduce LDL-C. The proposed dosing regimen for pediatric patients with HeFH is

- 150 mg once every 4 weeks administered subcutaneously (SC) using a single-dose pre-filled pen for patients with a body weight (BW) less than 50 kg,
- 300 once every 4 weeks administered SC using a single-dose pre-filled pen for patients with a BW of 50 kg or more.
- If the LDL-C response is inadequate, the dosage may be adjusted for patients with a BW less than 50 kg to 75 mg SC every 2 weeks or for patients with a BW of 50 kg or more to 150 mg SC once every 2 weeks.

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1.2. Conclusions on the Substantial Evidence of Effectiveness

In pediatric patients with HeFH, results from trial EFC14643 showed that:

- Alirocumab was superior to placebo in lowering LDL-C in both every 2 weeks (Q2W) and every 4 weeks (Q4W) dosing regimen cohorts after 24 weeks of treatment. The LS mean difference (alirocumab minus placebo) in percent LDL-C change from baseline to week 24 was -43.3% ($p<0.0001$) for the Q2W cohort and -33.8% ($p<0.0001$) for the Q4W cohort.
- Alirocumab was superior to placebo in improving other lipid parameters in both cohorts, including reductions in total cholesterol, non-HDL-C, and ApoB.

These results demonstrated clinically meaningful and statistically significant reductions in LDL-C and improvements in other lipid parameters for pediatric subjects with HeFH. For pediatric patients with HeFH whose LDL-C goals are not achieved with statins with or without ezetimibe because of reduced drug response to therapies involving the LDL receptor, poor treatment adherence, or side effects, PCSK-9 inhibitors, as an adjunct to diet and other LDL-C lowering therapies, can help achieve their LDL-C goals and potentially reduce their risk for cardiovascular disease. Evolocumab is currently the only PCSK-9 inhibitor approved for HeFH in pediatric patients aged 10 and older. Alirocumab offers another option for PCSK-9 therapy for these patients and will be the only PCSK-9 inhibitor approved for use in children aged 8 to 9 years.

In conclusion, the data presented in this submission support the use of alirocumab in pediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia who do not achieve sufficient LDL cholesterol lowering with a healthy lifestyle, optimal statin therapy, and ezetimibe or other LDL-C lowering therapies. The Applicant has submitted evidence of effectiveness that meets the statutory evidentiary standard. Based on data showing robust LDL-C reductions in the HeFH population, and an acceptable safety profile, this reviewer recommends approval of alirocumab for the following indication:

- As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C.

In addition, with the submission of final results for pediatric trials DFI14223 and EFC14643 in pediatric subjects with HeFH, the Applicant has fulfilled post-marketing requirement (PMR) 2927-1 in its entirety.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Praluent® (alirocumab) is currently indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease; as an adjunct to diet, alone or in combination with other LDL-C-lowering therapies, in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C; and as an adjunct to other LDL-C-lowering therapies in adults with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C. With this submission, Praluent should be approved as an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C. The treatment goal of HeFH is reduction in LDL-C to reduce CV risk.

Individuals with familial hypercholesterolemia (FH), an autosomal dominant genetic condition most often resulting from deficient or defective LDL receptor (LDLR) function, have elevated total cholesterol and LDL-C beginning in childhood and an increased risk of premature atherosclerotic cardiovascular disease. Heterozygous FH (HeFH) accounts for the majority of FH with an estimated overall prevalence of ~1:300. Treatment typically consists of maintaining a healthy lifestyle (low-cholesterol diet, exercise, not smoking, etc.) and statin therapy, starting at 8 to 10 years of age. Homozygous familial hypercholesterolemia (HoFH) is a more severe form of FH. Despite many effective lipid-lowering therapies available for primary hyperlipidemia, 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), cost, availability, and patient burden (lipid apheresis). Patients with HoFH typically have severe hyperlipidemia (LDL-C ≥190 mg/dL) even after treatment with multiple lipid-lowering agents. LDL-C is a well-established surrogate of cardiovascular risk; thus, reduction of LDL-C is the central therapeutic goal for patients with FH.

In support of the proposed indication "as an adjunct to diet and other LDL-C-lowering therapies in pediatric subjects aged 8 to 17 years with HeFH to reduce LDL-C", the Applicant conducted trial EFC14643, a 24-week, randomized, double-blind trial comparing alirocumab with placebo in 153 pediatric patients, aged 8 to <18 years, with HeFH. Following the week 24 timepoint, 145 of 153 patients were treated with open-label alirocumab for up to an additional 80 weeks. Patients were on optimized standard of care lipid-lowering therapy per locally applicable guidelines. Patients with either a genetic or clinical diagnosis of HeFH could be enrolled; 90% of HeFH patients had genetic evidence of an FH-causing mutation. The primary endpoint in randomized, double-blind trial EFC14643 was the percent change from baseline to week 24 in reflexive LDL-C.

In pediatric patients with HeFH, results from trial EFC14643 showed that alirocumab was superior to placebo in lowering LDL-C in both Q2W (LS mean reduction of -33.6% vs. 9.7%) and Q4W (LS mean reduction of -38.2% vs. -4.4%) dosing regimen cohorts after 24 weeks of treatment. The LS mean difference (alirocumab minus placebo) in percent LDL-C change from baseline to week 24 was -43.3% ($p<0.0001$) for the Q2W cohort

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and -33.8% (p<0.0001) for the Q4W cohort. LDL-C lowering in the alirocumab arms persisted to the end of the open label period. At week 104, LS mean reduction in LDL-C from baseline was -22.2% for the Q2W cohort and -23.7 for the Q4W cohort. Alirocumab was superior to placebo in improving other lipid parameters in both cohorts, including reductions in total cholesterol, non-HDL-C, ApoB, and Lp(a). Evolocumab is currently the only PCSK9 inhibitor approved for HeFH in pediatric patients aged 10 and older. Alirocumab offers another option for PCSK9 therapy for these patients and will be the only PCSK9 inhibitor approved for use in children aged 8 to 9 years.

In the HeFH trial, alirocumab was well-tolerated and the safety profile was consistent with reported safety and tolerability issues in the adult phase 3 and phase 4 program. No patients died during the trial. During the double-blind (DB) treatment period of trial EFC 14643, treatment emergent serious adverse events (TE-SAEs) were reported by 6 patients in the alirocumab cohort. No patterns emerged suggesting a causal relationship between these SAEs and alirocumab except for syncope in a female patient where syncope occurred directly after alirocumab injection and was likely an episode of vasovagal syncope. During the DB treatment period, 2 patients in the alirocumab group had TEAEs leading to permanent study drug discontinuation. One was due to syncope and the second was due to disturbance in attention and memory impairment. None of these events were considered related to alirocumab by this reviewer. The incidence of antidrug antibodies for patients treated with alirocumab was 3% (3/98). No alirocumab-treated pediatric patients tested positive for neutralizing antibodies. The most commonly reported adverse events, where the incidence with alirocumab was ≥ 5% and greater than placebo, were nasopharyngitis, headache, and injection site reaction. These safety concerns can be reasonably managed in the postmarket setting. There was no evidence of adverse effects on growth and development, cognition, or neurologic function.

In summary, patients with HeFH on background LDL-C-lowering therapy demonstrated a significant reduction in LDL-C with alirocumab, compared to placebo, and alirocumab was well-tolerated. The safety data for the trials in pediatric patients with HeFH does not suggest an increased risk or new safety findings in the pediatric population.

The favorable benefit:risk profile of alirocumab supports the use of alirocumab in addition to statin ± ezetimibe therapy in pediatric patients with HeFH to lower LDL-C levels and further reduce cardiovascular risk. Praluent should be approved for use as an adjunct to other LDL-C-lowering therapies for the treatment of pediatric patients aged 8 years and older with HeFH to reduce LDL-C.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Genetic condition, most often resulting from deficient or defective 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. o 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] o 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.
Current Treatment Options	Treatment options for pediatric patients with HeFH • Statins (-21 to -50% LDL-C reduction in HeFH) • Ezetimibe (-15% LDL-C reduction in HeFH) • Colesevelam (-13% LDL-C reduction in HeFH) • Evolocumab (-38% LDL-C reduction in HeFH)	HeFH: Treatment consists of maintaining a healthy lifestyle (low-cholesterol diet, exercise, not smoking, etc.) and statin therapy, starting at 8 to 10 years of age. Currently approved LDL-lowering therapies for pediatric patients with HeFH include statins as first-line treatment, followed by

[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
		ezetimibe, evolocumab, and colesevelam.
Benefit	Trial EFC14643 is a randomized, 24-week double-blind, placebo-controlled, parallel-group, multi-national, multi-center trial followed by an open label treatment period of 80 weeks. The primary efficacy endpoint was reduction in LDL-C, an accepted and validated surrogate for cardiovascular risk. • 153 pediatric patients with genetic or clinical diagnosis of HeFH, with mean baseline LDL-C values of 175 mg/dL despite LDL-lowering therapy (94% on statin [72% were on moderate-intensity or high-intensity statin]; 14% total on ezetimibe), were administered alirocumab either every 2 weeks (Q2W) or every 4 weeks (Q4W) versus placebo for 24 weeks. • The least squares mean reduction in LDL-C from baseline to Week 24 for the Q2W group was 33.5% (treatment difference from placebo was -43.2%); for the Q4W group it was 38.2% (treatment difference from placebo was -32.8%). The effect of alirocumab on cardiovascular morbidity and mortality in a pediatric population with FH has not been assessed.	The submitted data provide substantial evidence of alirocumab's effectiveness in reducing LDL-C in pediatric patients with HeFH on background LDL-lowering therapy.
Risk and Risk Management	• No subjects died during the trial. One subject with HeFH discontinued during the placebo-controlled period because of syncope which occurred 7 days after injection of alirocumab and one subject discontinued because of memory impairment/disturbance in attention. These events were considered resolved. • Overall, 3% (3/98) of subjects had treatment-emergent anti-drug antibodies (ADA). No subjects had persistent treatment emergent ADA or tested positive for neutralizing antibodies. • Although the data is limited in size and duration, there was no signal of	Potential risks of alirocumab in pediatric patients with FH were consistent with the findings in trials conducted for other indications. Adverse reactions reported in this pediatric population included nasopharyngitis, upper respiratory tract infection, headache, rash, and injection site reactions.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	adverse effects in growth and development with the use of alirocumab in this trial.	

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1.4. Patient Experience Data

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

☐	The subject experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual subject/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture subject experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with subject stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture subject experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

Heterozygous Familial Hypercholesterolemia (HeFH)

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. Heterozygous FH (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] In the United States, probable or definite FH was approximated as 0.40% (1 in 249) in White individuals, 0.47% (1 in 211) in Black individuals, 0.24% (1 in 414) in Mexican Americans, and 0.29% (1 in 343) among those of other races[7]. 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]),[8,9] and affects males and females equally.[10] 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.[11] A genetic basis for the disease is not found in all subjects and may be due to mutations in unidentified genes or from polygenic causes.[12] 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

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[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] 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 Mar 15;133(11):1067-72. doi: 10.1161/CIRCULATIONAHA.115.018791.
[8] 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.
[9] Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of familial hypercholesterolemia among the general population and subjects with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation 2020;141:1742-1759.
[10] 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.
[11] Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 223(2), 262–268 (2012).
[12] McGowan MP, Hosseini Dehkordi SH, Moriarty PM, Duell PB. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. J Am Heart Assoc. 2019;8(24):e013225.

phenotypic and genotypic strategy. Several diagnostic tools are available, such as the WHO Criteria/Dutch Lipid Clinical Network Criteria,[13] the UK Simon Broome Register Diagnostic Criteria,[14] the US Make Early Diagnosis to Prevent Early Death (MEDPED) criteria,[15] and the National Lipid Association expert panel recommendations.[16] 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.[17]

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 homozygous familial hypercholesterolemia (HoFH), typically respond well to statins and, therefore, can attenuate development of atherosclerosis and prevent CHD.[18] Treatment consists of maintaining a healthy lifestyle (low-cholesterol diet, exercise, not smoking, etc.) and statin therapy, starting at 8 to 10 years of age.[19] Identifying FH early in childhood allows for interventions to reduce LDL-C to start early in life and thus has a larger impact on reducing the

[13] 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.
[14] 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.
[15] 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.
[16] 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 subjects: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S1–S8.
[17] 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.
[18] 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.
[19] 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.

increased risk for CVD.[20,21] Despite available therapies, guideline-recommended LDL cholesterol levels are not achieved in many pediatric subjects with familial hypercholesterolemia.[22,23]

Current Treatment Options

Heterozygous Familial Hypercholesterolemia (HeFH)

United States (US) and European Union (EU) guidelines recommend consideration of pharmacologic treatment for pediatric subjects ≥8 years of age with elevated LDL-C. US pediatric guidelines[24,25] recommend considering pharmacologic intervention after initial treatment with lifestyle modification has failed in subjects ≥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)[26] recommend starting a heart-healthy diet early in life and consideration of statin treatment at 6–10 years of age.

The 2018 AHA/ACC guideline recommends an LDL-C <110 mg/dL as an acceptable lipid value, borderline as 110-129 mg/dL, and ≥130 mg/dL as an abnormal lipid value in pediatric subjects.[27]

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[20] 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.

[21] 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.

[22] 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.

[23] 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.

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

[25] 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.

[26] 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

[27] 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

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.[20]

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 subjects 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 subjects are listed in the table below along with estimates of the treatment effect on LDL-C.

2.2. Analysis of Current Treatment Options

APPEARS THIS WAY ON ORIGINAL

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.

Table 1 Drugs Currently Approved in the U.S. for the Treatment of HeFH in Pediatric Patients

Product Name	Relevant Indication	Year of Initial Approval	Route and Frequency of Administration	Efficacy Information (LDL-C Reduction)	Important Safety and Tolerability Issues	Other Indications
Statins (HMG-CoA inhibitors)						
Simvastatin (Zocor) NDA 19766	Adjunctive therapy to diet to reduce LDL-C in adults and pediatric subjects aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).	1991	5, 10, 20, 40 and 80 mg tablets, PO once daily; recommended dosing range in peds with HeFH is 10 to 40 mg/day *Zocor is no longer marketed in 5 and 80 mg strengths: available as generic simvastatin*	175 subjects (10-17 years); 106 on simva 40 mg/d, 67 on Pbo; LDL-C change from baseline: -37% (simva) vs +1% (pbo)	Skeletal muscle effects (myopathy/ rhabdomyolysis) with increased risk with 80 mg dose, liver enzyme abnormalities, hypersensitivity	Adjunctive therapy to diet to reduce LDL-C in adults with primary hyperlipidemia Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction (MI), stroke, and the need for revascularization procedures in subjects at high risk of coronary events As an adjunct to other LDL-C-lowering therapies to reduce LDL C in adults with homozygous familial hypercholesterolemia (HoFH). As an adjunct to diet for the treatment of adults with: ◦ Primary dysbetalipoproteinemia. ◦ Hypertriglyceridemia
Pravastatin (Pravachol) NDA 19898	Adjunctive therapy to diet to reduce LDL-C in adults and pediatric subjects aged 8 years and older with HeFH	1991	20, 40 and 80 mg tablet; PO once daily Rec. dose in 8-13 yrs is	214 subjects (8-18 years); 65 on prava 20 mg; 41 on prava 40mg; 108	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme	Adjunctive therapy to diet to reduce LDL-C in adults with primary hyperlipidemia Reduce the risk of MI, revascularization, and cardiovascular (CV) mortality in hypercholesterolemic adults without clinically evident CHD

Product Name	Relevant Indication	Year of Initial Approval	Route and Frequency of Administration	Efficacy Information (LDL-C Reduction)	Important Safety and Tolerability Issues	Other Indications
			20mg; 14-18 yrs is 40 mg	on Pbo; LDL-C change from baseline: -26% (prava 20 mg); -21% (prava 40 mg) vs -2% (pbo)	abnormalities, hypersensitivity	Reduce the risk of coronary death, MI, myocardial revascularization, stroke/TIA, and slow the progression of coronary atherosclerosis in adults with clinically evident CHD As an adjunct to diet for the treatment of adults with: ◦ Primary dysbetalipoproteinemia. ◦ Hypertriglyceridemia
Fluvastatin (Lescol, Lescol XL) NDA 20261, 21192	As an adjunct to diet to reduce LDL-C in adults and pediatric patients 10 years of age and older with HeFH who require 80 mg of fluvastatin daily	1993	20, 40 and 80 mg tablet; PO once daily	85 subjects (10-16 years); 80 mg LDL-C change from baseline: -28%	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in adults with clinically evident coronary heart disease. As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia.
Atorvastatin (Lipitor) NDA 20702	Adjunctive therapy to diet to reduce LDL-C in adults and pediatric subjects aged 10 years and older with HeFH	1996	Tablets: 10, 20, 40, and 80 mg PO once daily Rec. dose in 10-17 yrs is 10-20mg;	187 subjects (10 to 17 years); atorva 10 to 20 mg/day (N=140) and Pbo (N=47)	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalitie	Adjunctive therapy to diet to reduce LDL-C in adults with primary hyperlipidemia Reduce the risk of ◦ MI, stroke, revascularization procedures, and angina in adults without CHD, but with multiple risk factors ◦ MI and stroke in adults with type 2 diabetes without CHD, but with multiple risk factors

Product Name	Relevant Indication	Year of Initial Approval	Route and Frequency of Administration	Efficacy Information (LDL-C Reduction)	Important Safety and Tolerability Issues	Other Indications
				LDL-C change from baseline: -40% (atorva) vs 0% (pbo)	s, hypersensitivity	◦ non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in subjects with CHD As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL C in adults and pediatric subjects aged 10 years and older with HoFH. As an adjunct to diet for the treatment of adults with: ◦ Primary dysbetalipoproteinemia. ◦ Hypertriglyceridemia
Rosuvastatin (Crestor) NDA 21366	Adjunctive therapy to diet to reduce LDL-C in adults and pediatric subjects aged 8 years and older with HeFH	2003	5, 10, 20 and 40 tablets, PO once daily Rec. dose in 8 to <10 yrs is 5-10 mg/d; 10-17 yrs is 5- 20 mg/d	176 subjects (10-17 years) on rosuva 5mg (n=42); 10 mg (n=44); 20 mg (n=44); pbo (n=46) LDL-C change from baseline: Pbo: -1% 5 mg: -38% 10 mg: -45% 20 mg: -50%	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Adjunctive therapy to diet to reduce LDL-C in adults with primary hyperlipidemia To reduce the risk of stroke, MI, and arterial revascularization procedures in adults without established CHD who are at increased risk of CV disease based on age, hsCRP ≥2 mg/L, and at least one additional CV risk factor. Reduce LDL-C and slow the progression of atherosclerosis in adults As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL C in adults and pediatric subjects aged 7 years and older with HoFH. As an adjunct to diet for the treatment of adults with: ◦ Primary dysbetalipoproteinemia. ◦ Hypertriglyceridemia

Product Name	Relevant Indication	Year of Initial Approval	Route and Frequency of Administration	Efficacy Information (LDL-C Reduction)	Important Safety and Tolerability Issues	Other Indications
Pitavastatin (Livalo) NDA 22363	Adjunctive therapy to diet to reduce LDL-C in adults and pediatric subjects aged 8 years and older with HeFH	2009	Tablets: 1 mg, 2 mg, and 4 mg; PO once daily	4 mg dose: mean % change in LDL-C: -43%	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Adjunctive therapy to diet to reduce LDL-C in adults with primary hyperlipidemia
Therapies for HeFH in pediatrics, *as add-on to statin*						
Colesevelam Hydro-chloride (Welchol tablet, Welchol for oral suspension) NDA 22362	Reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH as monotherapy or in combination with a statin after failing an adequate trial of diet therapy	2000	Tablets 625 mg; 3.75 g pwd pkts.; 3.75 g PO once daily	3.75 g dose: n=64 Pbo: n=65 mean % change in LDL-C compared to Pbo: -13%	May reduce absorption of folic acids and fat-soluble vitamins such as A, D and K. Constipation.	Adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with a statin Improve glycemic control in adults with type 2 diabetes mellitus
Ezetimibe	In combination with a statin as an adjunct to diet to reduce elevated LDL-C in pediatric subjects 10 years of age and older	2002	10 mg tablet PO once daily	126 subjects (10-17 years) on simva*/ezetimibe vs 122 subjects on simva*	Elevations in liver enzymes, myopathy/ rhabdomyolysis	In combination with a statin, or alone when additional low density lipoprotein cholesterol (LDL-C) lowering therapy is not possible, as an adjunct to diet to reduce elevated LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH). In combination with fenofibrate as an adjunct to diet to

	with HeFH.			*(10, 20 or 40 mg) Ezetimibe led to an additional 15% reduction in LDL-C		reduce elevated LDL C in adults with mixed hyperlipidemia. In combination with a statin, and other LDL-C lowering therapies, to reduce elevated LDL C levels in adults and in pediatric subjects 10 years of age and older with homozygous familial hypercholesterolemia (HoFH). As an adjunct to diet for the reduction of elevated sitosterol and campesterol levels in adults and in pediatric subjects 9 years of age and older with homozygous familial sitosterolemia.
Simvastatin/ ezetimibe (Vytorin) NDA 21687	No indication. Study summarized in Section 8.4 Pediatric Use	2004	Tablets (ezetimibe mg/simvastatin mg): 10/10, 10/20, 10/40, 10/80; PO once daily	126 subjects (10-17 years) on simva*/ezetimibe vs 122 subjects on simva* *(10, 20 or 40 mg) Ezetimibe led to an additional 15% reduction in LDL-C	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Adjunctive therapy to diet to reduce elevated total-C, LDL-C, ApoB, TG, and non-HDL-C, and to increase HDL-C in subjects with primary (HeFH and non-familial) hyperlipidemia or mixed hyperlipidemia Reduce elevated total-C and LDL-C in subjects with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
Evolocumab (Repatha) BLA 125522	As an adjunct to diet and other LDL-C-lowering therapies in pediatric subjects aged 10 years and older with HeFH, to reduce LDL-C	2015	SC Injection; either 140 mg every 2 weeks OR 420 mg once monthly	104 subjects (10-17 years) on evolocumab 420 mg SC monthly vs 53 subjects on pbo	Hypersensitivity reactions (angioedema, rash, urticaria)	In adults with established CVD to reduce the risk of MI, stroke, and coronary revascularization As an adjunct to diet, alone or in combination with other LDL-C-lowering therapies, in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C As an adjunct to other LDL-C-lowering therapies in adults and pediatric subjects aged 10 years and older with HoFH, to

				Evolocumab led to an additional 38% reduction in LDL-C		reduce LDL-C

Source: Individual drug prescribing information
ApoB=apolipoprotein B; CHD=coronary heart disease; CVD=cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; HeFH=heterozygous familial hypercholesterolemia; HoFH= homozygous familial hypercholesterolemia; IV=intravenous; LDL-C=low-density lipoprotein cholesterol; MI=myocardial infarction; Pbo=placebo; PO=by mouth; SC= subcutaneous; TG=triglycerides; total-C=total cholesterol
(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Praluent (alirocumab) was first approved in the U.S. on July 24, 2015, for use as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL-C. Doses originally approved were 75 and 150 mg every 2 weeks. Subsequent efficacy supplements have added a dose regimen (300 mg every 4 weeks approved April 24, 2017) and information on use with LDL apheresis in subjects with severe heterozygous familial hypercholesteremia to alirocumab labeling.

On April 26, 2019, following review of the cardiovascular trial, OUTCOMES, Praluent was approved for reducing the risk of major adverse cardiovascular events (myocardial infarction, stroke, unstable angina requiring hospitalization) in adults with established cardiovascular disease. The treatment indication for subjects with HeFH or established CVD was expanded to treatment of adults with primary hyperlipidemia to reduce LDL-C.

An efficacy supplement for the use of Praluent in the treatment of adult subjects with homozygous familial hypercholesterolemia (HoFH) was approved in April 2021. The adult trial was a single 12-week placebo-controlled double-blind trial with 12-week open-label follow-on trial in 69 adults with HoFH. Treatment with Praluent 150 mg Q2W yielded a placebo-subtracted LS mean LDL-C reduction of -35.6% at week 12.

The initial Pediatric Study Plan (iPSP, Revision 2, IND 105574 dated January 18, 2017) was agreed upon on February 16, 2017 (in DARRTS dated 2/7/2017; Reference ID 4052546) and includes 2 clinical trials in subjects 8 to 17 years of age with HeFH (trial numbers DFI14223 and EFC14643). The pediatric trials in subjects with HeFH were designed in accordance with post-marketing requirement (PMR) 2927-1 which required the following:

- Conduct a dose-finding study (phase 2) and an efficacy and safety study (phase 3) evaluating alirocumab in subjects with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less than 18 years. If children younger than age 10 are included, the eligibility criteria should ensure that other available interventions to lower LDL-C have been insufficient. Phase 2 will be a randomized, open-label, 8-week, ascending repeated dose-finding study of alirocumab with an optional open-label extension study in subjects 10 years to less than 18 years of age with HeFH on stable lipid modifying therapy with LDL-C ≥ 130 mg/dL. Phase 3 will be a randomized, 6-month, double-blind, placebo-controlled, parallel group, multicenter efficacy and safety study followed by an 18-month open-label extension in subjects 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C ≥ 130 mg/dL. Subjects treated in phase 2, the dose-finding study, will be offered enrollment in phase 3, the efficacy and safety study.

Reference ID: 5326070

Based on the results from trial EFC14643, the Applicant proposes a monthly (or Q4W) starting dose of 150 mg or 300 mg based on body weight. If additional LDL-C-lowering is needed, the dose may be titrated to a Q2W regimen (75 mg or 150 mg, respectively). In the proposed labeling, the Applicant does not recommend the Q2W starting dose regimens (i.e., 40 mg or 75 mg Q2W based on body weight) that were evaluated in the phase 3 trial. The FDA had previously informed the Applicant to include a justification in the sBLA supported by data for the proposed dosing regimen in the pediatric subject population.[28]

A summary of the additional regulatory history for this pediatric supplement for HeFH is provided in the table below:

[28] FDA's Type C Meeting Written Response Only dated November 24, 2021 (Reference ID 4894327).

3.1. Summary of Presubmission/Submission Regulatory Activity

Date	Summary
November 20, 2017 IND 105574 Reference ID: 4183847	Dr. Jennifer Pippins submitted a memo to "Acknowledge final protocol for postmarketing requirement." She recommended the use of the pattern mixture model (PMM) rather than the mixed-effect model with repeated measures (MMRM) in the primary analysis. She also noted that the sponsor moved the primary endpoint assessment visit from week 12 to week 24 and added an adaptive up-titration scheme at week 12 based on the LDL-C value at week 8 for subjects randomized to the alirocumab treatment arm. However, the up-titration scheme does not include a randomized control group of subjects who do not achieve an LDL-C level <110 mg/dL and do not up-titrate, potentially making it difficult to conclude whether up-titration is beneficial. She recommended consideration of a two-stage randomization design.
January 10, 2018 SD 542 IND 105574	The Sponsor submitted the agreed-upon protocol for EFC14643. In response to FDA comments from November 20, 2017, the sponsor stated that 1) they intend to use MMRM for the primary analysis "due to the worldwide development and the general acceptance of the MMRM analysis" and 2) "We fully understand that with our current design, we are not able to compare the two alirocumab doses and can only approximate the additional LDL-C reduction achieved by up-titration. However, our experts advise that these pediatric subjects should not be above LDL-C goal for any longer than necessary…"
January 30, 2019	The Sponsor submitted protocol amendment 1 for EFC14643 to update the description of the independent physician involved in the monitoring of subjects reaching LDL-C levels <50 mg/dL during the 24-week double-blind treatment period to demonstrate that the physician is external to the EFC14643 study, but not necessarily external to the Sponsor.
February 1, 2019 SDN 583	The Sponsor submitted protocol amendment 2 for EFC14643 to include the Q4W dosing regimen alongside the Q2W dosing regimen. (Dr. Roberts's review dated May 22, 2019 acknowledged this change)
November 09, 2020; SDN 632 and January 15, 2021; SDN 638	The Sponsor submitted protocol amendment 3 for EFC14643 to enable changes in statistical analyses to reflect the sequential enrolment in the 2 dosing regimen cohorts of subjects, since enrolment in the every-4-weeks (Q4W) cohort started only when enrolment in the every-2-weeks (Q2W) cohort was completed. This amendment replaces the 2 primary efficacy hypotheses comparing each alirocumab treatment regimen (Q2W, Q4W) versus a pooled placebo group combining Q2W and Q4W regimens by a comparison of each alirocumab group versus its contemporaneously randomized placebo group (i.e., of the same dosing regimen cohort). (See responses by Dr. Mary Roberts December 3, 2020, and January 27, 2021)

Reference ID: 5326070

September 10, 2021; SD 656	The Sponsor submitted a Type C meeting request and briefing materials to seek the Agency's feedback on the proposed dosing regimens for labeling for the treatment of pediatric subjects with HeFH. Refer to the review by Dr. Mary Roberts (in DARRTS dated 11/29/2021, Reference ID: 4894422). Dr. Roberts noted that in each body weight strata and dose frequency there was a reduction in LDL-C compared to placebo at week 24. There appears to be a numerical greater reduction in LDL-C in the Q2W versus Q4W dosing frequency, however, the 97.5% confidence intervals include 1. It is unknown if the higher proportion of subjects that up-titrated at week 12 contributed to the numerically larger LDL-C observed at week 24 in the Q2W compared to the Q4W cohorts. No compliance data was submitted to support the sponsor's position that "In addition, the Applicant's assessment is that Q4W regimen can improve the adherence and compliance of a treatment with alirocumab by decreasing the frequency of administration and limiting the discomfort related to iterative subcutaneous injections in this vulnerable pediatric population. Indeed, a Q4W dosing regimen will limit disruption of the everyday life of children and adolescents."
October 21, 2021 SN0657 November 18, 2021 SN0660	The Sponsor submitted a Type C meeting request (SN0657) and briefing materials (SN0660) to discuss the need for additional clinical data (b) (4) The Agency recommended that they submit their HF validation study protocol and leveraging strategy for feedback from the Agency. Refer to the review by Dr. Mary Roberts (in DARRTS dated 12/22/2021, Reference ID: 4909859). Dr. Roberts states that the sponsor contends no additional clinical data are required to support the proposed PFP in the pediatric population for the following reasons: 1. PFS, DAI-PFP and proposed PFP devices have comparable design and performance characteristics; 2. In vivo pharmacokinetics of alirocumab administered by PFS, DAI-PFP and proposed PFP devices are similar in adults; and 3. In vivo pharmacokinetics of alirocumab administered by PFS are similar in adults and children. The sponsor intends to conduct a human factors study in adult users of the PFS to ensure acceptable transitioning to the new device. The sponsor does not intend to conduct a dedicated HF study in pediatric subjects with HeFH. Instead, they intend to leverage HF data from the proposed PFP from the Dupixent (monoclonal antibody blocking interleukin 4 and interleukin 13 used in adults and children 6 months of age and older with moderate-to-severe atopic dermatitis and other indications) program in pediatric subjects. An internal discussion was held on December 15, 2021, with the clinical, clin/pharm, CMC, DMEPA, and CDRH review teams. The team supported the bridging strategy proposed and at this time do not propose additional clinical studies. The approval of this proposed product will be based on the totality of the evidence provided in the supplement.

November 24, 2021 Reference ID 4894327 (WRO to the September 10, 2021 Type C Request)	The Agency noted that they could not agree that the monthly dosing regimen is the appropriate starting dose in the pediatric HeFH population based on the summary data provided, and that the Sponsor should submit complete efficacy and safety data for all doses used in the trial in an efficacy supplement for Agency review. The sBLA should include a justification supported by data for the Sponsor's position on the starting dose regimen in the subject population.
January 3, 2022 Reference ID 4913454 (WRO to the October 21, 2021 Type C Request)	The Agency noted that in general, they agree with the Sponsor's rationale; however, approval of the new ACCRA PFP will ultimately depend on review of the information submitted. CDRH requested additional information (see page 6 of 7 of the document (DARRTS 1/3/2022; Reference ID: 4913454).
January 31, 2022 (S/N 0667)	Regeneron provided a response to the Agency stating that they have no current plans to develop a 40 mg dose for the proposed PFP (ACCRA) device for children <50kg (b) (4) The Sponsor believes that the (b) (4) Q4W regimen is appropriate for pediatric subjects and intends to submit an sBLA for this starting dose regimen with justification supported by efficacy, safety, and PK data. The Sponsor provided completed verification testing with actual test results for the DAI and proposed PFP devices. Complete verification testing submission package, including testing after stability time points and shipping, will also be provided at the time of supplement submission. The Sponsor confirms that all verification testing was performed with final finished devices filled with the intended drug product.
February 10 and 18, 2022 and	The Sponsor submitted a supplemental HF validation study protocol and a comprehensive comparative analysis, seeking Agency concurrence on aspects of the proposed HF validation study design (b) (4) DMEPA 1 review of this protocol is in DARRTS (5/24/2022; Reference ID: 4988506). They found that the HF validation study protocol is not acceptable (see section 8.1 for their recommendations). They advised the Sponsor to implement the recommendations prior to commencing their HF validation study.

May 27, 2022 Reference ID: 4990658	FDA Human Factors team provided their advice to the sponsor. Their review of the human factors validation study protocol identified several areas of concern. They recommend that the sponsor implement all recommendations before commencing their human factors validation study.
April 1, 2022 Reference ID 4962819	The Agency provided an Advice/Information Request regarding the dosing regimen to be proposed for the pediatric population: We refer to your amendment dated January 31, 2022, containing your response to our January 3, 2022, meeting minutes for your October 21, 2021, meeting request. In your response you state that you have no plans to develop a 40 mg dose for the proposed pre-filled pen. You also state that the (b) (4) Q4W regimen is the appropriate starting dosage for pediatric subjects. We recommend that you schedule a pre-supplemental biologics license application (pre-sBLA) meeting with the Agency prior to submission of your sBLA. You also provided the comparative device performance data, as requested. For your future sBLA application, you should update the comparison of injection depth for the DAI device from attribute test to variable test.

April 27, 2022
SN0673

Regeneron submitted a clinical information amendment in response to the Agency's Advice/Information Request letter dated April 1, 2022 (Reference ID: 4962819). The sponsor stated that they would like to correct an error in the response document dated 31-Jan-2022 (S/N 0667); we do not intend to propose (b) (4) Q4W as the starting dosage for the pediatric subject population.

In the upcoming sBLA, the sponsor plans to propose starting dosing regimens consistent with what was studied in the Phase 3 trial: For children with body weight of <50 kg, considering the demonstrated efficacy and comparable safety to the 40 mg Q2W treatment regimen, the sponsor proposes 150 mg Q4W to improve the adherence and compliance with the treatment by decreasing the frequency of administration. For children with body weight ≥50 kg, the sponsor is evaluating the exact dosing regimen to be proposed (75 mg Q2W or 300 mg Q4W, as studied in EFC14643). Complete efficacy, safety, and PK data for all dosing regimens administered in the phase 3 trial EFC14643 will be included in the submission for the Agency's review, as well as justification supported by data for the dosage proposal. The sponsor also provided the number of subjects treated in each dosing regimen/cohort of the Trial EFC14643.

Dosing regimen	Body weight category	Initial dose	LDL-C at Week 8 visit	Dose change at Week 12 visit up to Week 24 and continued in the open-label part	Number of patients treated with this regimen
Q2W	<50kg	40mg Q2W	< 110mg/dL	No change	14
			≥ 110mg/dL	75mg Q2W	11
	≥ 50kg	75mg Q2W	< 110mg/dL	No change	13
			≥ 110mg/dL	150mg Q2W	11
Q4W	<50kg	150mg Q4W	< 110mg/dL	No change	15
			≥ 110mg/dL	75mg Q2W	5
	≥ 50kg	300mg Q4W	< 110mg/dL	No change	22
			≥ 110mg/dL	150mg Q2W	10

October 19, 2022	In response to the Sponsor's Type B meeting request, submitted August 19, 2022, the FDA agreed with (1) due to differences in the trial designs of the pediatric trials, the pediatric safety data would not be pooled for the Summary of Clinical Safety, (2) for the purpose of reporting financial disclosures and for providing summary level clinical site data, the phase 3 pivotal trial, EFC14643, is the only "covered study" in accordance with 21 CFR 54, (3) the Sponsor's proposed Study Data Standardization Plan, and (4) the Sponsor's proposed table of contents for the supplemental BLA. The FDA recommended that a summary of clinical efficacy for both trials EFC14660 and DFI14223 also be included in Module 2.7.3 and agreed that the main focus of Module 2.7.3 will be trial EFC14643. The FDA did not agree to a waiver of the 120-day safety update prior to the submission of the supplement. If all trials with alirocumab will be complete and there are no data to report, the sponsor was instructed that the 120-day safety update report may include a statement to that effect when the supplement is submitted, not prior to submission.

3.2. Foreign Regulatory Actions and Marketing History

Reference ID: 5326070

Alirocumab was first approved in 2015 in the US (July 24, 2015) and in the EU (September 23, 2015). Alirocumab is approved in 60 countries worldwide. Alirocumab is approved:

- In adults as adjunct therapy to diet for primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, alone or in combination with a statin and/or other lipid-lowering therapies (Note: The approved indication may vary locally).
- To reduce the CV risk in adults with established ASCVD (Note: This indication is not registered in all countries, the approved indication may vary locally including in the EU [11 March 2019], the US [26 April 2019] and China [26 December 2019].
- As an adjunct to other LDL-C-lowering therapies in adult patients with HoFH to reduce LDL-C (Note: This indication is only approved in the US [01 April 2021]).

Alirocumab is administered SC. The following dosing regimens have been approved:

- 75 mg Q2W, 150 mg Q2W and 300 mg Q4W (monthly) (this last dosing regimen is not approved in all countries worldwide).
- In addition, in Japan, a 150 mg Q4W dose regimen was approved on 21 November 2018 in patients at high CV risk who are not appropriate for statin therapy, in addition to the initially approved Q2W dosage regimens.

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

4.1. Office of Scientific Investigations (OSI)

An OSI audit was requested for 3 sites because of risk ranking, high efficacy ranking, and number of subjects randomized. Two foreign clinical investigators (CIs): Drs. Jean Bergeron (Canada; Site #1240001) and Victor Gerdes (Netherlands; Site #5280001), and one domestic CI: Dr. Macrae Linton (Site #8400003) were inspected for the phase 3 trial EFC14643.

Refer to the review by Dr. Ling Yang, Good Clinical Practice Assessment Branch (GCPAB), Division of Clinical Compliance Evaluation (DCCE), Office of Scientific Investigations (OSI), in DARRTS dated January 16, 2024.

In brief, the inspection reviewed the study protocol and amendments, Informed Consent Forms (ICFs)/ child assent and versions, documentation of eligibility criteria and enrollment logs, medical records [including visit data, laboratory tests, physical exam results, adverse events (AEs) and serious AEs (SAEs) reports], investigational product (IP) accountability records, paper Case Report Forms (CRFs) with electronic CRFs (eCRFs) entries, electronic data capture (EDC) system and the audit trail, protocol deviations and related regulatory documents [e.g., Institutional Review Board (IRB) approvals and communications, staff trainings, monitoring log, records retention, financial disclosures and delegation of authority].

The submitted data were verifiable with source records at the study site. The primary efficacy endpoint data of the percent change in LDL-C from baseline to Week 24 were centrally calculated by the sponsor and were available at the site. The inspection verified the data with no discrepancy noted. There were no underreporting of AEs or SAEs. In general, the inspection verified adequate source data for the inspected study subjects, with no deficiencies reported.

Dr. Yang concluded that based on the overall inspection results of these three CIs and the regulatory assessments, the data generated by these CI sites are verifiable. Trial EFC14643 appears to have been conducted adequately and the clinical data submitted by the sponsor appear acceptable in support of the respective indication.

4.2. Product Quality

Dr. Walsh (OBP/DBRR III) states that the Applicant submitted a request for categorical exclusion from environmental assessment requirements in accordance with 21 CFR 25.31(c). The claim of categorical exclusion is acceptable. No other chemistry, manufacturing, and controls (CMC) content is updated with this submission with the exception of the comparison of the prefilled syringe used in pediatric clinical studies, the prefilled syringe used in adult phase 3 clinical studies, and the currently approved prefilled pen (disposable auto-injector) for use in the adult population that is the proposed commercial presentation for the pediatric population. There is no difference in (b) (4) drug substance, drug product formulation, or the primary container closure systems used in these presentations. The submission is acceptable for approval from a product quality perspective (refer to Dr. Scott Walsh's review in DARRTS dated July 5, 2023). The final product quality review was pending at the time of the completion of this review.

4.3. Clinical Microbiology

Not applicable for this submission.

4.4. Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology data is included in this submission for review. The nonclinical information is cross-referenced to the previously approved original BLA 125559. Dr. Haile states that based on literature data and the nonclinical toxicology studies reviewed before for alirocumab, no additional juvenile toxicity studies are considered necessary to support the proposed pediatric age group (8 to 17 years of age) (refer to Dr. Lydia Haile's review in DARRTS dated June 15, 2023).

4.5. Clinical Pharmacology

The Applicant conducted the pivotal phase 3 trial and the phase 2 dose-finding trial in pediatric patients using the pre-filled syringe (PFS), and proposes to use the currently approved pre-filled autoinjector pen (DAI-PFP). The clinical pharmacology team state that based on meeting minutes dated January 3, 2022 and original BLA reviews, PFS and DAI-PFP result in similar PK

in adult patients. Therefore, it appears that no bridging study is needed to compare these two devices (refer to Dr.Tian Zhou's filing review in DARRTS dated July 5, 2023). The final clinical pharmacology review was pending at the time of the completion of this review.

4.6. Devices and Companion Diagnostic Issues

During DB treatment period sterile alirocumab drug product and placebo for alirocumab were provided in a PFS for SC injections with finger grip. During the OL treatment period, IMPs were all provided in a pre-filled syringe with a needle shield (PFS-S) for SC injection. Once approved, the Applicant will provide the product in the currently approved Praluent DAI Prefilled Pen.

The Human Factors review was pending at the time of completion of the primary clinical review.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Reference ID: 5326070

Figure 1. Listing of Clinical Trials Relevant to this BLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Trial Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Trial Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
EFC 14643	NCT 03510884	Phase 3, randomized, double-blind treatment, placebo-controlled, parallel group, multi-national, multi-center trial followed by an open label treatment period	Q2W trial: 40 mg for body weight (BW) <50 kg; 75 mg for BW ≥50 kg, then up titration dose adjustment at week 12 to 75 mg for BW <50 kg; 150 mg for BW ≥50 kg Q4W trial: 150 mg, for BW <50 kg; 300 mg, for BW ≥50 kg, then up titration dose adjustment at week 12 to 75 mg Q2W for BW <50 kg; 150 mg Q2W for BW ≥50 kg	Primary: Percent change in LDL-C from baseline to week 24 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment (ITT estimand)	24-week double-blind treatment, then 80-week open label treatment	Q2W Trial: 74 Q4W Trial: 79	Children and adolescents 8 to 17 years of age with HeFH and LDL-C ≥130 mg/dL (3.37 mmol/L) at screening despite stable lipid modifying therapies	43 centers in 24 countries
		Studies to Support Safety						
EFC 14660	NCT 03510715	Phase 3, multi-national, multicenter, open-label, treatment trial	Alirocumab 75 mg or 150 mg Q2W SC depending on body weight (75 mg for BW <50 kg and 150 mg for BW ≥50 kg). After week 12, the dose of alirocumab was adjusted in case of weight change after baseline, such that the dose corresponded to the subject's BW. For subjects treated with apheresis, the frequency was fixed to the individual subject's established schedule up to week 12. After week 12, the frequency	Primary: Percent change in LDL-C (pre-apheresis, if applicable) from baseline to week 12 (intent-to-treat [ITT] estimand)	Up to 62 weeks (4-week run-in, 2-week screening, 48-week treatment, and 8-week follow-up periods)	18	Children and adolescents of 8 to 17 years of age with confirmed HoFH by genetic testing and LDL-C ≥130 mg/dL at screening despite	10 centers in 10 countries

Reference ID: 5326070

			of apheresis could be adapted following investigator judgment.				treatment with stable lipid modifying therapies at optimal doses	
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
DFI 14223	NCT 02890992	Open-label, dose-finding, sequential group, multi-national, multi-center trial	Alirocumab Injection SC: • Cohort 1: 30 mg Q2W SC if BW <50 kg and 50 mg Q2W SC if BW ≥50 kg. • Cohort 2: 40 mg Q2W SC if BW <50 kg and 75 mg Q2W SC if BW ≥50 kg. • Cohort 3: 75 mg Q4W SC if BW <50 kg and 150 mg Q4W SC if BW ≥50 kg. • Cohort 4: 150 mg Q4W SC if BW <50 kg and 300 mg Q4W SC if BW ≥50 kg.	Primary: Percent change in calculated LDL-C from baseline to week 8.	Dose Finding Period: 8 weeks (cohorts 1, 2 and 3); 12 weeks (cohort 4) OLE Period: treatment with alirocumab continued until at least 10 weeks before the subject's entry into the pediatric HeFH phase 3 trial (EFC14643)	Dose Finding: 42 OLE: 41	Patients 8 to 17 years of age with HeFH	16 centers in 10 countries

Reference ID: 5326070

5.2. Review Strategy

The Applicant has conducted two trials to address PMR 2927-1 (see section 3.1 U.S. Regulatory Actions and Marketing History) from the July 24, 2015, BLA Approval letter:

1. Trial DFI14223, titled "An 8-week Open-Label, Sequential, Repeated Dose-Finding Study to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents With Heterozygous Familial Hypercholesterolemia Followed by an Extension Phase," and
2. Trial EFC14643 titled "A Randomized, Double-Blind, Placebo-Controlled Trial Followed by an Open Label Treatment Period to Evaluate the Efficacy and Safety of Alirocumab in Children and Adolescents with Heterozygous Familial Hypercholesterolemia."

In accordance with the written responses (dated October 22, 2022) to questions contained in the August 19, 2022, background package, the Summary of Clinical Efficacy for this supplement will consist of a summary of the efficacy results from Trial EFC14643, a phase 3, double-blind, placebo-controlled trial in pediatric subjects with HeFH. The summary of clinical efficacy will not include data from the phase 2 dose finding trial in HeFH subjects (DFI14223). The results of the phase 3 trial in pediatric subjects with HoFH (EFC14660) will also not be included in the summary of clinical efficacy.

Sections 6 and 7 of this review present the results of the Applicant's efficacy analyses along with the clinical reviewer's commentary, where relevant. However, the statistical reviewer conducted an independent review of the efficacy (refer to Dr. Kiya Hamilton's statistical review in DARRTS for details) and those findings will be the source of estimates presented in the prescribing information.

The written responses (dated October 22, 2022) also agreed that the Summary of Clinical Safety will include individual summaries of the three pediatric trials (EFC14643, phase 3 pediatric HeFH trial; DFI14223, phase 2 dose-ranging trial in pediatric subjects with HeFH; and EFC14660, phase 3 pediatric HoFH trial). However, due to important differences in subject populations and trial designs, pediatric safety data will not be integrated for the Summary of Clinical Safety. The applicant's analysis was verified and supplemented with the clinical reviewer's analysis, where applicable.

Review of the entire application will be done by a single clinical reviewer, in collaboration with the team lead.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. EFC14643 - A randomized, double-blind, placebo-controlled study followed by an open label treatment period to evaluate the efficacy and safety of alirocumab in children and adolescents with heterozygous

6.1.1. Study Design

Overview and Objective

Primary objective:

- To evaluate the efficacy of alirocumab administered every 2 weeks (Q2W) and every 4 weeks (Q4W) versus placebo after 24 weeks of double-blind (DB) treatment on low-density lipoprotein cholesterol (LDL-C) levels in subjects with heterozygous familial hypercholesterolemia (HeFH) 8 to 17 years of age on optimal stable daily dose of statin therapy ± other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins.

Secondary objectives:

- To evaluate the efficacy of alirocumab versus placebo on LDL-C levels after 12 weeks of DB treatment.
- To evaluate the effects of alirocumab versus placebo on other lipid parameters (e.g., apolipoprotein B [ApoB], non-high density lipoprotein cholesterol [non-HDL-C], total-cholesterol [Total-C], high-density lipoprotein cholesterol [HDL-C], lipoprotein [a] [Lp[a]], triglycerides [TGs], apolipoprotein A-1 [Apo A-1] levels) after 12 and 24 weeks of treatment.
- To evaluate the safety and tolerability of alirocumab after 24 weeks of treatment in comparison with placebo.
- To evaluate the efficacy, safety and tolerability of alirocumab after 80 weeks of open label treatment.
- To evaluate the development of anti-alirocumab antibodies after 24 weeks of treatment during the double-blind (DB) treatment period.

Trial Design

This trial is a randomized, 24-week DB, placebo-controlled, parallel-group, multi-national, multi-center trial followed by an open label treatment period of 80 weeks. Approximately 150 children and adolescents aged of 8 to 17 years with HeFH and LDL-C ≥130 mg/dL at screening visit despite stable LMTs will be randomized 2:1 (alirocumab:placebo). Two dosing regimens, Q2W and Q4W, will be evaluated with approximately 75 subjects in each dosing regimen cohort.

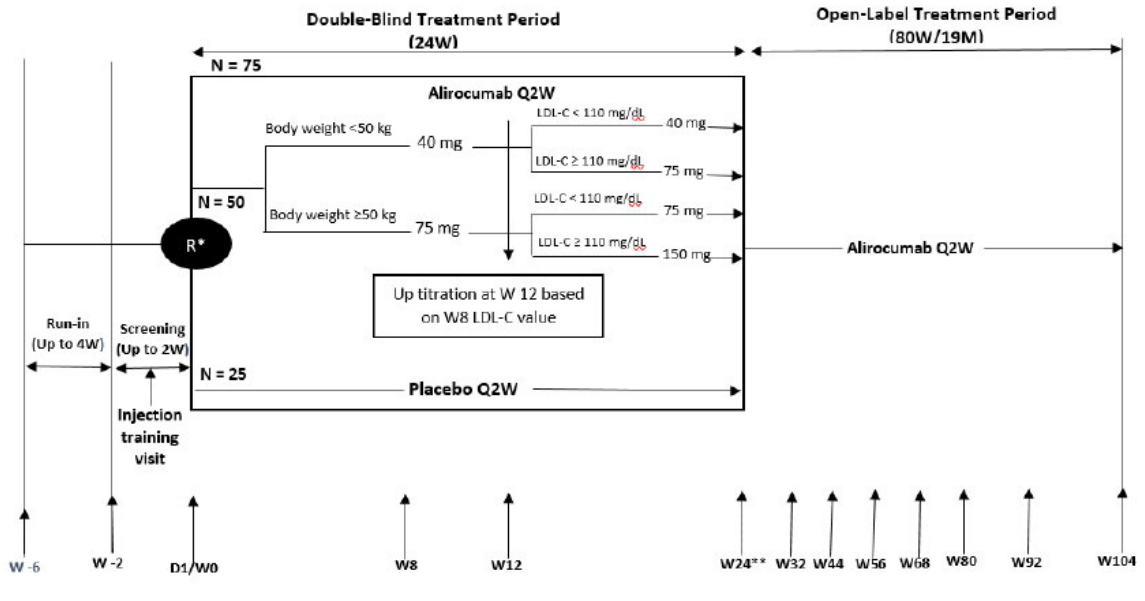
Stable LMTs are defined as stable optimal dose of statin ± other stable LMTs or stable dose of non-statin LMTs in statin intolerant subjects for at least 4 weeks prior to screening. The optimal dose of statin is defined as the dose prescribed based on regional practice or local guidelines or is the dose that is maximally tolerated due to adverse effects of higher doses. For subjects not receiving maximally tolerated statin, statin intensification should be carefully considered prior to randomization in this trial in order to ensure that the addition of a non-statin LDL-C lowering

therapy (such as alirocumab) would be the next appropriate step in the management of the subject's hypercholesterolemia. Statin intolerance is defined as the inability to tolerate at least 2 statins: one statin at the lowest daily starting dose, and another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.

Randomization was stratified according to previous participation (yes or no) in the phase 2 DFI14223 trial and baseline body weight (<50 or ≥50 kg).

The trial consists of a run-in period (as needed), screening period, double-blind treatment period, and an open label treatment period.

Figure 2 Trial Design, Q2W dosing regimen cohort

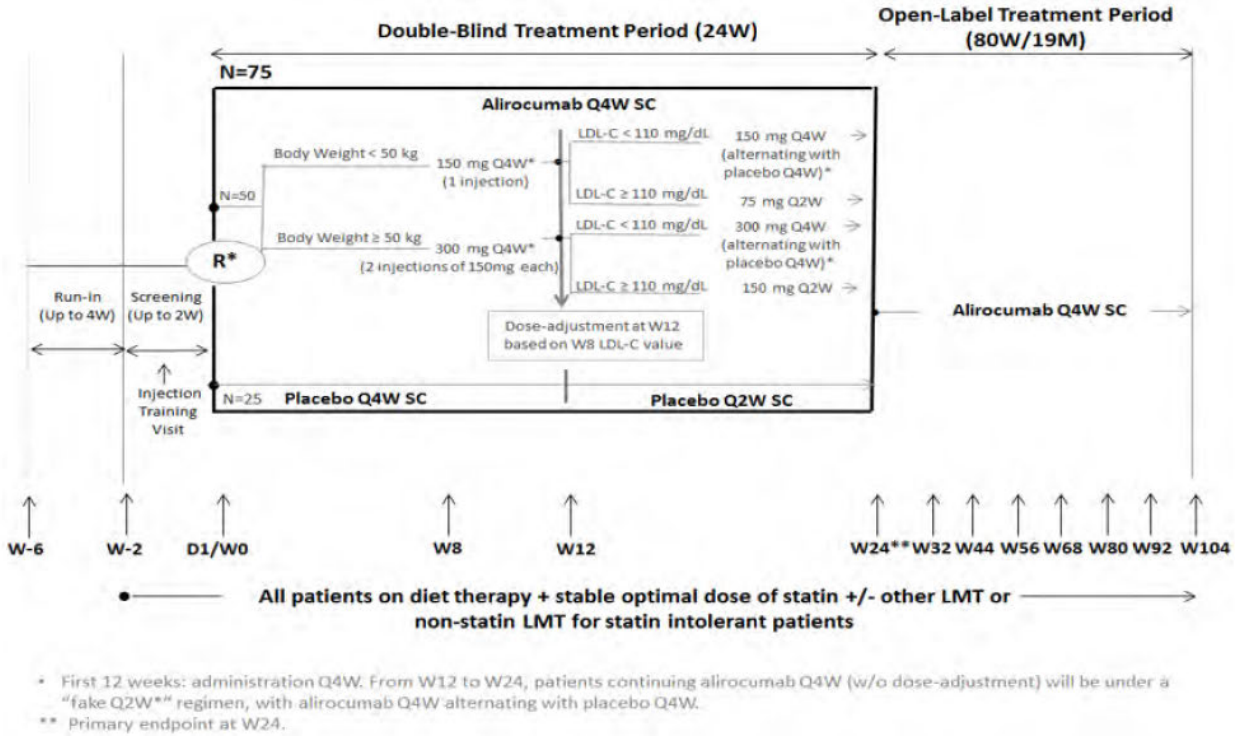


*Randomization will be stratified according to previous participation (yes or no) to the phase 2 DFI14223 study and baseline body weight (<50 or ≥50 kg)

**Primary efficacy endpoint at Week 24

Excerpted from Applicant's submission, CSR page 25
Abbreviations: W = week, M = Month, R = randomization, LMT = lipid modifying therapy

Figure 3 Trial Design, Q4W dosing regimen cohort



Excerpted from Applicant's submission, CSR page 26
Abbreviations: W = week, M = Month, R = randomization, LMT = lipid modifying therapy

Run-in period (as needed):
The run-in period is up to 4 weeks (+2 days) in duration.
Subjects who consent to participate in the trial but who have not been on stable LMTs for at least 4 weeks or require statin intensification when initially seen can participate in a run-in period until LMT dose(s) have been stable for at least 4 weeks. Subjects who require treatment with statin de novo are not allowed to enter the run-in period in order to avoid the potential for multiple titration steps. Another possible situation requiring the run-in period include subjects with suspected HeFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria. Such subjects will be asked to undergo centralized genetic testing during the run-in period.

Screening period:
The screening period is up to 2 weeks (+5 days) in duration.
An intermediate visit for injection training may occur during which the subject if aged 12 years and above (or another designated person such as parent, etc.) will be trained to self-inject/inject with placebo for alirocumab after the eligibility criteria have been checked and it is confirmed that the subject will likely be randomized.

Previous participation in phase 2 trial DFI14223:

Subjects who have previously participated in the DFI14223 trial and have received alirocumab administration during the open label extension of the DFI14223 trial will require a wash-out period of at least 10 weeks between the last injection of alirocumab and the screening lipid assessment at the entry of the screening period. However, as these subjects have already met this LDL-C requirement when they screened for the DFI14223 trial they will not be excluded based on the LDL-C value obtained during the screening for the EFC14643 trial.

Double-blind treatment period:
The double-blind treatment period is 24 weeks in duration.
Two dosing regimens will be evaluated - either Q2W or Q4W; the start of the recruitment in the Q4W dosing regimen cohort will depend on the status of the recruitment in the Q2W dosing regimen cohort and the status of the amendment approval. Subjects will be blinded to trial treatment and randomized to either alirocumab or placebo using a 2:1 ratio for each dosing regimen cohort.

Reviewer Comment: This trial was placebo-controlled, which was justified as subjects were receiving a background of stable, optimized statin therapy and could be receiving other lipid-lowering therapies, such as ezetimibe.

The Applicant made reasonable efforts to blind trial medication from subjects and investigators. However, subjects could be unblinded to their treatment assignment if they have an LDL-C assessment outside the trial, such as at a health fair.

Q2W dosing regimen cohort:
Approximately 75 subjects will participate in the Q2W dosing regimen cohort. Subjects with BW <50 kg will receive 1 subcutaneous (SC) injection of 0.5 mL Q2W of alirocumab or placebo. Subjects with BW ≥50 kg will receive 1 SC injection of 1 mL Q2W of alirocumab or placebo. For subjects randomized to receive alirocumab the following dose based on body weight (BW) will be initially administered:

- 40 mg for BW <50 kg or,
- 75 mg for BW ≥50 kg.

At week 12, subjects randomized to alirocumab will either:

- Continue alirocumab 40 mg or 75 mg Q2W if the week 8 LDL-C is <110 mg/dL, OR
- Dose up-titrate to alirocumab 75 mg (for subjects on 40 mg) or 150 mg (for subjects on 75 mg) if the week 8 LDL-C is ≥110 mg/dL.

Q4W dosing regimen cohort:
Approximately 75 subjects will participate in the Q4W dosing regimen cohort. During the first 12 weeks of the double-blind period and before any possible dose-adjustment to Q2W dosing regimen, all subjects will receive SC injection(s) Q4W to get a proper evaluation of this dosing regimen. After week 12, all subjects will receive SC injection(s) Q2W. Subjects receiving alirocumab will be under a "sham Q2W" regimen from week 12 to week 24, with alirocumab

Q4W alternating with placebo Q4W. For subjects randomized to alirocumab the following dose based on body weight (BW) will be initially administered:

- 150 mg Q4W for BW <50 kg or,
- 300 mg Q4W for BW ≥50 kg.

At week 12 subjects randomized to alirocumab will either:

- Continue alirocumab 150 mg or 300 mg Q4W, if the week 8 LDL-C is <110 mg/dL OR
- Have a dose-adjustment to 75 mg Q2W (for subjects on 150 mg Q4W) or 150 mg Q2W (for subjects on 300mg Q4W) if the week 8 LDL-C is ≥110 mg/dL.

Note on maintaining blinding: Lipid values obtained at week 8 for the purpose of up-titration will not be communicated to investigators to maintain the blind. The continuation or dose up-titration/dose-adjustment of alirocumab will occur in an automated process without site or subject awareness.

Dose selection:

Phase 2 trial DFI14223 evaluated a fixed dosage according to BW categories with 31 pediatric subjects in 3 different cohorts:

- Cohort 1
  - BW < 50 kg: 30 mg Q2W
  - BW ≥ 50 kg: 50 mg Q2W
- Cohort 2
  - BW < 50 kg: 40 mg Q2W
  - BW ≥50 kg: 75 mg Q2W
- Cohort 3
  - BW < 50 kg: 75 mg Q4W
  - BW ≥50 kg: 150 mg Q4W

The percent change from baseline in LDL-C at week 8 (primary efficacy endpoint) demonstrated a greater reduction in LDL-C, overall, in Cohort 2 using the Q2W dosing regimen (change in LDL-C -46.1%) with a mean reduction in both BW categories (-40.4% with 40 mg Q2W in the lower BW category, and -49.8% with 75 mg Q2W in the higher BW category), as compared with the Cohort 1 (change in LDL-C -41.2% with 30 mg Q2W in the lower BW category, and -7.9% with 50 mg Q2W in the higher BW category). For Cohort 3, there was a mean reduction of -17.5% with the 75 mg Q4W dose in the lower BW category and a mean increase of +4.0% with the 150 mg Q4W in the higher BW category. The cohort 3 results were unexpectedly low, and the applicant believed that the doses evaluated were likely not high enough to achieve larger and sustained reductions in the LDL-C over the entire dosing interval in children receiving statin as background therapy. Therefore, the applicant added cohort 4 to the phase 2 DFI14223 trial before investigating this Q4W dosing regimen in the phase 3 EFC14643 trial:

- Cohort 4
  - BW < 50 kg: 150 mg Q4W
  - BW ≥50 kg: 300 mg Q4W

LDL-C reduction in cohort 4 was -31.9% in the lower BW category and -59.8 % in the higher BW category. Based on these results, the doses selected to be evaluated for the EFC14643 trial are 40 mg Q2W for BW<50 kg and 75 mg Q2W for BW ≥50 kg in the Q2W dose regimen, and 150 mg Q4W for BW<50 kg and 300 mg Q4W for BW ≥50 kg in the Q4W dose regimen.

Although most subjects in DFI14223 achieved an LDL-C value <110 mg/dL (76.4% of subjects in Cohort 2, and 86.4% in Cohort 4), about 20% of subjects still had elevated LDL-C. Therefore, the applicant decided to use an up-titration/dose-adjustment scheme as done for adults. According to the applicant, doubling the dose of alirocumab should result in an additional decrease in LDL-C of about 10%, based on the data from phase 3 trials in adults. Of note, 75 mg Q2W and 300 mg Q4W are the approved dose regimens in the adult population. If the LDL-C response is inadequate in adults, the dosage may be adjusted to 150 mg subcutaneously every 2 weeks.

During DB treatment period sterile alirocumab drug product and placebo for alirocumab were provided in PFS for SC injections with finger grip. During the OL treatment period, IMPs were all provided in PFS-S for SC injection. Amounts used are as follows:

- BW <50 kg:
  - 0.5 mL of alirocumab 75 mg/mL solution for 40 mg dose,
  - 0.5 mL of alirocumab 150 mg/mL solution for 75 mg dose.
- BW ≥50 kg:
  - 1 mL of alirocumab 75 mg/mL solution for 75 mg dose,
  - 1 mL of alirocumab 150 mg/mL solution for 150 mg dose.

The first investigational medicinal product (IMP) injection (from the double-blind trial treatment kit allocated by interactive response technology [IRT]) will be done at the site on the day of randomization or as close as possible after randomization into the trial. The subsequent injections will be done at a subject-preferred location (e.g., at home). All the IMP injections can be performed by trained subject (self-injection if aged ≥12) or parent, or another designated person or alternative arrangements for injection administration will be allowed as needed (e.g., return to the clinic). Prior to any injection, a local topical anesthetic may be utilized as per the investigator.

Injection training:

- Further injection training can be provided at the randomization visit week 0/Day 1 when the subject/parent or a trained designated person injects the first IMP from the double-blind trial treatment kit allocated by IRT.
- Additional training can be offered at scheduled or unscheduled visits with the scheduled double-blind treatment, as per subject/parent or investigator's judgment.

The laboratory measurement of lipid parameters will be performed by a central lab. LDL-C will be calculated using the Friedewald formula. If TG values exceed 400 mg/dL then LDL-C will be measured reflexively via the beta quantification method instead. Specific results of the central

lab testing for lipid parameters from samples obtained after randomization and during the double-blind treatment period will not be communicated to the sites or to the Applicant's EFC14643 trial team. Instead, the central lab will inform sites if subjects exceed the triglyceride threshold of 500 mg/dL. Additionally, the site may receive alert related to LDL-C <50 mg/dL and associated safety concerns identified by the independent physician who will carefully monitor, under the auspices of the Data Monitoring Committee (DMC), the subject's LDL-C values during the double-blind treatment period. No local lab testing for lipid parameters should be performed after randomization and throughout the trial. Of note, the independent physician is external to the EFC14643 trial team and not part of any alirocumab activities.

Reviewer Comment: Measurement of LDL-C by beta quantification is considered the gold standard (Meeusen JW, Snozek CL, Baumann NA, Jaffe AS, Saenger AK. Reliability of Calculated Low-Density Lipoprotein Cholesterol. Am J Cardiol. 2015 Aug;116(4):538-40. Epub 2015 May 21).

Statin and other LMT (if applicable) should be stable during double-blind treatment period barring exceptional circumstances whereby overriding concerns (including but not limited to triglyceride alert posted by the central lab) warrant such changes, as per the investigator's judgment.

Subjects will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or local practice and they should be on this diet throughout the entire trial duration from screening.

Open label treatment period:
Subjects, who successfully complete the 24-week double-blind treatment period can enter the open label treatment period. The open label treatment period consists of 80 weeks of open label alirocumab SC Q2W or Q4W depending on the dosing regimen initiated at randomization. The first open label alirocumab injection(s) will be done at the site followed by monitoring of the subject for at least 30 minutes. At the first open label treatment period visit (i.e., week 24), after completion of the double-blind treatment period, depending on the dosing regimen cohort participation, both alirocumab and placebo treated subjects will receive alirocumab either 40 mg Q2W or 150 mg Q4W if BW is <50 kg, and 75 mg Q2W or 300 mg Q4W if body weight is ≥50 kg, from the weight obtained at the week 24 visit.

After week 24, the investigator will manage, based on his/her own judgment, adjustment of alirocumab dose based on changes in BW. However, related to this up-titration/adjustment of the dose, if the investigator considers that the up-titration/adjustment would potentially negatively impact subject safety, he/she can exercise his/her judgement in a manner that safeguards the safety and wellbeing of the subject. The following will be applied based on changes in BW:

- If currently on 40 mg Q2W then adjust dose to 75 mg Q2W if BW changes from <50 kg to ≥50 kg.
- If currently on 150 mg Q4W then adjust dose to 300 mg Q4W if

BW changes from <50 kg to ≥50 kg.

For subjects whose weight oscillates around 50 kg the dose will be adjusted only once during the open-label treatment period. The lipid levels will be communicated to the investigator during the open label treatment period from the second visit (i.e., week 32) onwards. The IRT system is set up to allow the investigator based on his/her own judgment related to the subject's LDL-C levels and the safety profile, to up-titrate, down-titrate, maintain the dose of alirocumab or discontinue alirocumab throughout the trial.

From week 32 onwards:
In the Q2W dosing regimen cohort, the following up-titration or down-titration of alirocumab doses will be possible:
Up-titration:

- 40 mg to 75 mg Q2W if BW <50 kg.
- 75 mg to 150 mg Q2W if BW ≥50 kg.

Down-titration:

- 75 mg to 40 mg Q2W if BW <50 kg.
- 150 mg to 75 mg Q2W if BW ≥50 kg.

In the Q4W dosing regimen cohort, dose-adjustment will be possible, as follows:

- 150 mg Q4W to 75 mg Q2W if BW <50 kg.
- 300 mg Q4W to 150 mg Q2W if BW ≥50 kg.

The statin dose should not be decreased to adjust to the degree of LDL-C lowering and should not be increased unless otherwise indicated. Other LMT (if applicable) can be modified based on the investigator's judgment throughout the trial. Further recommendations for the management and monitoring of subjects who achieve LDL-C levels <50 mg/dL on one or more occasion are provided.

Compliance was assessed in 2 ways:

- During the DB period only. Defined for each subject as 100 – (%days with under-planned dosing + %days with above-planned dosing) and expressed as a percent.
- Over DB and OL periods: Injection frequency, defined as the average number of days between 2 double-blind injections, that is: (last double-blind dose date - first double-blind dose date)/(number of double-blind injections -1).

Procedures and Schedule: See appendix 13.3 for trial schedule.

<u>Key inclusion criteria</u>

- Male and female children and adolescents aged 8 to 17 years diagnosed with heterozygous familial hypercholesterolemia (see diagnosis criteria below) inadequately controlled (see threshold mentioned in the exclusion criterion #2) despite treatment with optimal dose of statin with or without other LMTs, or non-statin LMTs if statin

intolerant, at stable dose(s) for at least 4 weeks (see Study Design section above for definitions of background therapy, including statin intolerance).

- A signed informed consent indicating parental permission with or without subject assent.

Diagnosis of HeFH must be made either by previous genotyping, current centralized genotyping, or clinical diagnosis. The clinical diagnosis should be based on the Simon Broome criteria for possible or definite HeFH. The Simon Broome Criteria includes the following factors to determine the possibility of having FH in pediatric subjects, defined as:

- Definite: total cholesterol > 260 mg/dL or LDL-C >155 mg/dL AND
  - tendon xanthoma in the subject or first/second-degree relative OR
  - presence of LDL receptor, ApoB, or PCSK9 mutation
- Probable: total cholesterol > 260 mg/dL or LDL-C >155 mg/dL AND
  - family history of MI before 50 years in a second-degree relative or before 60 years in a first-degree relative OR
  - family history of total cholesterol > 290 mg/dL in an adult first/second-degree relative or total cholesterol > 260 mg/dL in a child or sibling 16 years or younger.

Reviewer comment: Commonly used criteria to define HeFH in children include American Heart Association[29] and Simon Broome criteria. Different definitions of FH are used in different parts of the world, with Simon Broome used predominately in the United Kingdom.[30] The inclusion criteria, including the definition of HeFH, are appropriate.

Key exclusion criteria

- Children and adolescents aged less than 8 years or more than 17 years at the time of informed consent signature unless different local regulation applies. Note: Subjects aged 8 to less than 10 years who have not had previous attempts to lower LDL-C by other means will be excluded.
- Subjects with LDL-C <130 mg/dL (i.e., adequately controlled) obtained during the screening period after the subject has been on stable LMT (i.e., stable optimal dose of statin ± other stable LMTs, or stable non-statin LMTs in statin intolerant subjects) treatment for at least 4 weeks.
- Subjects with body weight less than 25 kg.
- Subjects aged 8 to 9 years not at Tanner Stage 1 and subjects aged of 10 to 17 years not at least at Tanner Stage 2 in their development.
- Subjects with secondary hyperlipidemia (such as decompensated hypothyroidism,

[29] Gidding, Champagne, de Ferranti, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. Circulation. 2015 Dec 1;132(22):2167-92. doi: 10.1161/CIR.0000000000000297. Epub 2015 Oct 28.

[30] De Ferranti, SD. Familial hypercholesterolemia in children. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on September 1, 2023.)

nephrotic syndrome, obstructive liver disease, anorexia nervosa, obesity, and drug treatment [e.g., isotretinoids]).

- Subjects diagnosed with homozygous familial hypercholesterolemia.
- Subjects who have received lipid apheresis treatment within 2 months prior to the screening period or have plans to receive it during the trial.
- Subjects with uncontrolled (i.e., HbA1c levels above local guidelines or equivalent) Type 1 or 2 diabetes mellitus.
- Subjects with known uncontrolled thyroid disease (i.e., thyroid stimulating hormone levels above or below the laboratory's reference range within the past 6 months that were obtained due to clinical indication).
- Subjects with uncontrolled (i.e., systolic blood pressure [SBP] or diastolic blood pressure [DBP] above local guidelines or equivalent) hypertension.
- Fasting triglycerides >350 mg/dL (3.95 mmol/L) at the screening visit.
- Severe renal impairment (i.e., estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m2) at the screening visit.
- Alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2 x upper limit of normal [ULN] (1 repeat lab is allowed).
- Creatine phosphokinase (CPK) >3 x ULN (1 repeat lab is allowed).

Reviewer Comment: The exclusion criteria are acceptable. Because the trial excluded subjects with recent or planned lipid apheresis treatment, results may not generalize to pediatric patients with HeFH severe enough to require frequent lipid apheresis.

In case of permanent treatment discontinuation, the Applicant recommended to limit the collection to critical data, i.e., primary endpoint/main secondary endpoint and safety endpoints. At the time of treatment discontinuation, the subject should have, as soon as possible, an unscheduled visit with assessments normally planned at end of treatment period visit. Subjects who withdrawal are not replaced.

Data Monitoring Committee (DMC):
An independent DMC for pediatric studies will monitor patient safety by conducting reviews of accumulated safety data. The DMC will provide the Applicant and the steering committee with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the subjects enrolled in the trial. The DMC will be charged with reviewing the safety of subjects with LDL-C <50 mg/dL and more particularly, will review AE potentially associated with LDL-C <50 mg/dL in conjunction with the independent physician that is external to the EFC14643 trial team and not part of any alirocumab activities. Only the independent physician will have access to the subject information during the double-blind treatment period.

Trial Endpoints

Primary endpoint:

- Percent change in LDL-C from baseline to week 24 in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment (ITT estimand).

LDL-C was calculated using the Friedewald formula by the central laboratory. If triglyceride values exceed 400 mg/dL then the central lab reflexively measured (via the beta quantification method) the LDL-C rather than calculating it.

Reviewer Comments:

LDL-C calculation using the Friedewald formula has generally been used in proposed labeling because this method of LDL-C measurement is widely available and is the predominant way in which LDL-C is assessed in the clinical setting. However, this method can return lower values when triglyceride levels are high; in this case, the beta quantification methods was used and is considered the gold standard.

The percent change from baseline in LDL-C is the most appropriate primary endpoint for this trial based on extensive evidence from cardiovascular outcome trials that there is a strong causal relationship between serum LDL cholesterol and the risk of CHD, stroke, and peripheral vascular disease. Reduction of LDL-C is a validated surrogate endpoint for CV risk reduction and has been used as the basis for approval in previous trials of lipid-lowering drugs. In addition, current US and European clinical treatment guidelines use LDL-C as a target for therapy. Percent change in LDL-C from baseline to week 24 was the endpoint used in the pivotal trial for HeFH in the pediatric population.

Key secondary efficacy endpoints:

- Percent change from baseline to week 12 (ITT estimand): LDL-C, ApoB, non-HDL-C, Total-C, Lp (a), HDL-C, fasting TG, Apo A-1
- Percent change from baseline to week 24 (ITT estimand): ApoB, non-HDL-C, Total-C, Lp (a), HDL-C, fasting TG, Apo A-1
- Proportion of subjects achieving an LDL-C level lower than 110 mg/dL and lower than 130 mg/dL at week 12 and week 24 (ITT estimand)

Other secondary and exploratory endpoints include:

- All primary and key secondary endpoints in the modified ITT (mITT) population, using all LDL-C values during the treatment period (on-treatment estimand).
- Absolute change in ApoB/Apo A-1 ratio to week 12 and week 24 (ITT and on-treatment estimands).
- Proportion of subjects achieving at least 30% reduction, 50% reduction in LDL-C at week 24 (ITT and on-treatment estimands).
- Proportion of subjects achieving at least 30% reduction, 50% reduction in LDL-C at week

12 (ITT and on-treatment estimands).

- Percent change in LDL-C from baseline to week 104 (ITT and on-treatment estimands).
- Serum alirocumab concentrations assessed throughout the trial.
- Anti-alirocumab antibodies assessed throughout the trial.

Reviewer Comments:

Key secondary endpoints that are relevant to clinical practice and are described in recent US labels for LDL-lowering therapies include percent change in non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and apolipoprotein B (ApoB).

Non-HDL-C, ApoB, Lp(a), and Apo A-1 as secondary efficacy endpoints and are useful markers of cardiovascular risk under certain circumstances [such as in subjects with CVD with normal LDL-C values and elevated Lp(a) values or using non-HDL-C to include other atherogenic lipoproteins such as very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL)] and because they may be employed as future targets for lipid lowering therapy.

Statistical Analysis Plan

Sample size: With a randomization ratio of 2:1 (alirocumab: placebo) for each dosing regimen cohort, a total sample size of 90 subjects (30 in each alirocumab dosing regimen group and 15 in each placebo dosing regimen group) will have 92% power to detect a difference in mean percent change in LDL-C of 30% between each alirocumab dosing regimen group and its contemporaneously randomized placebo dosing regimen group, with a 0.025 two-sided significance level per comparison and assuming a common standard deviation (SD) of 25%. Nevertheless, to have enough pediatric subjects for properly assessing the safety and tolerability of alirocumab, sample size was increased to 150 subjects in total (50 in each alirocumab dosing regimen group and 25 in each placebo dosing regimen group). The enrollment of 150 subjects will allow having a safety assessment over 2 years in approximately 128 subjects, assuming a discontinuation rate of 15%.

Analyses were performed separately for the double-blind treatment period and the open-label treatment period, unless otherwise noted.

Analysis sets:

- Intention to Treat (ITT) population: Defined as all randomized subjects. Subjects in the ITT population will be analyzed according to the treatment group allocated by randomization.
- Modified Intention to Treat (mITT) population: Defined as all randomized subjects who actually received at least one dose or partial dose of double-blind Investigational Medicinal Product (IMP). Subjects in the mITT population will be analyzed according to the treatment group allocated by randomization.
- Open label extension (OLE) population: Defined as subjects who actually received at

least one dose or partial dose of investigational product during the open label treatment period.

Primary Efficacy Estimand: The primary efficacy endpoint defined as percent change from baseline in LDL-C to week 24 will be analyzed using a mixed model for repeated measures (MMRM) model within each dosing regimen cohort. All post-baseline data available within week 8 to week 24 analysis windows will be used and missing data will be accounted for by the MMRM model. For the Q2W dosing regimen cohort, the model will include the fixed categorical effects of treatment group (alirocumab, placebo), randomization strata (previous participation [yes or no] to DFI14223 trial, baseline body weight [<50 or ≥50 kg]), time point (week 8, week 12, week 24), treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. The same model will be run for the Q4W dosing regimen cohort except that strata related to the previous participation in the DFI14223 phase 2 trial will not be included in the model, as too few subjects from this phase 2 trial are enrolled in the Q4W dosing regimen cohort due to the late start of enrollment in this cohort.

On-treatment Estimand (source: SAP 2.4.4.2.1): Secondary efficacy endpoints analyzed with the on-treatment estimand will be analyzed using the same MMRM models as for the primary efficacy estimand but only including on-treatment values in the mITT population. The treatment period is defined as:

- For the Q2W dosing regimen cohort, the period from the first double-blind IMP injection up to the day of last double-blind injection +21 days.
- For the Q4W dosing regimen cohort, the treatment period is defined as the period from the first double-blind IMP injection up to the day of last double-blind injection +35 days for subjects who stopped IMP before the switch to Q2W regimen (actual or sham), +21 days otherwise.

Sensitivity analyses: Robustness of this statistical method will be assessed via sensitivity analysis. In the primary efficacy analysis, missing data were taken into account using the MMRM methodology. The MMRM relies on the Missing at Random assumption. To assess the impact on the primary efficacy results, additional methodologies to handle missing data were considered: pattern mixture model (under Not Missing at Random assumption) and multiple imputations followed by ANCOVA (under Missing At Random assumption).

Reviewer's comment: While on-treatment estimands can be biased when intercurrent events, such as drug discontinuation and drop-outs, are common, more than 90% of subjects in all arms completed the trial and no subjects in the Q2W cohort and 2 (3.8%) subjects in the Q4W cohort (both in the alirocumab group) had permanent IMP discontinuation.

FDA recommended use of PMM, but the applicant preferred to use MMRM (see section 3.1 Summary of Presubmission/Submission Regulatory Activity dated November 20, 2017, and January 10, 2018).

FDA also recommended consideration of a two-stage randomization design for evaluation of the benefit of up-titration at 12 weeks, but the applicant did not agree, but recognized that "We fully understand that with our current design, we are not able to compare the two alirocumab doses and can only approximate the additional LDL-C reduction achieved by up-titration…" (see section 3.1 Summary of Presubmission/Submission Regulatory Activity dated November 20, 2017 and January 10, 2018).

Multiplicity: The Bonferroni adjustment will be applied to handle multiplicity for the comparison of each alirocumab dosing regimen group versus its contemporaneously randomized placebo group (i.e., alirocumab Q4W versus placebo Q4W and alirocumab Q2W versus placebo Q2W) for the primary efficacy endpoint (0.025 two-sided alpha level will apply for each comparison). To handle multiple key secondary endpoints, the overall Type-I error will be controlled by the use of a sequential inferential approach applied independently within each dosing regimen cohort (Q2W and Q4W). Statistical significance of the primary parameter at the 2-sided 0.025 alpha level is required before drawing inferential conclusions for that dosing regimen cohort about first key secondary parameter.

Subgroup analyses: The analysis of the open label extension (OLE) data will be performed on the OLE population defined as subjects who actually received at least one dose or partial dose of investigational product during the open label treatment period. No other subgroups analyses are planned for efficacy.

The exploratory endpoint of the flow mediated dilatation (FMD) sub-study was the absolute change from baseline to week 24 in flow mediated dilatation of the brachial artery (as determined by the central reading laboratory) regardless of adherence to treatment.

Protocol Amendments

Protocol amendment #2, dated January 2, 2019
This protocol amendment added the Q4W dosing regimen alongside the Q2W dosing regimen in the currently ongoing trial. See above under "Dose Selection."

Reviewer's comment: The clin/pharm review team concluded that there was no significant concern for the proposed new Q4W dose regimen from a clinical pharmacology perspective as the overall pediatric PK/PD data are within observed historic adult data. (See Dr. Mary Robertson's review dated 05/22/2019, Reference ID: 4436950)

Protocol amendment #3, dated January 6, 2021 (IND-105574 SDN638)
This protocol amendment replaced the 2 primary efficacy hypotheses comparing each

alirocumab treatment regimen (Q2W, Q4W) versus a pooled placebo group combining Q2W and Q4W regimens by a comparison of each alirocumab group versus its contemporaneously randomized placebo group (i.e., of the same dosing regimen cohort). This change was driven by a potential temporal bias introduced from sequentially randomizing subjects into the first dosing regimen cohort (Q2W), followed by the second dosing regimen cohort (Q4W). Two randomization schemes were produced for this trial, with a distinct randomization scheme for each dosing regimen cohort. Therefore, subject background characteristics are expected to be equally distributed between treatment groups within a dosing regimen cohort by the randomization process, but not necessarily between the 2 cohorts. Pooling placebo subjects' data from both dosing regimen cohorts could introduce a potential temporal bias that would not be balanced by a similar bias in each of the alirocumab cohort groups. This amendment plans that each alirocumab regimen group will be compared to the contemporaneously randomized placebo regimen group within each distinct cohort. This will align the primary efficacy hypothesis treatment comparisons with the randomization scheme for each distinct cohort.

Reviewer's comment: This change was acknowledged by FDA (See IND 105574 document dated 01/27/2021, Reference ID: 4737329).

6.1.2. Trial Results

Compliance with Good Clinical Practices

The applicant asserts that the trial was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practices, all applicable laws, rules, and regulations.

Financial Disclosure

Refer to Appendix 13.2 for the financial disclosure overview.

Six investigators or subinvestigators disclosed the following financial interests and arrangements:

- 57,901 USD as grants to fund ongoing research (i.e., investigator/Institution sponsored study) and honoraria for speaker fees
- 83,655 USD as grants to fund ongoing research (i.e., investigator/Institution sponsored study) and honoraria for speaker fees
- 91,173 USD as honoraria for advisory board, accommodation, travel, registration and other fees, consultancy, speaker and training programs

- 34,281 USD as honoraria for consultancy, speaker program, meeting with experts, and payments relating to a consulting contract. However, the investigator did not acknowledge the amounts reported by the Applicant.

- 49,797 USD as honoraria for a speaker program

- 36,849 USD as honoraria for customer interaction, medical general consulting, global round table/scientific meeting, speaker program and consultancy

The applicant implemented the following actions to protect the trial from potential bias by the following measures:

- This was a double-blind, placebo-controlled trial.

- A double-blind masking was employed for the collection of safety, pharmacokinetic and efficacy data. The subjects and the clinical investigators were blinded to the assigned active drug or placebo during the 24-week double blind, placebo-controlled trial period. In addition, for the first 8 weeks of the open-label treatment period, LDL-C results were not available for the subjects and the clinical investigators.

- Subjects were randomly assigned to treatment arms and were stratified by body weight category and previous participation in DFI14223 trial.

- A screening period ensured LDL-C levels remained stable following a stable LMT treatment for at least 4 weeks.

- Quality of data reported by clinical investigators and adherence to the protocol were followed during the trial by the global clinical team blinded to the treatment arms.

- Recruitment threshold was set up for each trial site to avoid trial results being driven by a few large sites. If further recruitment was authorized, it was done after careful blinded review of the quality of data. Recruitment was monitored by the global trial team.

- Lipid parameters used as primary and secondary efficacy endpoints were assessed by a central laboratory using validated methods.

Reviewer comment: The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators. These interests/arrangements do not raise questions about the integrity of the data because of the trial design (randomized, blinded, objective endpoints) and the small number of affected clinical investigators. The disclosed financial interests/arrangements do not affect the approvability of the application.

Subject Disposition

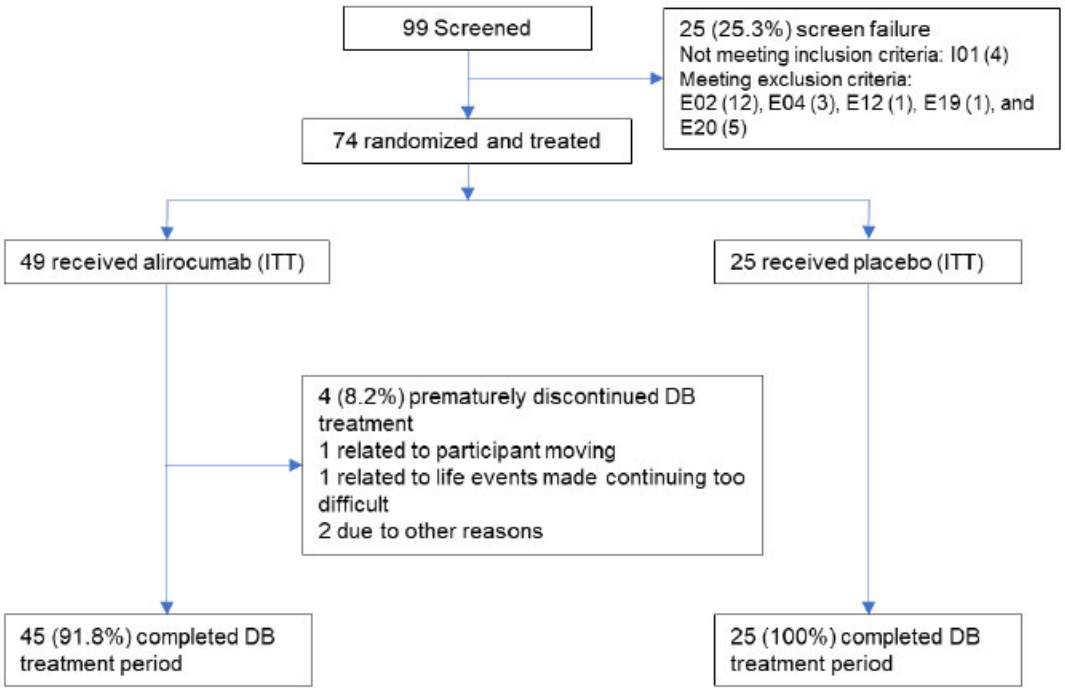
Trial EFC14643 was a multi-center trial conducted at 43 centers in 24 countries worldwide. The first subject first visit was on May 31, 2018, and the last subject completed their last visit on August 31, 2022.

Data from the double-blind and open-label treatment periods were analyzed separately.

Double-blind treatment period

Overall, 203 subjects were screened for this trial, of whom 50 (24.6%) subjects were screen failures. The most common reason for screening failure (26 or 12.8% of subjects) was meeting the exclusion criterion: Subjects with LDL-C <130 mg/dL obtained during the screening period after the subject had been on stable LMT treatment for at least 4 weeks. A total of 153 subjects were randomized to receive alirocumab or placebo intervention at 2:1 ratio. See figures below for disposition by dosing regimen cohort. All randomized subjects were treated with assigned trial intervention. Overall, in the randomized population, the rate of premature discontinuation of trial intervention was 6.9% in the combined alirocumab group and 1.9% in the combined placebo group.

Figure 4 Disposition of subjects, Double-blind Period, Q2W Cohort



Source: EFC14643 CSR Figure 3
Abbreviations: DB = double blind

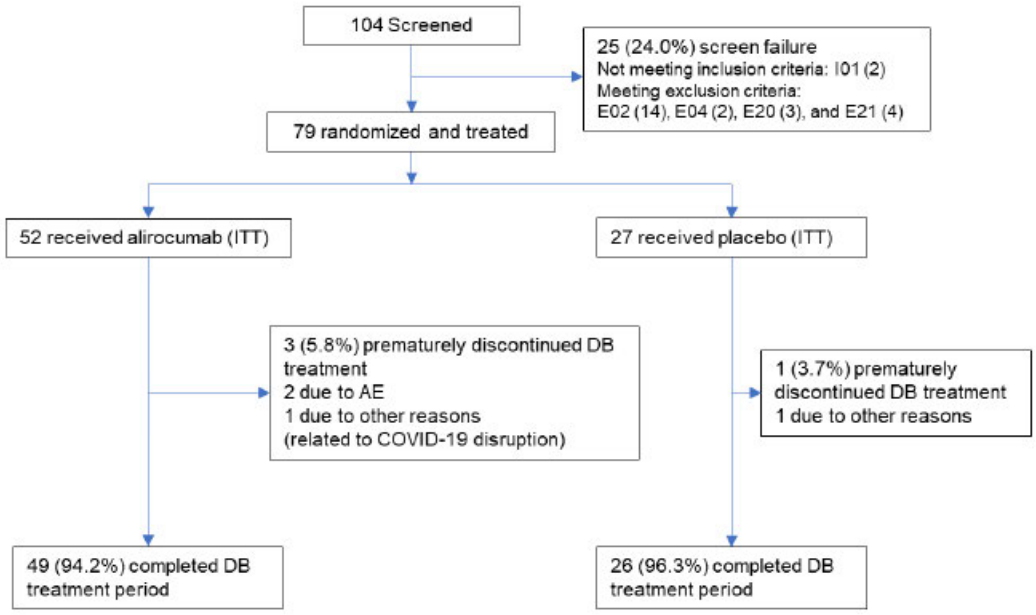
Table 2 Analysis populations, Double-blind Period, Q2W Cohort

	Placebo (N=25)	Alirocumab (N=49)	All (N=74)
Randomized population	25 (100%)	49 (100%)	74 (100%)
Efficacy populations	25 (100%)	49 (100%)	74 (100%)
ITT population	25 (100%)	49 (100%)	74 (100%)
mITT population	25 (100%)	49 (100%)	74 (100%)
Exploratory efficacy population	3	8	11
FMD sub-study population	3	8	11
Safety population	25	49	74
PK population	25	49	74
Anti-alirocumab antibody population	25	48	73
Population without trial impact (disruption) due to COVID-19 during DB period	25	49	74
OLE population	25	46	71
Population without trial impact (disruption) due to COVID-19 during OLE period	23	46	69

Note: The safety and PK population patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment

Source: EFC14643 CSR Table 11
Abbreviations: ITT = intention to treat, mITT = modified intention to treat, PK = pharmacokinetics, DB = double blind, OLE = open label extension, FMD = flow mediated dilatation

Figure 5 Disposition of subjects - Double blind period, Q4W Cohort



Source: EFC14643 CSR Figure 4
Abbreviations: DB = double blind

Table 3 Analysis Populations, Double-blind Period, Q4W Cohort

	Placebo (N=27)	Alirocumab (N=52)	All (N=79)
Randomized population	27 (100%)	52 (100%)	79 (100%)
Efficacy populations	27 (100%)	52 (100%)	79 (100%)
ITT population	27 (100%)	52 (100%)	79 (100%)
mITT population	27 (100%)	52 (100%)	79 (100%)

Reference ID: 5326070

Exploratory efficacy population	5	12	17
FMD sub-study population	5	12	17
Safety population	27	52	79
PK population	26	50	76
Anti-alirocumab antibody population	26	50	76
Population without trial impact (disruption) due to COVID-19 during DB period	21	46	67
OLE population	25	49	74
Population without trial impact (disruption) due to COVID-19 during OLE period	24	49	73

Note: The safety and PK population patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment

Source: EFC14643 CSR Table 12
Abbreviations: ITT = intention to treat, mITT = modified intention to treat, PK = pharmacokinetics, DB = double blind, OLE = open label extension, FMD = flow mediated dilatation.

Protocol Violations/Deviations

Double-blind treatment period (source: CSR Tables 9 and 10, CSR page 55/211)
During the DB treatment period, no critical protocol deviations were reported, and major protocol deviations were reported in 51/153 = 33% of subjects overall.
In the Q2W cohort, 18 subjects reported major protocol deviations (15 [30.6%] in the alirocumab group and 3 [12.0%] subjects in the placebo group). The most frequently reported major protocol deviations were in the categories:

- "Informed consent procedures" (4 [8.2%] and no subjects),
- "Assessments/Procedures" (4 [8.2%] and 2 [8.0%] respectively), and
- "source data records" (2 [4.1%] and 2 [8.0%] respectively).

In the Q4W cohort, 33 subjects reported major protocol deviations (20 [38.5%] subjects in the alirocumab group and 13 [48.1%] subjects in the placebo group). The most frequently reported major protocol deviations were in the categories:

- "IMP management" (12 [23.1%] and 5 [18.5%] respectively) and
- "Assessments/Procedures" (8 [15.4%] and 6 [22.2%] respectively).

Reviewer's comment: There are some imbalances between the Q2W and Q4W dosage cohorts and between the treatment arms within each cohort; however, the deviations appear minor and unlikely to affect the trial results.

Open-label treatment period (Source: CSR page 54-55)

During the open-label treatment period, no critical protocol deviations were reported, and major protocol deviation were reported in 25 (35.2%) subjects in the Q2W cohort and 15 (20.3%) subjects in the Q4W cohort. The Applicant stated that these deviations were sporadic with respect to the timing of their occurrence. No subject received the wrong IMP (alirocumab or placebo).

In the Q2W cohort, 25 subjects reported major protocol deviations. The most frequently reported deviations occurred in categories:

- "Randomization procedure" (8 [11.3%]),
- "IMP management" (6 [8.5%]),
- "Assessments/Procedures" (6 [8.5%]) and
- "Source data records" (6 [8.5%]).

In the Q4W cohort, 15 subjects reported major protocol deviations. The most frequently reported major protocol deviations were in the categories:

- "Randomization procedure" (5 [6.8%]) and
- "Assessment/Procedures" (4 [5.4%]).

Demographic Characteristics

As noted in Section 6.1.1, randomization was stratified according to previous participation (yes or no) in the phase 2 DFI14223 trial and baseline body weight (<50 or ≥50 kg). Table 4 shows that within each dosage regimen cohort (Q2W or Q4W), the stratification elements were balanced between the alirocumab and placebo groups. However, while 39.2% of Q2W cohort subjects participated in the DFI14223 trial, only 3.8% of Q4W cohort subjects did. This is because the Q4W cohort was added after the trial began, and most of the previous DFI14223 trial subjects had already enrolled in the Q2W cohort. These subjects were exposed to alirocumab in the DFI14223 trial and went through a wash-out period of at least 10 weeks between the last injection of alirocumab in the DFI14223 trial and the screening lipid assessment at entry in the screening period of this phase 3 trial. Also, more subjects in the Q4W cohort had a BW ≥ 50 kg (49 [62.0%]) than in the Q2W cohort (36 [48.6%]).

Table 4 Randomization Stratifications of the Primary Efficacy Analysis Population for Trial EFC14643

Stratification Element	Q2W			Q4W		
	Placebo (N= 25) n (%)	Alirocumab (N= 49) n (%)	Total (N= 74) n (%)	Placebo (N= 27) n (%)	Alirocumab (N= 52) n (%)	Total (N= 79) n (%)
Previous participation in DFI14223 trial						
Yes	10 (40.0)	19 (38.8)	29 (39.2)	1 (3.7)	2 (3.8)	3 (3.8)
No	15 (60.0)	30 (61.2)	45 (60.8)	26 (96.3)	50 (96.2)	76 (96.2)

Weight						
< 50 kg	13 (52.0)	25 (51.0)	38 (51.4)	10 (37.0)	20 (38.5)	30 (38.0)
≥ 50 kg	12 (48.0)	24 (49.0)	36 (48.6)	17 (63.0)	32 (61.5)	49 (62.0)

Source: EFC14643 16.2.4.1.1.6 and 16.2.4.1.1.11

Overall, demographic characteristics at baseline were different by gender, race, and ethnicity across the Q2W and Q4W cohorts (Table 5). More female subjects were included in the Q4W cohort (49 [62.0%]) than in the Q2W cohort (38 [51.4%]), more American Indian or Alaska Native subjects were included in the Q4W cohort (16 [20.3%]) than in the Q2W cohort (no subjects), and more Hispanic subjects were included in the Q4W cohort (24 [30.4%]) than in the Q2W cohort (4 [5.4%]). Analysis of the ADAE dataset showed that all the American Indian or Alaska Native subjects were enrolled in 2 sites in Mexico.

On October 2, 2023, FDA sent the Applicant the following information request:

> There were 16 subjects in the Q4W cohort with "American Indian or Alaska Native" race, constituting 20.3% of subjects in that cohort. We recommend using the Office of Management and Budget (OMB) definition described in the guidance for industry and FDA staff: Collection of Race and Ethnicity Data in Clinical Trials (October 2016), which defines "American Indian or Alaska Native" as "a person having origins in any of the original peoples of North or South American (including Central America), and *who maintains tribal affiliation or community attachment* [emphasis added]." Confirm if this definition is consistent with your data.

On October 20, 2023, the Applicant provided the following response (BLA 125559 SDN 1460):

> The Applicant confirms that consistent with the Office of Management and Budget (OMB) definition described in the October 2016 FDA guidance, race of 'American Indian or Alaska Native' was defined as "a person having origins in any of the original peoples of North and South America (including Central America), and who maintains tribal affiliation or community attachment (e.g.: Eskimo, Aleut, etc.)". The definition was provided to the site in the Case Report Form (CRF) Completion Instructions. Ethnicity and race information was either self-reported, when feasible in this pediatric trial population, or provided by a relative or other knowledgeable source when it was not feasible to collect directly from the subject.

In the Q2W cohort, demographics were balanced between intervention groups except for gender and age. More female subjects were in the alirocumab group than in the placebo group (30 [61.2%] versus 8 [32.0%] respectively). More subjects were ≥12 years of age in the placebo group (19 [76.0%], mean age 13.2 years, median 14 years) than in the alirocumab group (30 [61.2%], mean age 12.5 years, median 12 years).

In the Q4W cohort, demographics were balanced between intervention groups except for gender and ethnicity. More female subjects were in the alirocumab group (34 [65.4%]) than in the placebo group (15 [55.6%]). More Hispanic subjects were in the alirocumab group (18 [34.6%]) than in the placebo group (6 [22.2%]).

Reviewer Comment: As shown in detail in Table 5, baseline gender, race, and ethnicity were different between the Q2W and Q4W cohorts. Because the 2 cohorts are not formally compared to each other (due to separate randomization schemes), differences between cohorts are not as important as differences between arms within a cohort. Within the Q2W and Q4W cohorts more female subjects were enrolled in the alirocumab arm than in the placebo arm. In the Q2W cohort, the alirocumab arm was older and in the Q4W cohort, the alirocumab arm had more Hispanic subjects. Efficacy was similar by gender, age, and ethnicity in subgroup analyses (Figure 6, Figure 7, Table 10), so these differences are not expected to have a substantial impact on the interpretation of trial results.

Table 5 Demographic Characteristics of the Primary Efficacy Analysis Population for Trial EFC14643

Demographic Parameters	Q2W			Q4W		
	Placebo (N= 25) n (%)	Alirocumab (N= 49) n (%)	Total (N= 74) n (%)	Placebo (N= 27) n (%)	Alirocumab (N= 52) n (%)	Total (N= 79) n (%)
Sex						
Male	17 (68.0)	19 (38.8)	36 (48.6)	12 (44.4)	18 (34.6)	30 (38.0)
Female	8 (32.0)	30 (61.2)	38 (51.4)	15 (55.6)	34 (65.4)	49 (62.0)
Age						
Mean years (SD)	13.2 (2.4)	12.5 (2.7)	12.8 (2.6)	12.8 (3.0)	13.1 (3.0)	13.0 (3.0)
Median (years)	14.0	12.0	13.0	13.0	13.5	13.0
Min, max (years)	8, 17	8, 17	8, 17	8, 17	8, 17	8, 17
Age Group						
< 10 years	2 (8.0)	9 (18.4)	11 (14.9)	7 (25.9)	8 (15.4)	15 (19.0)
≥ 10 - < 12 years	4 (16.0)	10 (20.4)	14 (18.9)	3 (11.1)	12 (23.1)	15 (19.0)
≥ 12 years	19 (76.0)	30 (61.2)	49 (66.2)	17 (63.0)	32 (61.5)	49 (62.0)
Race						
White	23 (92.0)	42 (85.7)	65 (87.8)	22 (81.5)	38 (73.1)	60 (75.9)
Black or African American	0	1 (2.0)	1 (1.4)	1 (3.7)	1 (1.9)	2 (2.5)
Asian	1 (4.0)	1 (2.0)	2 (2.7)	0	0	0
American Indian or Alaska Native	0	0	0	4 (14.8)	12 (23.1)	16 (20.3)
Native Hawaiian or	0	1 (2.0)	1 (1.4)	0	0	0

Other Pacific Islander						
More than 1 race	1 (4.0)	4 (8.2)	5 (6.8)	0	0	0
Not reported	0	0	0	0	1 (1.9)	1 (1.3)
Ethnicity						
Hispanic or Latino	2 (8.0)	2 (4.1)	4 (5.4)	6 (22.2)	18 (34.6)	24 (30.4)
Not Hispanic or Latino	23 (92.0)	46 (93.9)	69 (93.2)	21 (77.8)	34 (65.4)	55 (69.6)
Not reported	0	1 (2.0)	1 (1.4)	0	0	0
Region						
Argentina	0 (0)	0 (0)	0 (0)	0 (0)	2 (3.8)	2 (2.5)
Austria	0 (0)	0 (0)	0 (0)	2 (7.4)	1 (1.9)	3 (3.8)
Brazil	1 (4.0)	2 (4.1)	3 (4.1)	1 (3.7)	2 (3.8)	3 (3.8)
Bulgaria	0 (0)	1 (2.0)	1 (1.4)	2 (7.4)	0 (0)	2 (2.5)
Canada	2 (8.0)	4 (8.2)	6 (8.1)	2 (7.4)	2 (3.8)	4 (5.1)
Czech Republic	3 (12.0)	6 (12.2)	9 (12.2)	1 (3.7)	2 (3.8)	3 (3.8)
Denmark	0 (0)	1 (2.0)	1 (1.4)	1 (3.7)	1 (1.9)	2 (2.5)
Finland	0 (0)	1 (2.0)	1 (1.4)	1 (3.7)	1 (1.9)	2 (2.5)
France	0 (0)	1 (2.0)	1 (1.4)	1 (3.7)	1 (1.9)	2 (2.5)
Hungary	1 (4.0)	2 (4.1)	3 (4.1)	0 (0)	0 (0)	0 (0)
Italy	1 (4.0)	0 (0)	1 (1.4)	3 (11.1)	1 (1.9)	4 (5.1)
Lebanon	0 (0)	1 (2.0)	1 (1.4)	0 (0)	4 (7.7)	4 (5.1)
Mexico	0 (0)	0 (0)	0 (0)	5 (18.5)	12 (23.1)	17 (21.5)
Netherlands	2 (8.0)	5 (10.2)	7 (9.5)	3 (11.1)	8 (15.4)	11 (13.9)
Norway	2 (8.0)	1 (2.0)	3 (4.1)	0 (0)	2 (3.8)	2 (2.5)
Poland	1 (4.0)	6 (12.2)	7 (9.5)	1 (3.7)	4 (7.7)	5 (6.3)
Russian Federation	3 (12.0)	0 (0)	3 (4.1)	1 (3.7)	4 (7.7)	5 (6.3)
Slovenia	0 (0)	2 (4.1)	2 (2.7)	0 (0)	0 (0)	0 (0)
South Africa	0 (0)	1 (2.0)	1 (1.4)	0 (0)	0 (0)	0 (0)
Spain	2 (8.0)	5 (10.2)	7 (9.5)	1 (3.7)	1 (1.9)	2 (2.5)
Sweden	2 (8.0)	0 (0)	2 (2.7)	0 (0)	0 (0)	0 (0)
Taiwan, Province of China	1 (4.0)	1 (2.0)	2 (2.7)	0 (0)	0 (0)	0 (0)
Turkey	1 (4.0)	3 (6.1)	4 (5.4)	1 (3.7)	1 (1.9)	2 (2.5)
United States	3 (12.0)	6 (12.2)	9 (12.2)	1 (3.7)	3 (5.8)	4 (5.1)

Source: EFC14643 16.2.4.1.1.6, 16.2.4.1.1.11, and ADAE dataset (Software: R version 4.2.2)

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

Table 6 Baseline Disease Characteristics of the Primary Efficacy Analysis Population for Trial EFC14643

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Baseline Characteristics	Q2W			Q4W		
	Placebo (N= 25)	Alirocumab (N= 49)	Total (N= 74)	Placebo (N= 27)	Alirocumab (N= 52)	Total (N= 79)
LDL-C[1] (mg/dL)						
Mean (SD)	175.29 (50.23)	169.69 (46.74)	171.58 (47.68)	176.57 (49.01)	176.79 (53.93)	176.71 (51.99)
Min, max	101.5, 289.6	103.9, 332.4	101.5, 332.4	78.8, 256.8	86.9, 326.3	78.8, 326.3
ApoB (mg/dL)						
Mean (SD)	115.2 (25.8)	115.7 (24.5)	115.5 (24.8)	118.4 (31.2)	119.7 (29.3)	119.2 (29.8)
Min, max	68, 168	73, 186	68, 186	64, 185	68, 195	64, 195
Non HDL-C (mg/dL)						
Mean (SD)	191.61 (50.64)	186.75 (48.29)	188.39 (48.81)	195.37 (53.98)	197.16 (55.14)	196.55 (54.41)
Min, max	114.0, 303.7	110.6, 350.1	110.6, 350.1	89.0, 290.1	97.9, 340.0	89.0, 340.0
Total-C (mg/dL)						
Mean (SD)	242.88 (59.06)	234.69 (49.65)	237.46 (52.75)	249.74 (53.49)	246.98 (57.66)	247.92 (55.94)
Min, max	144.0, 397.3	157.9, 385.3	144.0, 397.3	127.8, 341.3	146.7, 395.0	127.8, 395.0
Lp(a) (mg/dL)						
Mean (SD)	42.9 (44.3)	32.7 (41.8)	36.2 (42.7)	29.8 (32.5)	29.7 (38.5)	29.7 (36.3)
Min, max	2, 136	2, 188	2, 188	2, 150	2, 153	2, 153
HDL-C (mg/dL)						
Mean (SD)	51.16 (13.07)	48.24 (10.61)	49.23 (11.50)	54.74 (14.20)	49.62 (11.06)	51.37 (12.38)
Min, max	29.0, 84.9	32.0, 79.5	29.0, 84.9	30.1, 87.6	31.7, 84.9	30.1, 87.6
Fasting TG (mg/dL)						
Mean (SD)	79.01 (47.60)	75.74 (35.66)	76.84 (39.79)	92.53 (48.30)	101.27 (60.22)	98.25 (56.21)
Min, max	40.7, 262.8	29.2, 198.2	29.2, 262.8	31.0, 238.1	27.4, 413.3	27.4, 413.3
Family history of myocardial infarction,[2] n (%)	12 (48.0)	15 (30.6)	27 (36.5)	9 (33.3)	23 (44.2)	32 (40.5)

Diagnosis of HeFH by Clinical Simon Broome Criteria[3], n (%) Definite Possible	13 (92.9) 1 (7.1)	23 (79.3) 6 (20.7)	36 (83.7) 7 (16.3)	11 (100) 0	18 (81.8) 4 (18.2)	29 (87.9) 4 (12.1)
Diagnosis of HeFH made by genotyping, n (%)	19 (76.0)	43 (87.8)	62 (83.8)	26 (96.3)	50 (96.2)	76 (96.2)
Statin intolerant (protocol definition[3]), n (%)	1 (4.0)	2 (4.1)	3 (4.1)	3 (11.1)	5 (9.6)	8 (10.1)
Taking any statin, n (%)	24 (96.0)	49 (100)	73 (98.6)	24 (88.9)	48 (92.3)	72 (91.1)
Taking LMT other than statin[4], n (%)	4 (16.0)	5 (10.2)	9 (12.2)	4 (14.8)	15 (28.8)	19 (24.1)
Taking ezetimibe[5], n (%)	3 (12.0)	2 (4.1)	5 (6.8)	4 (14.8)	12 (23.1)	16 (20.3)

LMT is lipid modifying therapy;
1 LDL-C was calculated using the Friedewald formula. If TG values exceed 400 mg/dL then LDL-C was measured reflexively via the beta quantification method instead.
2 Includes family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
3 See Key inclusion criteria in section 6.1.1 Study Design for clinical Simon Broome criteria.
4 in combination with statins or not.
5 Included in "Taking LMP other than statin"
Source: EFC14643 CSR Tables 15, 16, 17, 18, 19, 20, 21, 22
Abbreviations: LMT = lipid modifying therapy, LDL-C = low density lipoprotein cholesterol, ApoB = apolipoprotein B, C = cholesterol, HDL-C = high density lipoprotein, TG = triglycerides, Lp(a) = lipoprotein (a), SD = standard deviation, SE = standard error.

In the Q2W cohort, the mean (SD) LDL-C at baseline was 169.69 (46.74) mg/dL and 175.29 (50.23) mg/dL (for alirocumab group and placebo group), respectively. In the Q4W cohort, the mean (SD) LDL-C at baseline was 176.79 (53.93) mg/dL and 176.57 (49.01) mg/dL, respectively.

Reviewer's comment: Most subjects overall had a "definite" diagnosis of HeFH by Clinical Simon Broome, but the proportion of subjects with a definite diagnosis was higher in the placebo groups for both Q2W and Q4W cohorts. Fulfilling the "definite" criteria usually implies worse disease and higher refractoriness to LDL lowering through the LDL-receptor compared with fulfilling the "possible" criteria; however, other baseline disease characteristics, including values

of lipid parameters, were similar across cohorts and intervention groups in the primary efficacy analysis population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Background lipid modifying therapy (LMT): During the double blind (DB) treatment period, no change in LMT occurred. One subject who was statin intolerant did not receive any concomitant LMTs during the entire DB treatment. Another subject missed his LMT (ezetimibe) doses during the entire DB treatment period but remained on stable statin dose. Both subjects were from the placebo group in the Q2W cohort, and their lack of adherence to background LMTs was captured as major protocol deviations.

Compliance in DB period
In the Q2W cohort, 100% of subjects in both alirocumab and placebo group had ≥80% compliance for IMP injections (i.e., subjects took ≥80% of their injections and at the scheduled times). In the Q4W cohort, 44 (84.6%) subjects in the alirocumab group and 23 (85.2%) subjects in the placebo group had ≥80% compliance for IMP injections. (Drug and Dose Compliance Data 16.2.5.1.2.1.1 and 6.2.5.1.2.1.4).

Reviewer comment: Q2W and Q4W cohorts are not directly comparable because the subjects were randomized at different times to these cohorts. However, it is notable that the compliance was lower in the Q4W than in the Q2W dosing regimen cohort, despite the Applicant's initial claim that a Q4W dosing schedule would result in increased compliance. However, this observation is complicated by the fact that after week 12, all subjects received SC injection(s) Q2W in order to maintain blinding for up-titration (subjects who needed to up-titrate switched to a Q2W dosing schedule).

Efficacy Results – Primary Endpoint

The primary endpoint is the percent change in LDL-C from baseline to week 24 (double-blind period) in the intent-to-treat (ITT) population, using all LDL-C values regardless of adherence to treatment. The primary endpoint analysis was provided based on a mixed model for repeated measures (MMRM) model on the ITT population, using LS means estimates at week 24.

The duration of treatment exposure was similar across intervention groups in both cohorts: in the Q2W cohort, the mean duration of exposure was 23.7 weeks for alirocumab group and 24.1 weeks for placebo group; in the Q4W cohort, the mean duration of exposure was 22.9 weeks for alirocumab group and 23.9 weeks for placebo group.

A statistically significant difference in favor of alirocumab compared to placebo was observed for the primary efficacy endpoint in both dosing regimen cohorts (Table 7):

- In the Q2W cohort, the LS mean (SE) percent change in LDL-C from baseline to week 24 was - 33.6% (3.4) in the alirocumab group compared to + 9.7% (4.3) in its placebo group

with a LS mean difference versus placebo of - 43.3% ([97.5% CI: - 56.0 to - 30.7]; p<0.0001).

- In the Q4W cohort, the LS mean (SE) percent change in LDL-C from baseline to week 24 was - 38.2% (4.0) in the alirocumab group compared to - 4.4% (3.7) in its placebo group, with a LS mean difference versus placebo of - 33.8% ([97.5% CI: - 46.4 to - 21.2]; p<0.0001).

Reviewer comment: The magnitude of mean difference in percent change in LDL-C in both the Q2W and Q4W cohorts are similar to the -38% for Repatha in pediatric patients aged 10-17 with HeFH. This constitutes a clinically significant improvement in LDL-C.

Table 7 Percent Change in LDL-C from Baseline to Week 24 Trial EFC14643 in the Primary Efficacy Analysis Population

LDL Cholesterol	Q2W		Q4W	
	Placebo (N= 25)	Alirocumab (N= 49)	Placebo (N= 27)	Alirocumab (N= 52)
Baseline (mg/dL)				
Mean (SD)	175.3 (50.2)	169.7 (46.7)	178.0 (49.4)	175.8 (54.8)
Median	169.9	154.4	171.4	164.3
Min, Max	102, 290	104, 332	79, 257	87, 326
Week 24 percent change from baseline (%)				
LS mean (SE)	9.7 (4.3)	-33.6 (3.4)	-4.4 (3.7)	-38.2 (4.0)
LS mean difference (SE) vs Placebo		-43.3 (5.5)		-33.8 (5.5)
97.5% CI		-56.0 to -30.7		-46.4 to -21.2
p-value		<0.0001		<0.0001

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata (body weight and previous enrollment in DFI14223 for Q2W and body weight only for Q4W), time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on subjects with a baseline value and a post-baseline value in at least one of the analysis windows used in the model. LDL-C was calculated using the Friedewald formula. If TG values exceed 400 mg/dL then LDL-C was measured reflexively via the beta quantification method instead.
Source: EFC14643 CSR Tables 27 and 28
Abbreviations: LS = least-squares, SD = standard deviation, SE = standard error, LDL = low density liproprotein, CI = confidence interval

In the alirocumab groups in both Q2W and Q4W dosing regimen cohorts, a rapid decrease in LDL-C from baseline was observed from week 8. Measurement of LDL-C at week 8, week 12, and week 24 showed a steady decrease at week 8 onwards then maintenance of efficacy until week 24.

Planned dose modification during double-blind period

At week 12 during the double-blind period, subjects randomized to alirocumab either continued their assigned dose or up-titrated based on LDL-C measured at week 8. Up-titration occurred if LDL-C was ≥ 110 mg/dL (see section 6.1.1 Study Design).

- Among the 74 subjects who were in the Q2W cohort and received at least 1 injection after week 12, 22 out of 49 (44.9%) subjects in the alirocumab group (11 with BW <50 kg and 11 with BW ≥50 kg) received automatic dose up-titration in a blinded manner.
- Among the 79 subjects who were in Q4W cohort and received at least 1 injection after week 12, 15 out of 52 (28.8%) subjects in the alirocumab group (5 with BW <50 kg and 10 with BW ≥50 kg) received automatic dose adjustment in a blinded manner. (Source: CFR 4.6.2 Dose Modification page 78/211)

Table 8 Percent Change in LDL-C from Baseline to Week 24 Trial EFC14643 in the Alirocumab group of the Primary Efficacy Analysis Population, by Up-titration Status

LDL Cholesterol	Q2W		Q4W	
	Without up-titration	With Up-titration	Without up-titration	With Up-titration
N	24	21	31	14
Mean (SD)	-38.2 (19.0)	-29.3 (26.7)	-42.1 (22.0)	-34.2 (28.3)
Median	-41.8	-36.8	-41.3	-43.1
Min, Max	-69, 5	-65, 39	-77, 19	-74, 19

Source: EFC14643 Efficacy Response Data 16.2.6.2.3.12.1 and 16.2.6.2.3.11.1
Abbreviations: LDL = low density lipoprotein, N = number, SD = standard deviation

Reviewer comment: Although more subjects in the Q2W cohort up-titrated at week 12 compared with the Q4W cohort, these 2 cohorts cannot be directly compared to each other because they had different randomization schemes. In both Q2W and Q4W cohorts, the magnitude of mean LDL-C change was numerically smaller in subjects who up-titrated compared with those who did not up-titrate. This could indicate that some subjects (likely those with more severe disease) did not respond as well to treatment despite up-titration, although the differences in the primary endpoint between subjects who up-titrated and those who did not were not large and could be due to random error given the small sample size. More subjects with BW > 50 kg up-titrated in the Q2W, but not in the Q4W, where equal numbers of those with higher and lower BW up-titrated, indicating that BW was not a substantial factor in the subjects' need to up-titrate.

Efficacy by randomization strata

As noted in Section 6.1.1, randomization was stratified according to previous participation in the phase 2 DFI14223 trial and baseline body weight (<50 or ≥50 kg). Table 9 shows efficacy results by randomization strata. Efficacy in higher and lower BW strata were similar in both cohorts. Subjects who previously participated in DFI14223 were mostly enrolled in the Q2W cohort,

which was the first cohort to enroll. The Q4W cohort was added as a protocol addendum and started later, so only 3 subject who previously participated in DFI14223 were enrolled in the Q4W cohort. Reviewer comment: In the Q2W cohort, the magnitude of placebo-subtracted LDL-C lowering in subjects who previously participated in DFI14223 was half that in subjects who did not participate in DFI14223. This could explain the overall lower efficacy in the Q2W compared with the Q4W cohort, although the differences are not large. Moreover, in the alirocumab arm of the Q2W cohort, prior DFI14223 subjects had an LDL-C decrease of -25.2 compared to the -38.2 in subjects who did not previously participate in DFI14223, so the difference is not large. The Q2W placebo arm had a 13.9% point increase in LDL-C, which increased the magnitude of the placebo-subtracted LDL-C in subjects who didn't participate in DFI14223. In summary, although there was an imbalance between the Q2W and Q4W cohorts in terms of previous participation in DFI14223, both cohorts demonstrated efficacy.

Table 9 Percent Change in LDL-C from Baseline to Week 24 Trial EFC14643 in the Primary Efficacy Analysis Population - Subgroup Analyses by Randomization Strata

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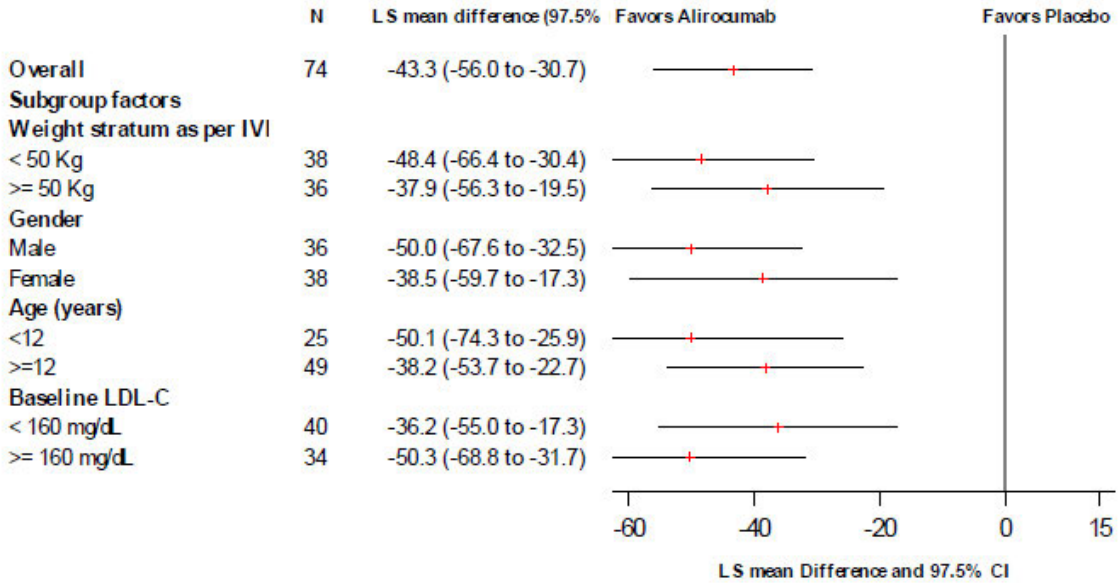
Randomization stratum, LDL Cholesterol	Q2W		Q4W		Q2W vs Q4W
	Placebo	Alirocumab	Placebo	Alirocumab	
Body weight < 50 kg					
Baseline (mg/dL) N Mean (SD)	 13 184.9 (48.2)	 25 179.2 (55.4)	 10 155.6 (46.6)	 20 158.3 (42.9)	
Week 24 percent change from baseline (%) LS mean (SE) LS mean difference (SE) vs placebo 97.5% CI LS mean difference (SE) between dose regimen 97.5% CI	 12.5 (5.9)	 -35.9 (4.8) -48.5 (7.6) -66.0 to -30.9	 -6.7 (7.1)	 -41.2 (6.5) -34.5 (9.5) -56.4 to -12.6	 -14.0 (12.2) -41.7 to 13.7
Body weight ≥ 50 kg					
Baseline (mg/dL) N Mean (SD)	 12 164.8 (52.4)	 24 159.8 (33.9)	 17 188.9 (47.4)	 32 188.3 (57.4)	
Week 24 percent change from baseline (%) LS mean (SE) LS mean difference (SE) vs placebo 97.5% CI LS mean difference (SE) between dose regimen 97.5% CI	 5.6 (6.4)	 -32.5 (5.0) -38.0 (7.8) -56.0 to -20.0	 -2.6 (5.0)	 -35.5 (5.0) -32.9 (7.0) -49.0 to -16.9	 -5.1 (10.4) -28.9 to 18.6
Previous participation in trial DFI14223 - Yes					
Baseline (mg/dL) N Mean (SD) Median Min, Max	 10 153.7 (51.7) 144.2 102, 253	 19 169.9 (52.9) 154.4 104, 332	 1 207.0 (.) 207.0 207, 207	 2 152.5 (4.9) 152.5 149, 156	

Week 24 percent change from baseline (%) LS mean (SE) LS mean difference (SE) vs placebo 97.5% CI LS mean difference (SE) between dose regimen 97.5% CI	1.5 (5.0)	-25.2 (5.8) -26.7 (7.7) -45.2 to -8.2	Non-calculable	Non-calculable	Non-calculable
Previous participation in trial DFI14223 - No					
Baseline (mg/dL) N Mean (SD) Median Min, Max	15 189.7 (45.3) 180.3 125, 290	30 169.5 (43.3) 153.1 116, 305	25 176.8 (50.1) 171.0 79, 257	48 176.8 (55.7) 167.6 87, 326	
Week 24 percent change from baseline (%) LS mean (SE) LS mean difference (SE) vs placebo 97.5% CI LS mean difference (SE) between dose regimen cohorts 97.5% CI	13.9 (6.0)	-38.2 (4.1) -52.1 (7.3) -69.3 to -34.8	-4.7 (3.8)	-37.7 (4.2) -33.0 (5.7) -46.0 to -19.9	 -20.3 (9.2) -41.4 to 0.9

Notes: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. ITT population.
The p-value is not adjusted for multiplicity and provided for descriptive purposes only.
Source: Individual Efficacy Response Data Listing 16.2.6.2.3.8.1, 16.2.6.2.3.7.1 (body weight), 16.2.6.1.3.3.1 and 16.2.6.1.3.4.1. (DFI14223), Applicant response to IR (BLA 125559 SDN 1460) Tables 2 and 3.
Abbreviations: LDL = low density lipoprotein, SD = standard deviation, SE = standard error, CI = confidence interval,

Subgroup analyses:
The primary endpoint was analyzed in subgroups according to body weight strata, sex, age (<12 or ≥12 years), and baseline LDL-C value categories (<160 mg/dL or ≥160 mg/dL) for the ITT population in both dosing regimen cohorts. Results showed consistent reduction of LDL-C from baseline to week 24 with alirocumab versus placebo across subgroup categories in both Q2W and Q4W cohorts (Figure 6, Figure 7, and Table 10).

Figure 6 Percent Change from Baseline in LDL-C at Week 24, Subgroup Analysis, Primary Efficacy Analysis Population, Q2W



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis

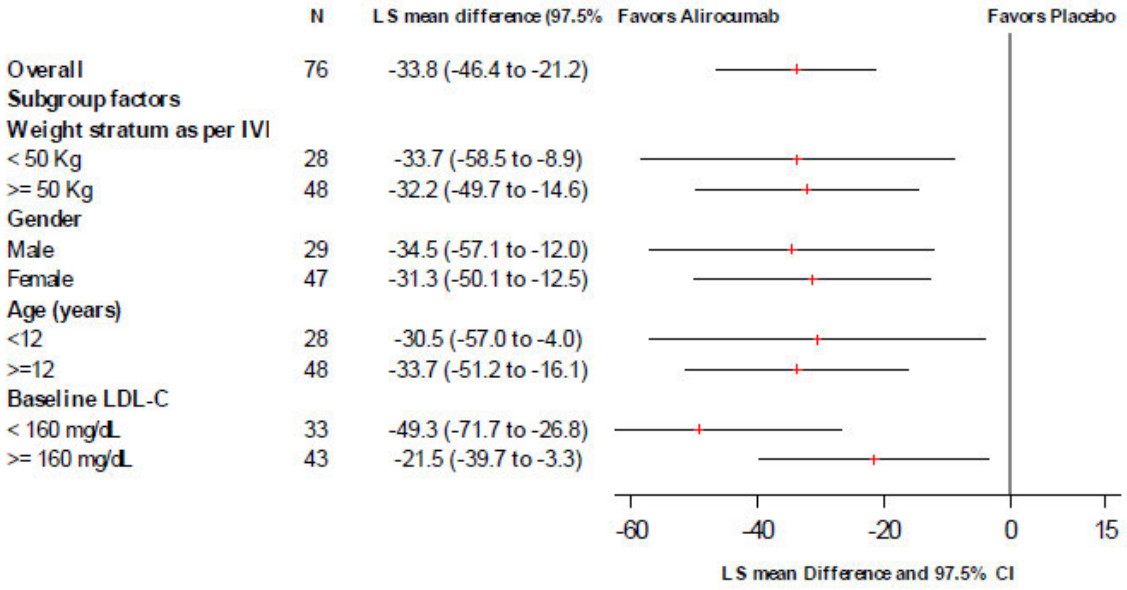
For age or gender as subgroup factor, the model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.

For BW as per IVRS as subgroup factor, the model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, and the interactions treatment-by-time point, strata-by-time point, treatment group-by-BW strata as per IVRS, and treatment group-by-BW strata as per IVRS-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.

For baseline LDL-C as subgroup factor, the model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point.

Source: EFC14643 CSR Figures 8, 9
Abbreviations: LS = least squares, N = number, LDL-C = low density lipoprotein, IRVS = interactive voice response systems

Figure 7 Percent Change from Baseline in LDL-C at Week 24, Subgroup Analysis, Primary Efficacy Analysis Population, Q4W



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis

For age or gender as subgroup factor, the model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.

For BW as per IVRS as subgroup factor, the model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, and the interactions treatment-by-time point, strata-by-time point, treatment group-by-BW strata as per IVRS, and treatment group-by-BW strata as per IVRS-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.

For baseline LDL-C as subgroup factor, the model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point.

Source: EFC14643 CSR Figure 9
Abbreviations: LS = least squares, N = number, LDL-C = low density lipoprotein cholesterol, IVRS = interactive voice recognition system

On July 13, 2023, FDA requested subgroup analyses for trial EFC14643 by race and ethnicity, which were not included in the supplement because "…the numbers of patients [sic] in the different subgroups were deemed too small to provide meaningful information…" according to the Applicant. The Applicant sent the requested information (see Table 10) on August 18, 2023 (BLA 125559 SDN 1451) but did not include results for the Q2W cohort because "…there was not an adequate number of patients [sic] in the other race or ethnicity categories and thus the Sponsor maintains subgroup analyses for race or ethnicity on the efficacy endpoints for the Q2W cohort would not be meaningful…" according to the Applicant.

Table 10 Percent Change from Baseline in LDL-C at Week 24, by Race and Ethnicity, Primary Efficacy Analysis Population, Q4W

Demographic Parameters	Q4W		
	Placebo LS means	Alirocumab LS means	LS mean Difference (97.5% CI)
Race			
White	n = 21 -3.9	n = 37 -34.7	-30.8 (-47.2 to -14.3)
Black or African American	n = 1 -0.2	n = 1 -60.4	-60.3 (-141.4 to 20.9)
American Indian or Alaska Native	n = 4 -13.6	n = 11 -47.1	-33.5 (-67.4 to 0.3)
Ethnicity			
Hispanic or Latino	n = 6 -17.4	n = 17 -42.5	-25.2 (-52.5 to 2.2)
Not Hispanic or Latino	n = 20 -1.3	n = 33 -35.9	-34.6 (-51.4 to -17.9)

Source: Tables 3 and 4, 1.11.3 Clinical Information Amendment BLA 125559 SDN 1451, dated August 18, 2023
Abbreviations: LS = least squares, CI = confidence interval

Data Quality and Integrity

The trial was well executed and largely adhered to the protocol. The protocol amendments were reasonable and unlikely to have had a negative impact on the integrity of the trial or our interpretation of the results. Protocol deviations were not believed to have a negative impact on trial results. Subject retention and trial completion were high as 97% of subjects completed investigational product and 99% of subjects completed the trial. Week 24 LDL-C values (primary endpoint) were missing in 5.4% of subjects in the Q2W cohort and 12.7% in the Q4W cohort (Efficacy response data 16.2.6.1.4.1.1 and 16.2.6.1.4.2.1). There were no notable financial conflicts of interest. There were no potential issues concerning the submitted data quality or integrity that raise questions about the purported efficacy results. Thus, the trial has generated data that are interpretable and supportive of the proposed indication.

Efficacy Results – Secondary and other relevant endpoints

A hierarchical procedure was used to test the key secondary endpoints for each alirocumab dosing regimen group versus its contemporaneously randomized placebo group, while controlling for multiplicity. Since statistical significance was reached for the primary efficacy endpoint, the hierarchical testing was applied to the key secondary endpoints following the order of listed key secondary endpoints in Table 11.

All key secondary endpoints showed statistically significant differences in favor of alirocumab

compared to placebo according to the hierarchical testing procedure down through and including the Lp (a) endpoint at week 24, in both the Q2W and Q4W cohorts (Table 11). Since the statistical significance was not reached for the change from baseline in Lp (a) at week 12, key secondary endpoints related to HDL-C, fasting TG, and Apo A-1 (shaded grey below in Table 11) were tested, but are presented for descriptive purposes only.

Table 11 Secondary Efficacy Endpoints for Trial EFC14643, Primary Efficacy Analysis Population

	Treatment Difference Alirocumab vs. placebo	
	Q2W	Q4W
Percent change from baseline in LDL-C at week 12, LS mean difference (p-value)	-45.5 (<0.0001*)	-41.5 (<0.0001*)
Percent change in ApoB from baseline to week 24, LS mean difference (p-value)	-37.8 (<0.0001*)	-30.7 (<0.0001*)
Percent change in non-HDL-C from baseline to week 24, LS mean difference (p-value)	-40.7 (<0.0001*)	-31.9 (<0.0001*)
Percent change in Total-C from baseline to week 24, LS mean difference (p-value)	-30.8 (<0.0001*)	-23.3 (<0.0001*)
Percent change in ApoB from baseline to week 12, LS mean difference (p-value)	-38.9 (<0.0001*)	-32.8 (<0.0001*)
Percent change in non-HDL-C from baseline to week 12, LS mean difference (p-value)	-42.8 (<0.0001*)	-37.5 (<0.0001*)
Percent change in Total-C from baseline to week 12, LS mean difference (p-value)	-32.7 (<0.0001*)	-27.9 (<0.0001*)
Proportion reaching LDL-C <130 mg/dL at week 24, odds ratio (p-value)	77.6 (0.0001*)	14.9 (<0.0001*)
Proportion reaching LDL-C <130 mg/dL at week 12, odds ratio (p-value)	26.6 (<0.0001*)	40.9 (<0.0001*)
Proportion reaching LDL-C <110 mg/dL at week 24, odds ratio (p-value)	52.7 (0.0011*)	43.1 (0.0006*)
Proportion reaching LDL-C <110 mg/dL at week 12, odds ratio (p-value)	41.3 (<0.0001*)	104.8 (0.0005*)
Percent change in Lp (a) from baseline to week 24, combined estimate for adjusted mean difference (p-value)	-15.2 (0.0237*)	-24.9 (0.0043*)
Percent change in Lp (a) from baseline to week 12, combined estimate for adjusted mean difference (p-value)	-5.6 (0.4288)	-13.5 (0.1148)
Percent change in HDL-C from baseline to week 24, LS mean difference (p-value)	6.4 (0.0161)	4.4 (0.2079)

Percent change in TG from baseline to week 24, Combined estimate for adjusted mean difference (p-value)	4.3 (0.6836)	-19.0 (0.0582)
Percent change in Apo A-1 from baseline to week 24, LS mean difference (p-value)	1.1 (0.7133)	8.9 (0.0096)
Percent change in HDL-C from baseline to week 12, LS mean difference (p-value)	5.6 (0.1387)	7.5 (0.0646)
Percent change in TG from baseline to week 12, Combined estimate for adjusted mean difference (p-value)	-8.7 (0.3311)	-8.1 (0.4328)
Percent change in Apo A-1 from baseline to week 12, LS mean difference (p-value)	-1.6 (0.5175)	5.7 (0.1217)

Note: Since the statistical significance was not reached for the change from baseline in Lp (a) at week 12, key secondary endpoints related to HDL-C, fasting TG, and Apo A-1 (shaded grey) were tested and are presented for descriptive purposes only.
* The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the type-I error rate at the 0.025 level within a dosing regimen cohort.
Source: EFC14643 CSR Tables 25 and 26
Abbreviations: LDL-C = low density lipoprotein, HDL-C = high density lipoprotein cholesterol, TG = triglycerides, ApoB = apolipoprotein B, Lp(a) = lipoprotein (a), Apo A-1 = apolipoprotein A-1, C = cholesterol, LS = least squares.

Reviewer comment: Large differences in odds ratios for secondary endpoints of proportion reaching LDL-C <130 mg/dL at week 24 (77.6 vs. 14.9) and proportion reaching LDL-C <110 mg/dL at week 12 (41.3 vs. 104.8). However, both cohorts showed high estimates for efficacy. Moreover, differences in the randomization schemes for the Q2W and Q4W cohorts preclude formal comparisons.

Durability of Response

As shown in Figure 8, the reductions in LDL-C persisted from week 8 throughout the open-label extension trial (up to week 104) in ITT analyses. In both the Q2W and Q4W cohorts, the effect of alirocumab on LDL-C lowering appeared to wane between the end of the DB treatment period (week 24) and the end of the OL period. In the Q2W cohort, the magnitude of LDL-C reduction from baseline was -33.6% at week 24 and -22.2% at week 104 in the alirocumab treatment group. In the Q4W cohort, the magnitude of LDL-C reduction from baseline was -38.2% at week 24 and -23.7% at week 104 in the alirocumab treatment group (sources: Figure 7 above, EFC14643 Response data 16.2.6.14.1.1.1.1 and 16.2.6.14.1.1.2.1).

The applicant performed post hoc analyses to investigate this finding with the following results (source: CSR section 5.1.3.1.2.3):

- Compliance to statin and ezetimibe in the OL period: Only one subject discontinued statin and no subjects discontinued ezetimibe during the OL period. Therefore, compliance or lack of compliance to statin and ezetimibe did not explain the

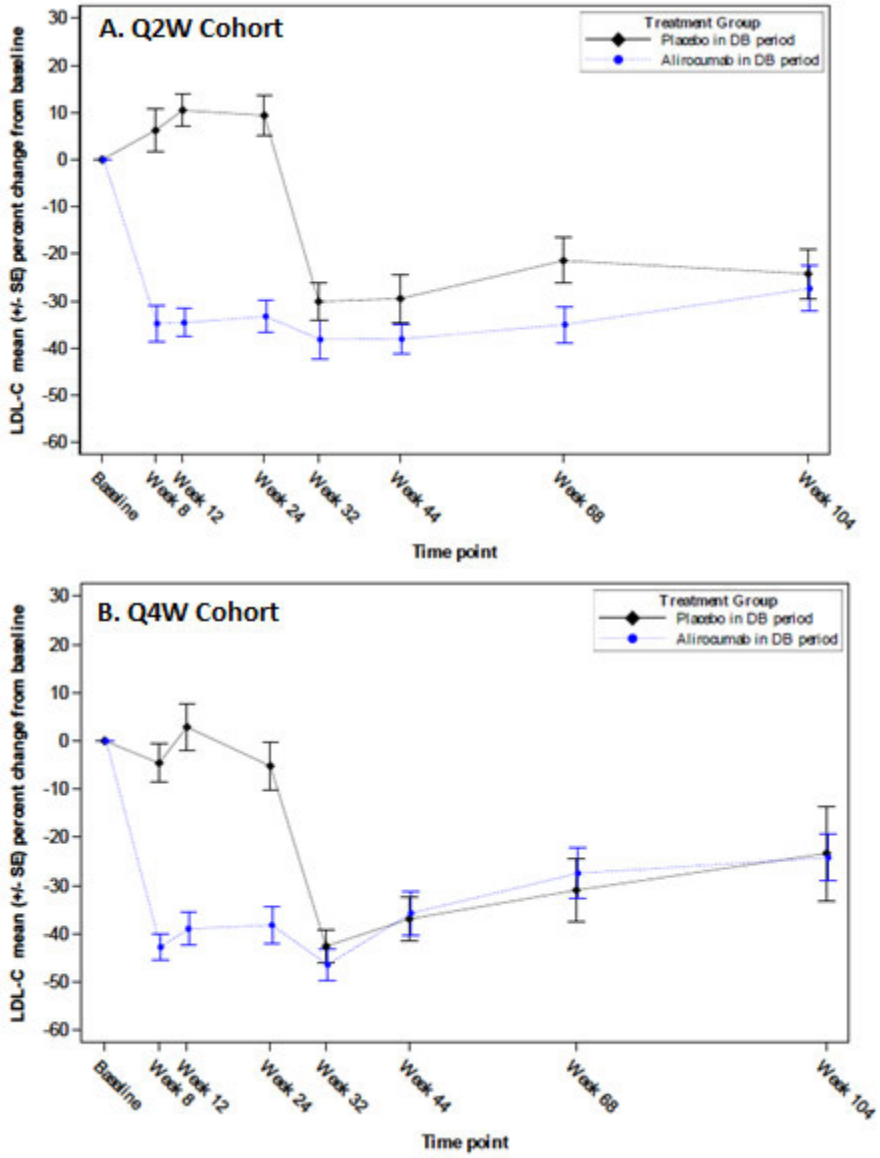
observations, according to the applicant.

- Analysis of the percent change from baseline in LDL-C during the course of the trial showed that results after 6 months of treatment (week 24 for Alirocumab arm and week 44 for placebo arm) were rather consistent. The decrease of the magnitude of LDL-C reduction seemed to occur after week 44. In addition, the mean percent changes from baseline in LDLC in the "Alirocumab in DB" and "Placebo in DB" group were of comparable magnitude, at the same time points in both cohorts. These results suggest that the changes in LDL-C in the OL period did not follow the same progression as in the DB period and were not related to the duration of exposure to alirocumab but more to the trial duration. This may indicate that observed decrease in LDL-C reduction is not due to a loss of efficacy of Alirocumab, but rather to less strict conditions of administrations in OL period, according to the applicant.
- Adherence to alirocumab in the OL period: Subjects were categorized as adherent and nonadherent to alirocumab treatment based on the BW measured at the last check before week 104 and the LDL-C levels measured at week 32, 44 or 68: an LDL-C value ≥110 mg/dL (as it was scheduled during the DB period) or BW increased to 50 kg or above was considered as a potential trigger for dose-titration or dose-adjustment. Adherent and non-adherent to alirocumab treatment were defined as follows:
    - Non - adherent subjects were those with at least one LDL-C value between week 32 and week 68 ≥110 mg/dL and a last dose intake not corresponding to the optimal dose.
    - Adherent subjects were all other subjects, namely (1) those with at least one LDL-C result ≥ 110mg/dL between week 32 and week 68 and last dose intake corresponding to the optimal dose and (2) those with all LDL-C results <110mg/dL between week 32 and week 68, included. This group includes subjects who responded well to alirocumab and did not require a dose adjustment.

  A total of 27 (38%) subjects in the Q2W cohort and 40 (54%) subjects in the Q4W cohort were considered as non-adherent which can account for the difference in efficacy between week 24 and after week 44, according to the applicant. Greater reduction and higher proportion of subjects at target (LDL-C <110 mg/dL) were observed at week 104 in the adherent subjects mentioned above. Of note, the adherent subgroup also included the subjects who had LDL-C always below 110 mg/dL without requiring dose adjustment.

Reviewer's comment: This reviewer agrees with the applicant's conclusion based on their analysis that the apparent decrease in magnitude of LDL-C lowering over the OL period in the Q4W cohort was likely due to relatively lax dose adjustment compared with the Q2W cohort. However, conditions during the OL period more closely resemble real-world clinical conditions (e.g., no blinding to treatment by patient and provider, ability of provider to adjust dose based on clinical course). Therefore, health care providers will need to monitor BW and LDL-C levels for appropriate dose adjustment.

Figure 8 LDL-C mean (+/- SE) percent change from baseline to end of Open-Label Extension, On Treatment Analysis.



Source: EFC14643 CSR Tables 10, 11.
Abbreviations: LDL-C = low density lipoprotein cholesterol, SE = standard error, DB = double blind

Table 12 Percent change in LDL-C from Baseline to End of Double-Blind Period (Week 24) and End of Open Label Extension (Week 104), On-treatment Analysis

LDL Cholesterol (mg/dL)	Q2W		Q4W	
	Placebo	Alirocumab	Placebo	Alirocumab
Week 24 percent change from baseline (%)				
N	25	49	27	50
LS mean (SE)	9.7 (4.3)	-33.6 (3.4)	-4.4 (3.7)	-38.2 (4.0)
LS mean difference (SE) vs placebo		-43.3 (5.5)		-33.8 (5.5)
97.5% CI		-56.0 to -30.7		-46.4 to -21.2
Week 104 percent change from baseline (%)				
N	25	46	23	47
LS mean (SE)	-22.8 (5.1)	-25.8 (4.9)	-27.6 (7.6)	-23.4 (4.7)

Note: Placebo and alirocumab in the header of the column refers to the treatment received during the DB period. Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value by time-point interaction.
MMRM model and baseline description run on subjects with a baseline value and a post-baseline value in at least one of the analysis windows used in the model (mITT population).
Sources: Efficacy response data 16.2.6.2.2.1.1, 16.2.6.2.2.2.1; EFC14643 CSR Tables 49, 50;
Abbreviations: LDL = low density lipoprotein, N = number, LS = least squares, SE = standard error, CI = confidence interval

Persistence of Effect

The effect of alirocumab after treatment is stopped or withheld was not evaluated in this trial.

Dose/Dose Response

Not applicable as there was just one dose.

Additional Analyses Conducted on the Individual Trial

Flow Mediated Dilatation (FMD) substudy:
The applicant carried out an exploratory FMD study to evaluate endothelium function. Normal endothelial function, presumably through production of nitric oxide, plays a key role in protection against atherosclerosis. Endothelial dysfunction leads to decreased bioavailability of nitric oxide and may play a role in atherogenesis even before clinical atherosclerosis. FMD is non-invasive and involves measuring the brachial artery diameter at baseline and after an increase in blood flow caused by inflating then deflating a forearm blood pressure cuff. The proportional increase in luminal diameter induced by hyperemia is calculated and used as a

marker of systemic endothelial function.
The exploratory efficacy endpoint of the FMD sub-study was the absolute change from baseline to week 24 in FMD of the brachial artery (as determined by the central reading laboratory) regardless of adherence to treatment (ITT estimand). The analysis consisted of the comparison of alirocumab to placebo, regardless of the dosing regimen cohort. FMD sub-study included 28 subjects in the DB period (20 subjects from the combined alirocumab group and 8 subjects from the combined placebo group), all of them completed the DB treatment period and entered the OL treatment period. No difference between the alirocumab and the placebo group was observed for the absolute change in percent change in FMD from baseline to week 24.

Reviewer comment: DDLO views imaging-based studies primarily as proof-of-concept studies or drug development tools rather than definitive trials demonstrating a therapeutic agent's effectiveness. The results are included here for completeness.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

In accordance with the written responses (dated October 22, 2022) to questions contained in the August 19, 2022, background package, the review of effectiveness is based on the efficacy results from a single trial, namely EFC14643, a phase 3, double-blind, placebo-controlled trial in pediatric subjects with HeFH (see section 5.2 Review Strategy). Assessment of efficacy for trial EFC14643 is contained in section 6.1.2 Trial Results.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the single pivotal trial, EFC14341, Q2W and Q4W dosing cohorts were tested, and both were shown to be efficacious. The Applicant included only the Q4W dosing strategy in the proposed prescribing information, based on their assessment that Q4W regimen can improve the adherence and compliance of a treatment with alirocumab by decreasing the frequency of administration and limiting the discomfort related to iterative subcutaneous injections in this pediatric population. As noted in section 6.1.2, compliance was actually lower in the Q4W than in the Q2W dosing regimen cohort, despite the Applicant's initial claim. However, this observation is complicated by the fact that after week 12, all subjects received SC injection(s) Q2W in order to maintain blinding for up-titration (subjects who needed to up-titrate switched to a Q2W dosing schedule at week 12).

The entry criteria and exclusions were appropriate for the population that will likely receive the drug in clinical practice. Black or African American individuals were underrepresented and

American Indian or Alaska Native individuals were overrepresented in the Q4W cohort; however, in both Q2W and Q4W cohorts, the differences in efficacy were similar among all race and ethnicity groups for whom estimates were calculable. In the United States, the prevalence of HeFH is highest in the white and black populations and lower in Mexican American and other race groups.

As noted in section 6.1.2, the apparent decrease in magnitude of LDL-C lowering over the OL period in the Q4W cohort was likely due to relatively lax dose adjustment compared with the Q2W cohort. However, conditions during the OL period more closely resemble real-world clinical conditions. Therefore, health care providers will need to monitor BW and LDL-C levels for appropriate dose adjustment.

The benefit demonstrated in the clinical trials can reasonably be expected to be achieved in the postmarket setting.

7.2.2. Other Relevant Benefits

There is currently only one PCSK-9 inhibitor approved for treatment of HeFH in the pediatric population - Evolocumab. Evolocumab is also given as a SC injection, but can be given either 140 mg every 2 weeks OR 420 mg once monthly. The dosage scheme proposed by the Applicant is somewhat more complicated in that body weight has to be taken into account because initial doses are different for pediatric patients who are below vs. above 50 kg. Additionally, the proposed labeling includes instructions to increase the dose (and switch to a Q2W dosing) if the LDL-C response is inadequate.

One clear benefit of alirocumab over evolocumab is that alirocumab was studied in a pediatric population down to 8 years of age, whereas evolocumab is labeled for use in pediatric patients aged 10 years and older.

7.3. Integrated Assessment of Effectiveness

In pediatric patients with HeFH, results from trial EFC14643 showed that:

- Alirocumab was superior to placebo in lowering LDL-C in both Q2W (LS mean reduction of -33.6% vs. 9.7%) and Q4W (LS mean reduction of -38.2% vs. -4.4%) dosing regimen cohorts after 24 weeks of treatment. The LS mean difference (alirocumab minus placebo) in percent LDL-C change from baseline to week 24 was -43.3% ($p<0.0001$) for the Q2W cohort and -33.8% ($p<0.0001$) for the Q4W cohort.
- LDL-C lowering in the alirocumab arms persisted to the end of the open label period. At week 104, LS mean reduction in LDL-C from baseline was -22.2% for the Q2W cohort and -23.7 for the Q4W cohort.
- Alirocumab was superior to placebo in improving other lipid parameters in both cohorts, including reductions in total cholesterol, non-HDL-C, ApoB, and Lp(a).

Results from these two studies demonstrated clinically meaningful and statistically significant reductions in LDL-C and improvements in other lipid parameters for pediatric subjects with HeFH. For pediatric patients with HeFH whose LDL-C goals are not achieved with statins with or without ezetimibe because of reduced drug response to therapies involving the LDL receptor, poor treatment adherence, or side effects, PCSK-9 inhibitors, as an adjunct to diet and other LDL-C lowering therapies, can help achieve their LDL-C goals and potentially reduce their risk for cardiovascular disease. Evolocumab is currently the only PCSK-9 inhibitor approved for HeFH in pediatric patients aged 10 and older. Alirocumab offers another option for PCSK-9 therapy for these patients and will be the only PCSK-9 inhibitor approved for use in children aged 8 to 9 years.

In conclusion, the data presented in this submission support the use of alirocumab in pediatric patients 8 years of age and older with heterozygous familial hypercholesterolemia who do not achieve sufficient LDL cholesterol lowering with a healthy lifestyle, optimal statin therapy, and ezetimibe or other LDL-C lowering therapies. The Applicant has submitted evidence of effectiveness that meets the statutory evidentiary standard. Based on data showing robust LDL-C reductions in the HeFH population, and an acceptable safety profile, this reviewer recommends approval of alirocumab for the following indication:

- As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 8 years and older with HeFH to reduce LDL-C.

8. Review of Safety

8.1. Safety Review Approach

The primary demonstration of safety comes from placebo-controlled data from 153 pediatric subjects with HeFH in trial EFC14643, which includes a 24- week DB period and 80-week OL period. Supportive safety data was obtained from 42 pediatric subjects with HeFH in DFI14223, a phase 2 dose-ranging trial, and 18 pediatric subjects with HoFH in EFC14660.

The full analysis set (FAS), defined as all randomized subjects who received at least 1 dose of investigational product, was used for safety analyses. Subjects were analyzed according to the actual treatment received. Only adverse events that occurred in the FAS population and were treatment-emergent (occurring after the first dose of trial drug) were analyzed.

Safety parameters included adverse events (AE), serious AE (SAE), AE of special interest (AESI), laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage and were assessed throughout the trial.

Adverse events of special interest, defined by the protocol and based on the known safety

profile of alirocumab, theoretical concerns in pediatric populations, and standard safety review practices, included: general allergic events, local injection site reactions, pregnancy, symptomatic overdose of IMP, neurologic events, neurocognitive events, and ALT >3 ULN (if baseline ALT < ULN), or ALT ≥2 times the baseline value (if baseline ALT ≥ ULN).

In addition, the following groupings of events of interest were provided: hepatic disorder events, diabetes mellitus or diabetic complications, and cataract (see 16-1-9-sap [2.1.4.1] for definitions).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 13 Safety Population

	Safety Database for Alirocumab Individuals exposed to any treatment in this development program for the indication under review N = 212 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	Q2W		Q4W	
	Placebo* (n= 25)	Alirocumab (n= 87)	Placebo* (n= 27)	Alirocumab (n= 73)
Controlled trials conducted for this indication – EFC14643	25	49	27	52
All other trials conducted for this indication - DFI14223	n/a	20	n/a	21
Controlled trials conducted for HoFH - EFC14660	n/a	18	n/a	n/a

*Placebo indicates subjects who were randomized to placebo during the double-blind period and received alirocumab during the open label period. Sources: Clinical Study Reports for EFC14643, DFI14223, and EFC14660.

The duration of alirocumab exposure in the combined DB and OL periods for trial EFC14643 was similar across intervention groups in both dosing cohorts: in the Q2W cohort, the mean (SD) duration of exposure was 100.8 (13.9) weeks for alirocumab group and 75.9 (16.7) weeks for placebo group; in the Q4W cohort, the mean (SD) duration of exposure was 78.4 (10.1) weeks for placebo group and 104.4 (1.7) weeks for alirocumab group (Table 14).

Table 14 Duration of Exposure to Alirocumab in Trial EFC14643 Double Blind and Open Label Periods Combined

	Q2W		Q4W	
	Placebo (N= 25)	Alirocumab (N= 49)	Placebo (N= 27)	Alirocumab (N= 52)
Duration of alirocumab exposure (weeks)				
Mean (SD)	75.9 (16.7)	100.8 (13.9)	78.4 (10.1)	104.4 (1.7)
Median	80.0	104.1	80.0	104.1
Min, Max	16, 86	31, 110	31, 85	100, 109

Note: Placebo and alirocumab in the header of the column refers to the treatment received during the DB period.
Sources: 16.2.5 Dosing and drug concentration data 16.2.5.1.3.1.1.1.1, 16.2.5.1.3.1.1.2.1, 16.2.5.1.3.1.1.2.4, 16.2.5.1.3.1.1.1.4

Device:
During DB treatment period sterile alirocumab drug product and placebo for alirocumab were provided in PFS for SC injections with finger grip. During the OL treatment period, IMPs were all provided in PFS-S for SC injection.

The applicant intends to use the same DAI-PFP that is currently used in the adult formulation available as follows:

- 75 mg/mL single-dose pre-filled pen
- 150 mg/mL single-dose pre-filled pen

(Source: draft Prescribing Information)

8.2.2. Relevant characteristics of the safety population:

Trial EFC14643: The safety population is exactly the same as the full analysis set used to evaluate efficacy. Demographic and baseline characteristics are the same as presented in Table 5 and Table 6 in section 6.1.2.

Trial DFI14223 (HeFH dose finding): Overall, 54.8% of patients were male. The majority of patients were White (92.9%), and 2 patients (4.8%) were Black. A total of 3 patients (7.1%) were Hispanic or Latino. Overall, the median age was 12.0 years (ranged from 8 to 17 years). Six patients (14.3%) were below 10 years. Twenty-nine patients were adolescents (12 to 17 years). The mean BMI for the BW <50 kg category was 17.7 kg/m² (range: 14 to 24), and for the BW ≥50 kg category was 23.3 kg/m² (range: 16 to 36).

Trial EFC14660 (HoFH): The mean (SD) age of the enrolled patients was 12.4 (2.8) years overall (range: 9 to 17 years). The gender distribution between male and female in enrolled patients was balanced overall (50% each) and across the 2 alirocumab groups. Overall, 61.1% of patients (11 of 18) were White, along with 16.7% Asian (3 patients), 16.7% American Indian or Alaska Native (3 patients), and 5.6% Black or African American (1 patient). The mean (SD) BMI at

baseline was 20.5 (4.0) kg/m2 overall (range: 15 to 27 kg/m2), 17.9 (3.1) kg/m2 in the alirocumab 75 to 150 mg Q2W group, and 23.1 (2.9) kg/m2 in the alirocumab 150 mg Q2W group.

8.2.3. Adequacy of the safety database:

The alirocumab clinical development program has an extensive safety database, primarily in adults, including the ODYSSEY OUTCOMES cardiovascular outcome trial in 18,924 adult patients (9462 alirocumab; 9462 placebo) and followed for up to 5 years, from which the safety profile of alirocumab has been previously evaluated.

The Applicant submitted an adequate exposure to assess the safety of alirocumab in the pediatric HeFH population, with 101 subjects exposed to alirocumab for a mean of ~102 weeks and 52 subjects exposed for a mean of ~77 weeks in the combined Q2W and Q4W cohorts.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

In general, this reviewer found no important deficiencies regarding data quality or the quality of the overall submission that had an effect on the safety review.

8.3.2. Categorization of Adverse Events

For trial EFC14643, the Applicant assessed adverse events (AE), serious AEs (SAE), AEs of special interest (AESI), laboratory data, vital signs, body weight, height, Cogstate battery test, and Tanner stage throughout the trial. Treatment emergent was defined as follows:

- Double-blind treatment-emergent adverse event (TEAE) period:
  - The double-blind TEAE observation period is defined as the time from the first dose of double-blind IMP to the last dose of double-blind IMP injection +70 days (10 weeks) for those subjects not proceeding into the open label treatment period as residual effect of alirocumab is possible until 10 weeks after the stop of treatment IMP injection, or up to the day before first dose of open label IMP for those subjects proceeding into the open label treatment period.
  - Double-blind treatment-emergent adverse events are AEs that developed or worsened or became serious during the double-blind TEAE period.
- Open label TEAE period:
  - The open label TEAE observation period is defined as the time from the first dose of open label IMP to the last dose of open label IMP injection +70 days (10 weeks).
  - Open-label treatment-emergent adverse events are AEs developed or worsened or became serious during the open-label TEAE period.

Revewer comment: The definitions of TEAE are appropriate.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0 in Trial EFC14643.

Reviewer Comment: The translation of investigator-reported verbatim terms (lower-level terms) to preferred terms was examined by this reviewer. Overall, few errors in translation were identified, and no adverse events were reclassified. Based on comparing the reported term to the lower-level term, this reviewer believes that AEs were generally categorized appropriately.

Definitions of severity of local injection site reactions were adapted from the toxicity grading scale table from the FDA Draft Guidance for Industry: Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials April 2005. The definitions of severity for AE's other than local injection site reactions were as follows:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects clinical status. The event possesses a significant risk of harm to the research participant and hospitalization may be required.

The Applicant defined serious adverse events (SAE) as any untoward medical occurrence that at any dose:
• Results in death
• Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
• Requires inpatient hospitalization or prolongation of existing hospitalization, or Results in persistent or significant disability/incapacity
• Is a congenital anomaly/birth defect
• Is a medically important event (an event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above)

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The

list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (i.e., agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.)
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc.)
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study
- Chronic neurodegenerative diseases (newly diagnosed)
- Suspected transmission of an infectious agent

8.3.3. Routine Clinical Tests

Laboratory tests:

The laboratory specimens were collected in accordance with the trial schedule (see Section 6.1.1) and forwarded to the central laboratory:

- Hematology - complete blood cell count including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count and platelets
- Chemistry - glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, urea nitrogen, creatinine, uric acid, lactate dehydrogenase, total protein, albumin, and gamma GT
- Liver panel: ALT, AST, alkaline phosphatase (ALP) and total bilirubin (in case of total bilirubin values above the normal range, differentiation into conjugated and nonconjugated bilirubin occurred automatically)
- Creatine Phosphokinase (CPK)
- HbA1c
- Hs-CRP
- CPK-MB, troponin
- Adrenal gland hormones: cortisol (with reflexive adrenocorticotrophic hormone [ACTH] levels if cortisol <LLN) and dehydroepiandrosterone sulfate (DHEAS)
- Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
- Gonadal hormones: testosterone (male) and estradiol (females)
- Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone)
- Pregnancy test: pregnancy test was done on females of childbearing potential or females who have experienced menarche. The Screening (week -2) pregnancy test was a

blood test. All other pregnancy tests were a local urine pregnancy test.

- Urinalysis: macroscopy was performed at the central lab. If abnormal, then a standard microscope assessment was conducted.
- Serum samples for assessment of alirocumab concentration was obtained periodically. Blood samples was collected before IMP injection. PK samples were also used for free and total PCSK9 analysis.

Notes: Any clinically relevant abnormal laboratory value was to be immediately rechecked (whenever possible using the central laboratory) for confirmation. Decision trees for the management of neutropenia, thrombocytopenia, increased ALT, increased serum creatinine, and increased CPK, by Sanofi, are provided in the protocol (Protocol Appendix H).

Physical exam:
A general physical examination was performed in accordance with the trial schedule (see Section 6.1.1). If a new clinically significant abnormality or worsening from baseline was detected after randomization, then an AE was reported, and the subject was considered for further clinical investigations and/or specialist consultation as per the investigator's medical judgment.

Blood pressure (BP) and heart rate:
BP was measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus if possible (after the subject has rested comfortably in sitting position for at least 5 minutes) with age related cuff size. At the first screening visit, BP was measured in both arms. The arm with the highest diastolic pressure was determined at this visit and BP was measured on this arm throughout the trial. This highest value was recorded in the e-CRF.
Heart rate was measured in sitting position at the time of the measurement of BP.

Cogstate battery test:
The Cogstate battery test included a detection test, identification test, one-card learning test, and Groton maze learning test. These individual tests assess maturing cognition across a broad number of key developmental functions such as processing speed, attention, visual learning, and executive functioning, respectively. The battery of tests was administered by trained clinical site personnel and took the subject approximately 16 to 19 minutes to complete.

Tanner stages:
The Tanner stages were measured by the investigator at the time points indicated in the trial schedule flowchart Section 6.1.1. Tanner stages were provided in Appendix B of the protocol.

Body weight and height:
Body weight was obtained with the subject wearing undergarments or very light clothing

and no shoes, and with an empty bladder. The same scale was used throughout the trial, if possible. The use of calibrated balance scales was mandatory. Self-reported weights were not acceptable; subjects were not allowed to read the scales themselves. Height had to be measured as self-reported heights were not acceptable.

Anti-alirocumab antibody:
The anti-alirocumab antibody analysis was performed on all treated subjects (safety population) with a blood sample on week 0 (baseline) and at least one evaluable blood sample for antibodies post first double-blind IMP injection.

Reviewer Comment: The timing and components of the Applicant's safety monitoring plan were generally adequate.

8.4. Safety Results

Table 15 Overview of Adverse Events during the Double-Blind Period, Trial EFC14643, On treatment, Safety Population

	Q2W Cohort			
n (%)	Placebo N = 25	Alirocumab N = 49	Risk difference (95% CI)	Relative risk (95% CI)
Any TEAE	13 (52.0)	26 (53.1)	1.1 (-23.0, 25.1)	1.0 (0.6, 1.6)
Any Grade 2 or 3 TEAE	6 (24.0)	5 (10.2)	-13.8 (-30.6, 3.1)	0.4 (0.1, 1.3)
Any Grade 3 TEAE	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)
Any Serious TEAE	1 (4.0)	4 (8.2)	4.2 (-7.9, 16.2)	2.0 (0.2, 17.3)
Any TEAE Leading to Permanent Discontinuation	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Any TE AESI	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	
Any TEAE Leading to Death	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Any Treatment-related TEAE	1 (4.0)	4 (8.2)	4.2 (-7.9, 16.2)	2.0 (0.2, 17.3)
	Q4W Cohort			
n (%)	Placebo N = 27	Alirocumab N = 52	Risk difference (95% CI)	Relative risk (95% CI)
Any TEAE	16 (59.3)	26 (50.0)	-9.3 (-32.4, 13.9)	0.8 (0.6, 1.3)
Any Grade 2 or 3 TEAE	4 (14.8)	12 (23.1)	8.3 (-10.3, 26.9)	1.6 (0.6, 4.4)
Any Grade 3 TEAE	1 (3.7)	2 (3.8)	0.1 (-8.7, 9.0)	1.0 (0.1, 10.9)
Any Serious TEAE	1 (3.7)	2 (3.8)	0.1 (-8.7, 9.0)	1.0 (0.1, 10.9)

Any TEAE Leading to Permanent Discontinuation	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
Any TE AESI	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-
Any TEAE Leading to Death	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Any Treatment-related TEAE	0 (0.0)	7 (13.5)	13.5 (0.6, 26.3)	-

	Combined Q2W+Q4W			
n (%)	Placebo N = 52	Alirocumab N = 101	Risk difference (95% CI)	Relative risk (95% CI)
Any TEAE	29 (55.8)	52 (51.5)	-4.3 (-21.0, 12.4)	0.9 (0.7, 1.3)
Any Grade 2 or 3 TEAE	10 (19.2)	17 (16.8)	-2.4 (-15.1, 10.3)	0.9 (0.4, 1.8)
Any Grade 3 TEAE	2 (3.8)	3 (3.0)	-0.9 (-6.8, 5.1)	0.8 (0.1, 4.5)
Any Serious TEAE	2 (3.8)	6 (5.9)	2.1 (-5.3, 9.5)	1.5 (0.3, 7.4)
Any TEAE Leading to Permanent Discontinuation	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Any TE AESI	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Any TEAE Leading to Death	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Any Treatment-related TEAE	1 (1.9)	11 (10.9)	9.0 (0.1, 17.8)	5.7 (0.8, 42.7)

Source: ADAE dataset; Software: R version 4.2.2

8.4.1. Deaths

There were no TEAEs leading to death reported in trial EFC14643.

8.4.2. Serious Adverse Events

Detailed estimates of treatment-emergent serious adverse events in the double-blind period are presented in Table 16. A summary of relevant findings is presented below.

During the DB treatment period, TE-SAEs were experienced by 5 subjects in the Q2W cohort (4 [8.2%] subjects in the alirocumab group and 1 [4.0%] subject in the placebo group) and 3 subjects in the Q4W cohort (2 [3.8%] and 1 [3.7%])(Table 15). All treatment-emergent SAEs were reported as resolved or recovered at the end of the DB period. During the OL treatment period, treatment-emergent SAEs were reported in 4 (5.6%) subjects in the Q2W cohort and 5 (6.8%) subjects in the Q4W cohort. All treatment-emergent SAEs were resolved/resolving at the end of the OL period.

List of subjects with TE-SAE in DB or OL periods (source: Applicant's narrative summaries):
Q2W Cohort

Alirocumab

- Pharyngitis streptococcal: A male subject presented to ER with bilateral

clavicular pain, throat pain, and fever. A throat culture revealed streptococcal pharyngitis. He was admitted for evaluation but was negative for bone pathology and was discharged 2 days later. Symptoms resolved and IMP was uninterrupted.

- Abdominal pain: A female subjects with history of H. pylori infection was hospitalized on trial day 38 for abdominal pain. She was diagnosed with mesenteric lymphadenitis and discharged on trial day 42. She has recovered and with no interruption in IMP.
- Sympathetic posterior cervical syndrome: A male subject had symptoms of headache and sinusitis on trial day 65 and was hospitalized for sympathetic posterior cervical syndrome. He was discharged on day 70 and fully recovered by the end of the trial. IMP was uninterrupted.
- Calculus urinary: A male subject was hospitalized with nephrolithiasis on trial day 220. He underwent surgical treatment and was discharged on day 222. He recovered with no interruption in IMP.
- Hypertension: A female subject was hospitalized for hypertension on trial day 349. She was treated with ramipril and was discharged on day 356. She was still recovering at the time of submission. There was no interruption in IMP.
- Abdominal hernia: A female subject was diagnosed with abdominal hernia on trial day 26. She was hospitalized on day 97 for planned repair. She was discharged the same day and recovered. There was no interruption in IMP.
- Pneumonia: A male subject presented to the ER with loss of taste sensation and cough on trial day 637. He was admitted and diagnosed with pneumonia, treated with antibiotics and discharged on day 648. There was no interruption in IMP.
- Major depression: A female subject decided to permanently discontinue IMP on trial day 113 due to difficult life events. On day 160, she was hospitalized for worsening major depression, was treated, and discharged on day 178.

Placebo

- Appendicitis: A male subject was hospitalized on trial day 97 for appendicitis, underwent appendectomy and was discharged on day 99. There was no interruption in IMP.

Q4W Cohort

Alirocumab

- Myocarditis and Angina pectoris: A female subject developed radiating L shoulder pain > 1 month after receiving first COVID vaccine. She was hospitalized, diagnosed with myocarditis, treated, and discharged. Six days after discharged, she was readmitted with angina pectoris and discharged after 2 days.
- Syncope: A female subject reported AEs of syncope (severe), fall, head injury, and concussion (severe) on trial day 8, 7 days after IMP administration. IMP was permanently discontinued. She recovered.
- Syncope: A female subject had an episode of syncope on trial day 29 after

dispensing week 4 IMP. She recovered on the same day with no interruption in IMP.

- Ligament rupture: A female subject experienced a L posterior cruciate ligament tear on trial day 236. She was hospitalized on day 375 to undergo Achilles tendon allograft and she was discharged on day 376 with no interruption in IMP.
- Syncope: A female subject on trial day 217 started having cramps in her arms and lost consciousness within 3 minutes without stopping breathing. Workup by a specialist did not reveal the cause. She recovered the same day with no interruption in IMP.

Placebo

- Non-cardiac chest pain: A male subject started military service and did an intense march on day 34 of the trial when he began to experience severe thoracic pain. He was hospitalized and noted to have elevated CK, myoglobin, and CK-MB. Lab abnormalities suggested strenuous exercise as the cause and he was discharged on day 36 of trial with no interruption in IMP.
- Appendicitis: A female subject was hospitalized for appendicitis on trial day 711. She was treated with antibiotics and discharged home on day 713. There was no interruption in IMP.
- Syncope: A female subject had an episode of syncope on trial day 223. It was reported that she did not have enough intake of food and fluid. She recovered the same day with no interruption in IMP.

Reviewer's comment: No patterns emerged suggesting a causal relationship between these SAEs and alirocumab except for syncope in the female subject in the Q4W cohort where syncope occurred directly after IMP injection. Adolescent females are known to have an increased of vasovagal syncope.[31]

Table 16 Treatment-emergent Serious Adverse Events, Double Blind Period, Safety Population

MedDRA Term	Q2W Cohort			Q4W Cohort		
	Placebo N = 25	Alirocumab N = 49	Risk difference (95% CI)	Placebo N = 27	Alirocumab N = 52	Risk difference (95% CI)
Infections and infestations	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Appendicitis	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Psychiatric disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Major depression	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)

[31] Coupal KE, Heeney ND, Hockin BCD, Ronsley R; Armstrong, K; Sanatani et al. Pubertal Hormonal Changes and the Autonomic Nervous System: Potential Role in Pediatric Orthostatic Intolerance. Front Neurosci. 2019;13:1197.1-20.

Syncope	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)
Gastrointestinal disorders	0 (0.0)	2 (4.1)	4.1 (-3.7, 11.8)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Abdominal hernia	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Abdominal pain	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Sympathetic posterior cervical syndrome	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)

	Combined Q2W+Q4W		
MedDRA Term	Placebo N = 52	Alirocumab N = 101	Risk difference (95% CI)
Infections and infestations	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)
Appendicitis	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)
Psychiatric disorders	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)
Major depression	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)
Nervous system disorders	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)
Syncope	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)
Gastrointestinal disorders	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)
Abdominal hernia	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)
Abdominal pain	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)
Sympathetic posterior cervical syndrome	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)
General disorders and administration site conditions	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)
Non-cardiac chest pain	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)

Source: ADAE dataset; Software: R version 4.2.2

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

During the DB treatment period, no subjects in the Q2W cohort and 2 (3.8%) subjects in the Q4W cohort (both in the alirocumab group) had TEAEs leading to permanent IMP discontinuation. One discontinuation was due to syncope which was also reported as an SAE (see details of SAE in section 8.4.2). The second subject was treated concomitantly with

atorvastatin and permanently discontinued the intervention treatment due to 2 neurocognitive AESIs (PT: disturbance in attention and memory impairment). This was a female who had previously reported 2 episodes of rash on the upper limbs and chest several hours after the first injection on trial day 1 and after the second injection on trial day 29. In both cases, the rash resolved on the same day. On Day 32 of the study, AEs of Disturbance in attention (mild) (decreased concentration) and Memory impairment (mild) (impaired short-term memory) were reported. Neither was associated with a pre-existing condition or with the subject's medical history. The Applicant reported that the event of disturbance in attention could not be assessed objectively. The subject was withdrawn from the trial by the parents as they noticed decreased concentration of the subject. On trial day 42, the subject recovered from the events of disturbance in attention and memory impairment.

During the OL treatment period in the Q2W cohort, 1 (1.4%) subject had a TEAE (PT: low density lipoprotein decreased) which led to permanent IMP injection discontinuation. The LDL-C level was 44.8 mg/dL at week 32 which led to treatment discontinuation.

8.4.4. Significant Adverse Events

Significant adverse events– defined by this reviewer as an SAE, severe (grade 3) AE, or AE leading to permanent discontinuation – reported in trial EFC14643 are listed in Table 17 (for DB period) and Table 18 (for OL period). Detailed estimates for all reported grade 3 AEs are presented in Table 19

Table 17 List of Significant Adverse Events* in Trial EFC14643 Double Blind Period, Safety Population

Treatment group	Preferred Term (1 subject/row)	SAE	Permanent d/c	AESI	Grade 3	Related (by Reviewer)	Resolved
Alirocumab Q2W	Abdominal pain	X					X
Alirocumab Q2W	Abdominal hernia	X					X
Alirocumab Q2W	Sympathetic posterior cervical syndrome	X					X
Alirocumab Q2W	Major depression (subject had discontinued IMP due to life events 47 days earlier)	X			X		X
Alirocumab Q4W	1) Syncope (study day 8, 7 days after IMP, unknown etiology) 2) Fall	1) X 2) - 3) -	X		1) X 2) - 3) -		X

	3) Head injury						
Alirocumab Q4W	Syncope (study day 29, just after dispensing week 4 IMP)	X			X	X	X
Alirocumab Q4W	1) Disturbance in attention 2) Memory impairment		X	Neurologic & Neurocognitive event			X
Placebo Q2W	Migraine				X		X
Placebo Q2W	Appendicitis	X					X
Placebo Q4W	Non-cardiac chest pain	X			X		X

Source: ADAE, Software R version 4.2.2.
*Significant adverse events are defined as a serious or severe (grade 3) adverse event or an adverse event leading to permanent discontinuation.
Abbreviations: IMP is investigational medical product, d/c is discontinued, AESI is adverse event of special interest

Table 18 List of Significant Adverse Events* in Trial EFC14643 Open Label Period, Safety Population

Treatment group**	Preferred Term (1 subject/row)	SAE	Permanent d/c	AESI	Grade 3	Related (Reviewer)	Resolved
Alirocumab Q2W	Pharyngitis, streptococcal	X					X
Alirocumab Q2W	Calculus urinary	X					X
Alirocumab Q2W	Hypertension	X					X
Alirocumab Q2W	Pneumonia	X					X
Alirocumab Q4W	Ligament rupture (due to “sporting”)	X					X
Alirocumab Q4W	1) Myocarditis 2) Angina pectoris	1) X 2) X					X
Alirocumab Q4W	Syncope (associated with muscle spasm in arms, unknown etiology)	X		Neurologic & Neurocognitive event			X
Placebo Q2W	Low density lipoprotein decreased		X			X	X
Placebo Q4W	Appendicitis	X					X
Placebo Q4W	Syncope (dehydration)	X					X

** as assigned in DB period

Source: ADAE, Software R version 4.2.2.
*Significant adverse events are defined as a serious or severe (grade 3) adverse event or an adverse event leading to permanent discontinuation.
Abbreviations: IMP is investigational medical product, d/c is discontinued, AESI is adverse event of special interest

Table 19 Treatment-emergent Severe (Grade 3) Adverse Events, Double Blind Period, On Treatment, Safety Population

MedDRA Term	Q2W Cohort				Q4W Cohort			
	Placebo N = 25	Alirocumab N = 49	Risk difference (95% CI)	Relative risk (95% CI)	Placebo N = 27	Alirocumab N = 52	Risk difference (95% CI)	Relat risk
Psychiatric disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Major depression	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Nervous system disorders	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
Syncope	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
Migraine	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-
Concussion	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-
Head injury	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-

MedDRA Term	Combined Q2W+Q4W			
	Placebo N = 52	Alirocumab N = 101	Risk difference (95% CI)	Relative risk (95% CI)
Psychiatric disorders	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Major depression	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Nervous system disorders	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Syncope	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Migraine	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
General disorders and administration site conditions	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Non-cardiac chest pain	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Injury, poisoning and procedural complications	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Concussion	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Head injury	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-

Source: ADAE, Software R version 4.2.2.

Reviewer's comment: All but 2 significant AEs in the double-blind period and 1 in the open-label period were SAEs that were reviewed in section 8.4.2.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

See Appendix 13.4 for detailed estimates of TEAEs for trial EFC14643 by MedDRA system organ class, high level term, and preferred term. A summary of relevant results is presented in this section.

The most commonly reported adverse events (placebo, alirocumab), where the incidence with alirocumab was greater than 5% and greater than placebo, were:

- Q2W Cohort
  - Nasopharyngitis: 2 (8.0%), 7 (14.3%)
  - Tonsillitis: 1 (4.0%), 3 (6.1%)
  - Injection site reaction: 0, 3 (6.1%)
- Q4W Cohort
  - Headache: 1 (3.7%), 4 (7.7%)
- Combined Q2W+Q4W
  - Nasopharyngitis: 4 (7.7%), 8 (7.9%)
  - Headache: 3 (5.8%), 7 (6.9%)

None of these were serious or led to discontinuation of IMP.

Table 20 TEAE Preferred Terms Reported by >2% of subjects in the alirocumab group in either Q2W or Q4W cohort or combined (where alirocumab>placebo), Trial EFC14643 Double-blind Period, On-treatment, Safety Population

MedDRA Preferred Term	Q2W Cohort			
	Placebo N = 25	Alirocumab N = 49	Risk difference (95% CI)	Relative risk (95% CI)
Nasopharyngitis	2 (8.0)	7 (14.3)	6.3 (-9.4, 22.0)	1.8 (0.4, 8.0)
Tonsillitis	1 (4.0)	3 (6.1)	2.1 (-8.8, 13.0)	1.5 (0.2, 14.0)
Respiratory tract infection viral	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Syncope	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Headache	2 (8.0)	3 (6.1)	-1.9 (-14.0, 10.2)	0.8 (0.1, 4.3)
Rash	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-
Injection site reaction*	0 (0.0)	3 (6.1)	6.1 (-3.3, 15.5)	-
	Q4W Cohort			
	Placebo N = 27	Alirocumab N = 52	Risk difference (95% CI)	Relative risk (95% CI)
Nasopharyngitis	2 (7.4)	1 (1.9)	-5.5 (-14.3, 3.3)	0.3 (0.0, 2.7)

Tonsillitis	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-
Respiratory tract infection viral	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
Syncope	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
Headache	1 (3.7)	4 (7.7)	4.0 (-7.3, 15.3)	2.1 (0.2, 17.7)
Rash	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
Injection site reaction*	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-
	Combined Q2W+Q4W			
	Placebo N = 52	Alirocumab N = 101	Risk difference (95% CI)	Relative risk (95% CI)
Nasopharyngitis	4 (7.7)	8 (7.9)	0.2 (-8.8, 9.2)	1.0 (0.3, 3.3)
Tonsillitis	2 (3.8)	3 (3.0)	-0.9 (-6.8, 5.1)	0.8 (0.1, 4.5)
Respiratory tract infection viral	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Syncope	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Headache	3 (5.8)	7 (6.9)	1.2 (-7.1, 9.4)	1.2 (0.3, 4.5)
Rash	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Injection site reaction*	0 (0.0)	5 (5.0)	5.0 (-0.9, 10.8)	-

Source: ADAE; Software R version 4.1.1.; MedDRA version 25.0
*The MedDRA preferred term "injection site reaction" was the only term reported under the high level term "injection site reactions."

Reviewer Comments: These adverse reactions are consistent with the known adverse drug reactions for alirocumab seen in other clinical trials and described in product labeling, such as nasopharyngitis, upper respiratory tract infection, and injection site reactions.

8.4.6. Laboratory Findings

This reviewer reviewed mean change from baseline at 24 weeks and counts of subjects with ≥ abnormal values (DB period, where available) in the combined Q2W and Q4W cohorts provided by the Applicant (EFC14643 16.2.8 Clinical laboratory data and 16.2.7 Other safety observations) and found no clinically meaningful differences between alirocumab and placebo groups for the following tests:

Hematology: hematocrit, hemoglobin, red blood cell count, white blood cell count, and platelets
Chemistry: fasting glucose, total protein, albumin, creatinine, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, urea nitrogen, uric acid, lactate dehydrogenase, estimated glomerular filtration rate (eGFR)
Liver panel: ALT, AST, alkaline phosphatase (ALP), gamma GT, total bilirubin, Lactate dehydrogenase
Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone)
Other: HbA1c, Hs-CRP, CPK-MB, troponin

8.4.7. Vital Signs

This reviewer reviewed mean change from baseline at 24 weeks in the combined Q2W and Q4W cohorts provided by the Applicant (EFC14643 16.2.7 Other safety observations) and found no clinically meaningful differences between alirocumab and placebo groups for heart rate, systolic, and diastolic blood pressure.

8.4.8. Electrocardiograms (ECGs)

Not applicable

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Double-blind period

- Q2W:
  - 1 subject had ADA at baseline (alirocumab group)
  - 2 transient and 1 indeterminate TE ADA (alirocumab group, no persistent)
- Q4W:
  - 4 subjects had ADA at baseline (alirocumab group)
  - No TE ADA

OL Period

- Q2W:
  - No subjects with ADA at baseline
  - No TE ADA
- Q4W:
  - No subjects with ADA at baseline
  - 1 subject with transient TE ADA (placebo group in DB period, no persistent)

No subject had

- Persistent treatment-emergent ADA response
- ADA response with neutralizing status in this trial

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. General Allergic Events (Hypersensitivity) and Injection Site Reactions

Hypersensitivity in trial EFC14643 DB period: In the Q2W cohort, no subjects in either intervention group reported general allergic events. In the Q4W cohort, 2 (3.8%) subjects in the

alirocumab group and no subjects in the placebo group reported at least 1 general allergic TEAE. These 2 subjects are included in Table 20 under “rash” and were of mild or moderate severity. An analysis of the Hypersensitivity Broad FMQ for the double-blind period revealed only these 2 cases of rash.

Injection site reactions in trial EFC14643 DB period: In the Q2W cohort, 3 (6.1%) subject in the alirocumab group and no subjects in the placebo group experienced at least 1 local injection site reaction. In the Q4W cohort, 2 (3.8%) subjects in the alirocumab group and no subjects in the placebo group experienced at least 1 local injection site reaction. All events were of mild intensity and no subject had experienced more than 1 event. These events are listed in Table 20 and includes all events under the MedDRA high level term “injection site reaction.” An analysis of Local Administration Reaction Broad FMQ revealed only these 5 events.

Reviewer Comment: The incidence of hypersensitivity and injection site reaction events observed in trials EFC14643 were consistent with the known safety profile of alirocumab.

8.5.2. Neurologic Events, Neurocognitive Events, and Cogstate Battery Test

Neurologic events were selected based on MedDRA SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following preferred terms “acute respiratory distress syndrome”, “asthenia”, “respiratory arrest” and “respiratory failure” and including selected PTs from SMQ "optic nerve disorders" (see Statistical Analysis Plan Appendix D, Table 8 for the list of terms).

During the DB treatment period of the study, no subjects in the Q2W cohort experienced any neurologic events. In the Q4W cohort, 1 (1.9%) subject in the alirocumab group and no subject in the placebo group experienced at least 1 neurologic event (EFC1643 CSR Table 70). This participant reported a non-serious hypoesthesia and did not permanently discontinue study treatment due to this event. During the OL treatment period of the study, no participants in the Q2W and Q4W cohorts experienced any neurologic events.

Neurocognitive events were selected based on the following 5 MedDRA high level grouping terms: “deliria (including confusion)”, “cognitive and attention disorders and disturbances”, “dementia and amnestic conditions”, “disturbances in thinking and perception”, and “mental impairment disorders”.

During the DB treatment period, no neurocognitive disorder TEAEs were reported in the Q2W cohort, while in the Q4W cohort, 1 (1.9%) subject in the alirocumab group and no subject in the placebo group experienced at least 1 neurocognitive event (source: 16-2-7-ae-data [16.2.7.4.18.1], [16.2.7.4.18.2] and [16.2.7.4.18.3]). This subject experienced 2 neurocognitive events: “disturbance in attention” and “memory impairment” (EFC1643 CSR Table 71). Both events were not serious but led to treatment discontinuation. In the OL period, 1 (1.4%) subject in the Q2W cohort experienced neurocognitive event of “memory impairment” (source: 16-2-7-

ae-data [16.2.7.8.4.11.2] and [16.2.7.8.4.12.2]) and in the Q4W cohort, 1 (1.4%) participant reported neurocognitive disorder of “attention deficit hyperactivity disorder” (source: 16-2-7-ae-data [16.2.7.8.4.11.3] and [16.2.7.8.4.12.3]). Both events were not serious and did not lead to treatment discontinuation.

Cogstate battery test: These individual tests assess maturing cognition across a broad number of key developmental functions such as processing speed, attention, visual learning, and executive functioning (see section 8.3.3). This reviewer reviewed mean values of each test results (Detection test; Identification test; One Card Learning test; Groton Maze Learning test) at baseline and at Week 24 for the Q2W and Q4W cohorts separately and combined (source: EFC14643 Other safety observations, section 16.2.7.3). Differences at week 24 compared to baseline were similar between alirocumab and placebo groups.

8.6. Safety Analyses by Demographic Subgroups

This section provides analyses of safety information by age, sex, and racial subgroups in trial EFC14643 (combined Q2W and Q4W) to explore the effect of possible interactions on safety signals/events. Adverse event data were reviewed by race, however, no meaningful information resulted from this review because of the small sample size of non-white subjects. Adverse events were similar in males compared with females except that all 5 injection site reactions reported were in females. Adverse events were similar by age >= 12 and < 12 years. (Source: ADAE; Software R version 4.1.1.; data table not shown)

8.7. Specific Safety Studies/Clinical Trials

There were no specific studies or clinical trials conducted to evaluate a specific safety concern for this supplement.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no new information on human carcinogenicity or tumor development in this submission.

8.8.2. Human Reproduction and Pregnancy

In trial EFC14643, no pregnancies were reported in the DB period. There was 1 pregnancy reported during the OL treatment period in a 16-year-old subject in the Q4W cohort. The subject had elective termination and no action was taken with IMP.

8.8.3. Pediatrics and Assessment of Effects on Growth

A majority of subjects were pubescent at baseline in trial EFC14643. In the combined Q2W and Q4W cohorts, 27 (73.0%) subjects from the alirocumab groups and 17 (58.6%) subjects in the placebo groups were at pubescent stage at baseline in safety population of boys, and 29 (45.3%) subjects from the alirocumab groups and 14 (60.9%) subjects from the placebo groups were at pubescent stage at baseline in safety population of girls.

Table 21 Change in Tanner Stage in Trial EFC14643, Double-blind Period, Combined Q2W and Q4W Cohorts, Safety Population

Change in Tanner stage **≥1**	Placebo	Alirocumab
Boys		
External genitalia, n/N (%)	11/29 (39.3)	5/37 (14.7)
Pubic hair, n/N (%)	11/29 (39.3)	6/37 (17.6)
Girls		
Breast development, n/N (%)	2/23 (10.0)	10/64 (18.2)
Pubic hair, n/N (%)	5/23 (25.0)	10/64 (18.2)

Source: EFC14643 Tables 16.2.7.2.2.1, 16.2.7.2.3.1, 16.2.7.2.5.1, 16.2.7.2.6.1.

Reviewer comment: The lower proportion of boys in the alirocumab groups who had a change in Tanner stage compared with boys in the placebo groups is likely due to the higher proportion of boys in the alirocumab groups who were already pubescent at baseline compared with the placebo groups.

There was no clinically meaningful differences in mean height change from baseline at 24 week between the alirocumab and placebo groups for the Q2W and Q4W separately and combined (1.94 cm in combined placebo vs. 2.20 cm in combined alirocumab).

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No symptomatic overdose was reported in the Q2W or Q4W cohorts. No new evaluation of overdose, drug abuse potential, or withdrawal and rebound were performed in this submission.

8.8.5. Other Sources of Safety Evaluation

Phase 2 DFI14223 (source: CSR synopsis with supplement submission)
This was an 8-week open-label, sequential, repeated dose-finding study to evaluate the efficacy and safety of alirocumab in children and adolescents with HeFH followed by an extension phase. The primary objective was to evaluate the effect of alirocumab administered every 2 weeks (Q2W) or every 4 weeks (Q4W) on low-density lipoprotein cholesterol (LDL-C) levels after 8 weeks of treatment in HeFH patients aged of 8 to 17 years, with LDL-C ≥130 mg/dL (3.37 mmol/L) on optimal stable daily dose of statin therapy ± other lipid modifying therapies (LMTs) or a stable dose of non-statin LMTs in case of intolerance to statins, for at least 4 weeks prior to the screening period. Forty-two subjects were treated. Overall, 31 patients experienced at least

one TEAE. All TEAEs were mild or moderate. No treatment-emergent SAEs and no deaths were reported. Two TEAEs leading to permanent treatment discontinuation were reported: one patient with decreased neutrophils already noted at screening experienced neutropenia which resolved after IMP discontinuation; and one patient experienced fatigue that resolved after IMP discontinuation. There were no adverse events of special interest reported. Of note, a few TEAEs pertaining to the groups of events of special interest, but which did not meet the AESI definition criteria, were reported in the study, 3 local injection site reactions, 1 general allergic reaction (asthma in a patient with a medical history of asthma) and 1 neurological event (hypoesthesia). Two patients enrolled in the study experienced a type 1 diabetes mellitus adverse event, one patient had a history of elevated glycaemia before entry into the study and a second patient in the post-treatment period (3.5 months after the last IMP injection). In both patients, the type 1 diabetes mellitus was assessed to be of autoimmune origin. In general, no clinically significant changes over time were observed in the safety hematology and serum chemistry parameters assessed in the study. No significant changes over time among cohorts were observed in cortisol and vitamins A, D and K. As observed in the adult population, a decrease in vitamin E parallel to the decrease in LDL-C levels was observed in all cohorts from baseline to Week 8 and a positive correlation between calculated LDL-C and vitamin E was observed. No patients had vitamin E values lower than normal range. No significant changes over time were observed over time in gonadal and pituitary hormones in boys or girls.

HoFH study (Source: Dr. Mary Robert's review dated July 22, 2021, for IND 105574)
The Applicant completed trial EFC14660, an open-label study of Praluent in children and adolescents with HoFH, which was a multi-national, open-label, 48-week study of Praluent 75 mg or 150 mg administered subcutaneously (depending on body weight) every 2 weeks in 18 children and adolescents with confirmed HoFH by genetic testing (excluding patients with two null LDL receptor alleles) and LDL-C ≥130 mg/dL despite stable optimal lipid modifying therapy, including apheresis. All patients received either Praluent 75 mg (body weight <50 kg) or 150 mg (body weight ≥50 kg) every two weeks without any dose adjustment up to Week 12. Praluent was generally well-tolerated, and the safety profile appears consistent with reported safety and tolerability issues in the Phase 3 program in adults. Seventeen (94.4%) of the 18 patients reported at least one treatment-emergent adverse event. The 3 most frequently reported TEAEs by PT were: nasopharyngitis (3 [16.7%]), headache (3 [16.7%]), and aortic valve incompetence (3 [16.7%]). Of the 3 patients with "aortic valve incompetence" TEAE, a medical history related to valve disorders was reported in 2 patients: cardiac murmur related to aortic valve insufficiency in one patient and mitral valve insufficiency in another patient. A 12-year-old boy with underlying valvular disease died due to Stage 4 cardiac failure. This patient's premature death is most likely related to his underlying medical condition. There were no other deaths, serious adverse events, or discontinuations due to adverse event. A single AESI of ALT increase (<3x ULN) was reported in a patient in the Praluent 150 mg Q2W group. No other AESIs occurred, including allergic events or local injection site reactions or neurological events that would have required consultation with another physician, neurocognitive events, pregnancy, or symptomatic overdose with Praluent. No other significant events of interest occurred such as

new-onset diabetes, or diabetic complications. There were no patients with two consecutive LDL-C values <25 mg/dL. The incidence of laboratory values that met criteria for potentially clinically significant abnormalities was low and no safety signal was identified. No patient had a positive anti-drug antibody response to Praluent.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Alirocumab was first approved in 2015 in the US and is approved in 60 countries worldwide. The cumulative exposure among adults to parenteral alirocumab was estimated to be 453.8 million patient days corresponding to 1.2 million patient years as of July 31, 2023. The adverse reactions "Hypersensitivity reactions: Angioedema" and "Influenza-like illness" have been reported during post-approval use of alirocumab, according to the currently approved label. Based on the information collected and analyzed by the Applicant during the period from July 25, 2022 to July 24, 2023, no new important risks were identified (Source: Development Safety Update Report submitted September 21, 2023).

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable as alirocumab (Repatha) is currently marketed. See Section 8.9.1.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

The safety profile of alirocumab in adults is well characterized and based on a large clinical development program and post-marketing experience.

Exposure to alirocumab supporting this current submission includes approximately 150 pediatric patients with HeFH, who completed trial EFC 14643, which includes a 24- week DB period and 80-week OL period, and 18 pediatric patients with HoFH who were administered alirocumab, as an adjunct to standard of care, for 48 weeks. In trial EFC 14643, approximately 100 pediatric patients with HeFH were exposed to alirocumab for approximately 102 weeks and 50 pediatric patients with HeFH were exposed for approximately 77 weeks in the combined Q2W and Q4W cohorts.

No patients died during trial EFC 14643 or in the supportive dose finding trial DFI14223. One male patient aged ≥12 to <18 years with HoFH in the alirocumab Q2W cohort and receiving alirocumab 75 mg to 150 mg Q2W group died during trial EFC14660. The patient died due to decompensated heart failure and severe aortic stenosis. The SAE of cardiac failure was not considered related to the study drug by the review team as it is related to his underlying

During the DB treatment period of trial EFC 14643, TE-SAEs were experienced by 6 subjects in the alirocumab cohort and 2 subjects in the placebo cohort. No patterns emerged suggesting a causal relationship between these SAEs and alirocumab except for syncope in a female subject where syncope occurred directly after alirocumab injection and was likely an episode of vasovagal syncope.

During the DB treatment period, 2 subjects in the alirocumab group had TEAEs leading to permanent IMP discontinuation. One discontinuation was due to syncope and the second subject discontinued the intervention treatment due to 2 neurocognitive AESIs (PT: disturbance in attention and memory impairment). None of these events were considered related to alirocumab by this reviewer.

In trial EFC 14643, five events in the alirocumab group (major depression, syncope, concussion, head injury) and two events in the placebo group (migraine, non-cardiac chest pain) were reported as an adverse event that was Common Terminology Criteria for Adverse Events (CTCAE) grade 3. These events were not considered definitively related to alirocumab by this reviewer.

Adverse events of special interest, defined by the protocol and based on the known safety profile of alirocumab, theoretical concerns in pediatric populations, and standard safety review practices, included: allergic events, local injection site reactions, pregnancy, symptomatic overdose of IMP, neurologic events, neurocognitive events, and ALT increases. In the DB period, AESIs that occurred in more subjects in the alirocumab group include allergic events (PT: rash), local injection site reactions, and one report of a neurologic event (PT: hypoesthesia); these events were nonserious and did not lead to IMP discontinuation. In addition, neurocognitive events of disturbance in attention and memory impairment were reported in 1 subject in the alirocumab group which led to treatment discontinuation. There were no cases of pregnancies, symptomatic overdose with study drug, hepatic disorders (including ALT increase), or diabetes mellitus/diabetic complications. In the OL period, AESI included general allergic events (seasonal allergy, dermatitis allergic, rash, asthma) and injection site reactions which were nonserious and did not lead to IMP discontinuation. Neurocognitive events (PT: memory impairment and attention deficit hyperactivity disorder) was reported in 1 subject each. Both events were not serious and did not lead to treatment discontinuation. There was 1 case of pregnancy (with elective termination at gestational age estimated to be between 5 to 6 weeks) in a 16-year-old female subject. Two subjects reported ALT increased; the events were nonserious and not believed to be related to study drug.

The most commonly reported adverse events in the Q2W and Q4W cohort combined, where the incidence with alirocumab was ≥ 5% and greater than placebo, were nasopharyngitis, headache, and injection site reaction. These adverse reactions, with the exception of headache

[3 (5.8%), 7 (6.9%)] are consistent with the known adverse drug reactions for alirocumab seen in other clinical trials and described in product labeling, such as nasopharyngitis, upper respiratory tract infection, and injection site reactions. None of these were serious or led to discontinuation of IMP.

There was no evidence of adverse effects on growth and development, cognition, or neurologic function.

In conclusion, no new adverse drug reaction (with the exception of headache) or change in the safety profile was identified from the evaluation of alirocumab administered to pediatric patients 8 to 17 years of age with HeFH or HoFH who participated in trial EFC 14643 or trial EFC14660. Alirocumab was generally well-tolerated, and the safety profile appears consistent with reported safety and tolerability issues in the phase 3 program and the cardiovascular outcomes trial in adults.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Supplement 39: Prescribing Information – Review of PI submitted May 10, 2023

1. Section 1 Indications: Minor edits made to clarify age range.
2. Section 2.1 Recommended Dosage: The clinical team has no edits to this section but defers to the clinical pharmacology and labeling teams.
3. Section 6 Adverse Reactions: The applicant's language was replaced with the clinical team's proposed language:
    a. In the HeFH placebo-controlled trial in which 101 pediatric patients were exposed to PRALUENT and 52 pediatric patients were exposed to placebo for a median of 24 weeks, common adverse reactions (at least 5% of patients treated with PRALUENT and occurring more frequently than placebo) included nasopharyngitis (7.9% PRALUENT, 7.7% placebo), headache (7% PRALUENT, 6% placebo), and injection site reaction (5% PRALUENT, 0% placebo).
4. Section 6.2 Immunogenicity was moved to Section 12.6

5. Section 8.4 Pediatric Use: Edits were made in this section to provide language that is consistent with the language in the Repatha label and to be consistent with the Labeling Review Tool.
6. Section 14 Clinical Studies: Trial 12 (EFC14643, NCT03510884): Additional information was added to describe the entire HeFH trial population, not just those in the Q4W cohort.

Supplement 39: Prescribing Information – Review of PPI submitted May 10, 2023

1. Section "What is REPATHA": Language changed to be consistent with the language in PI Section 1 Indications for pediatric HeFH population and Section 8.4.
2. The clinical team defers to the Patient Labeling review team's assessment for the remainder of the PPI edits.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of alirocumab, there are no additional risk management strategies required.

12. Postmarketing Requirements and Commitments

The Applicant has submitted final results for pediatric trials DFI14223 and EFC14643 in pediatric subjects with HeFH, which fulfills post-marketing requirement (PMR) 2927-1 in its entirety.

No new PMRs or PMCs will be issued based on this submission.

13. Appendices

13.1. References

References are listed as footnotes throughout this document.

13.2. Financial Disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 143		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: n/a	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Trial Schedule

Table 22 Trial schedule

	Run-in (if needed)[a]	Screening		Double- Blind Treatment Period				Open label Treatment Period							
VISIT	1	2	3	4	5	6	7	7	8	9	10[gg]	11	12[gg]	13	14
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W8	W12	W24[c]	W24	W32	W44	W56	W68	W80	W92	W104[d]
Visit Window (+/- days)	+2	+5	+/-7		+/-7	+/-7	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed consent	X[e]														
heFH genotyping informed consent (if needed)[e, f]	X														
Inclusion criteria	X	X		X											
Exclusion criteria	X	X		X											
Patient demography	X[g]														
Medical/surgical/family medical history	X[g]														
Alcohol/smoking habits	X[g]														
Prior medication history	X[g ,h]														
General physical examination	X[g]						X			X		X			X
Measured body weight	X[g]			X		X	X		X	X		X		X	X
Measured height	X[g]						X			X		X			X
Tanner stage[i]	X[g]						X			X		X			X
IRT contact	X	X	X	X		X	X[ff]	X	X	X	X	X	X	X	X
Randomization				X											
Treatment:															
Injection training			X[j, l]	X[k, l]											
IMP administration Q2W or Q4W regimen (depending on treatment allocation) [l ,m]				X	←----------										→

	Run-in (if needed)[a]	Screening		Double- Blind Treatment Period				Open label Treatment Period							
VISIT	1	2	3	4	5	6	7	7	8	9	10[gg]	11	12[gg]	13	14
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W8	W12	W24[c]	W24	W32	W44	W56	W68	W80	W92	W104[d]
Visit Window (+/- days)	+2	+5	+/-7		+/-7	+/-7	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Double-blind IMP kit dispensation[n]				X		X									
Compliance check of IMP and data collection on IMP administration					X	X	X		X	X		X		X	X
Open label IMP kit dispensation[n]								X	X	X	X	X	X	X	
Concomitant medication				X	X	X	X	X	X	X	X	X	X	X	X
Check of stability of background LMT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of diet[o]	X[g]			X		X	X		X	X	X	X	X	X	X
Efficacy:															
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C[p, q]		X		X	X	X	X		X	X		X			X
Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp(a)[p, q]				X		X	X								X
Safety:															
AE/SAE recording (if any)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[r]		X		X		X	X		X	X		X			X
Cogstate battery practice test[s]				X											
Cogstate battery test[t]				X			X					X			X
Laboratory testing[p]:															
heFH genotyping[f]	X														
Hematology and chemistry[u]		X				X	X		X	X		X			X
HbA_{1c}		X					X					X			X
Creatine phosphokinase (CPK)		X				X	X		X	X		X			X
Liver panel[v]		X				X	X		X	X		X			X

	Run-in (if needed)[a]	Screening		Double- Blind Treatment Period				Open label Treatment Period							
VISIT	1	2	3	4	5	6	7	7	8	9	10[gg]	11	12[gg]	13	14
Week	Up to W-6	Up to W-2	Up to W-1[b]	W0/D1	W8	W12	W24[c]	W24	W32	W44	W56	W68	W80	W92	W104[d]
Visit Window (+/- days)	+2	+5	+/-7		+/-7	+/-7	+/-3	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Urinalysis[w]				X			X								
hs-CRP				X			X								
CPK-MB and troponin[x]				X			X								
Adrenal gland hormones[y]				X			X			X		X			X
Gonadal and pituitary hormones[z]				X			X			X		X			X
Fat soluble vitamins[aa]				X			X			X		X			X
Pregnancy test[bb]		X		X			X		X	X		X		X	X
Anti-alirocumab (drug) antibodies (ADA)[cc]				X		X	X					X			X
Serum alirocumab concentration (Pharmacokinetics)[dd]				X	X	X	X								
Flow mediated dilatation assessment[ee]				X			X								

a Patients, who have not been on stable lipid modifying therapy (LMT)s for at least 4 weeks or require statin intensification when initially seen can participate in a run-in period until LMT dose(s) have been stable for at least 4 weeks. Patients with suspected heFH but without confirmation by previous genetic testing and not meeting Simon Broome criteria can undergo centralized genetic testing during the run-in period.
b The W-1 visit (injection training visit) can take place at the same visit as D1 as per the site or patient preference.
c End-of-double-blind treatment period visit. This visit will overlap with the first visit of the open label treatment period.
d End-of-open label treatment period visit.
e Informed consent should be obtained only once. If patient enters the run-in period then informed consent will be obtained prior to entry into the run-in period. If patient does not require a run-in period, then informed consent will be obtained prior to entry into the screening period.
f Genotyping for heFH will be conducted from a specimen of whole blood, saliva, or buccal swab in patients consenting to undergo genotyping testing. This test will be recommended for all patients but will be mandatory only for patients without clinical diagnosis or no previous documented genotyping. In case of non-mandatory genotyping the sample could be taken preferentially during the screening period but could be done at any visit during the double-blind treatment period.
g The corresponding assessment should be obtained only once. If patient enters the run-in period then the corresponding assessment will be obtained during the run-in period. If patient does not require a run-in period, then the corresponding assessment will be obtained during the screening period.
h Document prior medication history within the previous 12 weeks, especially for LMT (including statin) and nutraceutical products that may affect lipids (eg, omega-3 fatty acids, plant stanols such as found in Benecol, flax seed oil, psyllium).

i See Appendix B for Tanner stage evaluation.
j Injection training at screening period visit Week -1 is performed with placebo for alirocumab. Investigators will have the option of providing a second placebo kit for alirocumab for patients/parents who require additional injection training prior to randomization.
k Further injection training can be provided at the randomization visit Week 0/Day 1 when the patient/parent or a trained designated person injects the first IMP from the double-blind study treatment kit allocated by IRT. Additional training can be offered at scheduled or unscheduled visits with the scheduled double-blind treatment, as per patient/parent or Investigator's judgment.
l Prior to the injection, a local topical anesthetic may be utilized as per the Investigator.
m The first IMP injection during the double-blind treatment period will be done at the site on the day of randomization and as close as possible after randomization into the study. The subsequent injections will be done at a patient-preferred location (home…). These injections can be performed by trained patient ≥12 years (self-injection) or parent, or another designated person or alternative arrangements for injection administration will be allowed as needed. It is suggested that patients ≥12 years old, who are trained to self-inject, do so with parental (or another designated person) supervision; however, this is not mandatory. The Investigator may evaluate the sustained reliability of this practice on a case by case basis given the variable adolescent ages, maturity levels, availability of the caregiver, or other relevant considerations, with the patient. The final decision as to whether supervision is appropriate for self-injection of alirocumab for patients ≥12 years old is per Investigator discretion. For the Q4W dosing regimen cohort study treatment will be administered every 4 weeks (Q4W) for the first 12 weeks of the double-blind period.
n Along with kit dispensation, the treatment administration package (see Section 8.5) should be given as well as the patient diary and injection instruction manual, as needed. Open label IMP kit delivery direct to patient (DTP) on Visit 10 and 12.
o Patients will be instructed to follow a diet to treat their hypercholesterolemia in accordance with local guidelines or local practice.
p Prior to any laboratory testing, the site may utilize a local topical anesthetic as per the Investigator. In case only a limited amount of blood can be drawn, specific tests performed for each sample obtained will be prioritized (estimated total blood volume of 194.8 mL for the entire study); see Section 10.
q The lipid levels will be blinded throughout the double-blind treatment period. The lipid levels will be communicated to the Investigator during the open label treatment period from Week 32 onwards.
r Vital signs include: heart rate, systolic and diastolic BP in sitting position.
s Cogstate battery practice test will be administered at randomization visit with recommended 15 minutes break before recorded Cogstate battery test. Morning administration is also recommended for all Cogstate tests.
t Cogstate battery test consists of identification test, detection test, one card learning test, and the Groton maze learning test. Morning administration is also recommended for all Cogstate tests. For further details see Section 9.2.4.5.
u Hematology includes: complete blood cell count (CBC) including hematocrit, hemoglobin, red blood cell count, white blood cell count with differential count, and platelets. Chemistry includes: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, lactate dehydrogenase (LDH), total protein, albumin, and γGT. (eGFR and creatinine clearance will be calculated at screening; creatinine clearance will be calculated for all subsequent visits where chemistry lab testing is performed)
v Liver panel: ALT, AST, alkaline phosphatase (ALP), and total bilirubin (in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically).
w Urinalysis: macroscopy will be performed at the central lab. If abnormal, then a standard microscope assessment will be conducted.
x CPK-MB and troponin levels will be assayed at baseline and at Week 24 and in case of any clinically relevant cardiovascular effect observed in patients.
y Adrenal gland hormones: cortisol (with reflexive adrenocorticotrophic hormone (ACTH) levels if cortisol < lower limit of normal [LLN]) and dehydroepiandrosterone sulfate (DHEAS).
z Gonadal hormones: testosterone (males) and estradiol (females). Pituitary hormones: luteinizing hormone (LH) and follicle-stimulating hormone (FSH).
aa Fat soluble vitamins: A (retinol), D (25 hydroxy vitamin D), E (alpha-tocopherol), and K (phylloquinone).
bb Pregnancy test with a local urine pregnancy test should be done on females of childbearing potential or females who have experienced menarche (they must have a confirmed negative pregnancy test at screening). Pregnancy tests may be performed more frequently in some countries due to local legislations related to women of childbearing potential randomized in clinical trials see Appendix J. The Screening (Week -2) pregnancy test should be a blood test. All other pregnancy tests will be with a local urine pregnancy test.
cc Patient who prematurely discontinue the alirocumab injections or who complete the study but have a titer at or above 240 for ADA at their last visit will have additional ADA samples, at 6 to 12 months after the last alirocumab administration and thereafter, about every 3 to 6 months until titer returns below 240.
dd Blood samples should be collected before IMP injection. PK samples will also be used for free and total proprotein convertase subtilisin/kexin type 9 (PCSK9) analysis.
ee Flow mediated dilatation assessment will be part of a substudy performed at selected sites (see Appendix E).
ff IRT contact for patient who do not continue in the open label treatment period.
gg Telephone contact.

Source: Excerpted from Applicant's submission, CSR page 27-30.

13.4. Treatment Emergent Adverse Events, by MedDRA System Organ Class, High Level Term, and Preferred Term, trial EFC14643 Double-blind Period, On-treatment, Safety Population

Reference ID: 5326070

	Q2W Cohort				Q4W Cohort				Combined Q2W+Q4W			
MedDRA Term	Placebo N = 25	Alirocumab N = 49	Risk difference (95% CI)	Relative risk (95% CI)	Placebo N = 27	Alirocumab N = 52	Risk difference (95% CI)	Relative risk (95% CI)	Placebo N = 52	Alirocumab N = 101	Risk difference (95% CI)	Relative risk (95% CI)
Infections and infestations	7 (28.0)	17 (34.7)	6.7 (-15.8, 29.2)	1.2 (0.6, 2.6)	8 (29.6)	11 (21.2)	-8.5 (-28.3, 11.3)	0.7 (0.3, 1.6)	15 (28.8)	28 (27.7)	-1.1 (-16.2, 13.9)	1.0 (0.6, 1.6)
Abdominal and gastrointestinal infections	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Appendicitis	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Gastroenteritis	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Gastrointestinal infection	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Bacterial infections NEC	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	1 (3.7)	1 (1.9)	-1.8 (-9.1, 5.5)	0.5 (0.0, 8.0)	2 (3.8)	1 (1.0)	-2.9 (-7.5, 1.8)	0.3 (0.0, 2.8)
Gastroenteritis bacterial	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Paronychia	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	2 (3.8)	0 (0.0)	-3.8 (-7.6, -0.1)	-
Ear infections	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Otitis externa	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Herpes viral infections	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Oral herpes	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Influenza viral infections	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Influenza	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Streptococcal infections	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Pharyngitis streptococcal	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-

Upper respiratory tract infections	6 (24.0)	14 (28.6)	4.6 (-16.8, 25.9)	1.2 (0.5, 2.7)	6 (22.2)	6 (11.5)	-10.7 (-27.2, 5.8)	0.5 (0.2, 1.5)	12 (23.1)	20 (19.8)	-3.3 (-16.9, 10.3)	0.9 (0.5, 1.6)
Laryngitis	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Nasopharyngitis	2 (8.0)	7 (14.3)	6.3 (-9.4, 22.0)	1.8 (0.4, 8.0)	2 (7.4)	1 (1.9)	-5.5 (-14.3, 3.3)	0.3 (0.0, 2.7)	4 (7.7)	8 (7.9)	0.2 (-8.8, 9.2)	1.0 (0.3, 3.3)
Pharyngitis	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Rhinitis	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Sinusitis	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Tonsillitis	1 (4.0)	3 (6.1)	2.1 (-8.8, 13.0)	1.5 (0.2, 14.0)	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	2 (3.8)	3 (3.0)	-0.9 (-6.8, 5.1)	0.8 (0.1, 4.5)
Upper respiratory tract infection	3 (12.0)	3 (6.1)	-5.9 (-19.0, 7.2)	0.5 (0.1, 2.3)	3 (11.1)	3 (5.8)	-5.3 (-17.6, 6.9)	0.5 (0.1, 2.4)	6 (11.5)	6 (5.9)	-5.6 (-14.5, 3.4)	0.5 (0.2, 1.5)
Urinary tract infections	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Urinary tract infection	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Viral infections NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	3 (5.8)	5.8 (-3.0, 14.6)	-	0 (0.0)	3 (3.0)	3.0 (-1.6, 7.6)	-
Gastroenteritis viral	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Respiratory tract infection viral	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Blood and lymphatic system disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Lymphatic system disorders NEC	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Lymphadenitis	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Immune system disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Allergic conditions NEC	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Allergy to arthropod bite	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-

Psychiatric disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Depressive disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Major depression	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Mood alterations with depressive symptoms	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Depressive symptom	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Nervous system disorders	4 (16.0)	3 (6.1)	-9.9 (-23.8, 4.0)	0.4 (0.1, 1.6)	2 (7.4)	10 (19.2)	11.8 (-4.7, 28.3)	2.6 (0.6, 11.0)	6 (11.5)	13 (12.9)	1.3 (-9.7, 12.4)	1.1 (0.5, 2.8)
Disturbances in consciousness NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Syncope	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Headaches NEC	2 (8.0)	3 (6.1)	-1.9 (-14.0, 10.2)	0.8 (0.1, 4.3)	1 (3.7)	4 (7.7)	4.0 (-7.3, 15.3)	2.1 (0.2, 17.7)	3 (5.8)	7 (6.9)	1.2 (-7.1, 9.4)	1.2 (0.3, 4.5)
Headache	2 (8.0)	3 (6.1)	-1.9 (-14.0, 10.2)	0.8 (0.1, 4.3)	1 (3.7)	4 (7.7)	4.0 (-7.3, 15.3)	2.1 (0.2, 17.7)	3 (5.8)	7 (6.9)	1.2 (-7.1, 9.4)	1.2 (0.3, 4.5)
Memory loss (excl dementia)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Memory impairment	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Mental impairment (excl dementia and memory loss)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Disturbance in attention	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Migraine headaches	2 (8.0)	0 (0.0)	-8.0 (-15.6, -0.4)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	2 (3.8)	1 (1.0)	-2.9 (-7.5, 1.8)	0.3 (0.0, 2.8)
Migraine	2 (8.0)	0 (0.0)	-8.0 (-15.6, -0.4)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	2 (3.8)	1 (1.0)	-2.9 (-7.5, 1.8)	0.3 (0.0, 2.8)
Neurological signs and symptoms NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	1 (1.9)	-1.8 (-9.1, 5.5)	0.5 (0.0, 8.0)	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Dizziness	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	1 (1.9)	-1.8 (-9.1, 5.5)	0.5 (0.0, 8.0)	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)

Paraesthesias and dysaesthesias	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Hypoaesthesia	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Vascular disorders	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Haemorrhages NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Haematoma	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Peripheral vascular disorders NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Hot flush	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Respiratory, thoracic and mediastinal disorders	2 (8.0)	1 (2.0)	-6.0 (-15.4, 3.4)	0.3 (0.0, 2.7)	0 (0.0)	3 (5.8)	5.8 (-3.0, 14.6)	-	2 (3.8)	4 (4.0)	0.1 (-6.4, 6.6)	1.0 (0.2, 5.4)
Coughing and associated symptoms	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Cough	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Nasal congestion and inflammations	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Nasal congestion	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Nasal disorders NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Epistaxis	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Upper respiratory tract signs and symptoms	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Oropharyngeal pain	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Rhinorrhoea	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Gastrointestinal disorders	4 (16.0)	4 (8.2)	-7.8 (-22.7, 7.0)	0.5 (0.1, 1.9)	3 (11.1)	3 (5.8)	-5.3 (-17.6, 6.9)	0.5 (0.1, 2.4)	7 (13.5)	7 (6.9)	-6.5 (-16.1, 3.1)	0.5 (0.2, 1.4)
Abdominal hernias NEC	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Abdominal hernia	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-

Dental pain and sensation disorders	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Toothache	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Diarrhoea (excl infective)	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Diarrhoea	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Gastritis (excl infective)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Gastritis	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Gastrointestinal and abdominal pains (excl oral and throat)	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	2 (7.4)	1 (1.9)	-5.5 (-14.3, 3.3)	0.3 (0.0, 2.7)	3 (5.8)	2 (2.0)	-3.8 (-9.7, 2.1)	0.3 (0.1, 2.0)
Abdominal pain	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Abdominal pain upper	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	2 (7.4)	0 (0.0)	-7.4 (-14.5, -0.3)	-	2 (3.8)	0 (0.0)	-3.8 (-7.6, -0.1)	-
Gastrointestinal atonic and hypomotility disorders NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Constipation	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Gastrointestinal signs and symptoms NEC	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Abdominal discomfort	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Nausea and vomiting symptoms	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	2 (3.8)	1 (1.0)	-2.9 (-7.5, 1.8)	0.3 (0.0, 2.8)
Nausea	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Vomiting	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	2 (3.8)	1 (1.0)	-2.9 (-7.5, 1.8)	0.3 (0.0, 2.8)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	3 (3.0)	3.0 (-1.6, 7.6)	-

Papulosquamous conditions	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Pityriasis rosea	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Rashes, eruptions and exanthems NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Rash	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Musculoskeletal and connective tissue disorders	2 (8.0)	3 (6.1)	-1.9 (-14.0, 10.2)	0.8 (0.1, 4.3)	1 (3.7)	3 (5.8)	2.1 (-8.1, 12.2)	1.6 (0.2, 14.3)	3 (5.8)	6 (5.9)	0.2 (-7.7, 8.0)	1.0 (0.3, 4.0)
Arthropathies NEC	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Sympathetic posterior cervical syndrome	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Joint related signs and symptoms	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Arthralgia	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Muscle related signs and symptoms NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Muscle spasms	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Muscle tone abnormalities	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Torticollis	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Musculoskeletal and connective tissue pain and discomfort	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Neck pain	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Pain in extremity	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Tendon disorders	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Tendonitis	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Renal and urinary disorders	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Urinary abnormalities	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-

Proteinuria	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Reproductive system and breast disorders	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	1 (3.7)	1 (1.9)	-1.8 (-9.1, 5.5)	0.5 (0.0, 8.0)	2 (3.8)	2 (2.0)	-1.9 (-7.2, 3.5)	0.5 (0.1, 3.6)
Menstruation and uterine bleeding NEC	1 (4.0)	1 (2.0)	-2.0 (-9.8, 5.8)	0.5 (0.0, 7.8)	1 (3.7)	1 (1.9)	-1.8 (-9.1, 5.5)	0.5 (0.0, 8.0)	2 (3.8)	2 (2.0)	-1.9 (-7.2, 3.5)	0.5 (0.1, 3.6)
Dysmenorrhoea	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	1 (3.7)	1 (1.9)	-1.8 (-9.1, 5.5)	0.5 (0.0, 8.0)	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Menstrual discomfort	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
General disorders and administration site conditions	0 (0.0)	4 (8.2)	8.2 (-2.6, 18.9)	-	1 (3.7)	4 (7.7)	4.0 (-7.3, 15.3)	2.1 (0.2, 17.7)	1 (1.9)	8 (7.9)	6.0 (-1.8, 13.8)	4.1 (0.5, 32.1)
Febrile disorders	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Pyrexia	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
General signs and symptoms NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Influenza like illness	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Injection site reactions	0 (0.0)	3 (6.1)	6.1 (-3.3, 15.5)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	5 (5.0)	5.0 (-0.9, 10.8)	-
Injection site reaction	0 (0.0)	3 (6.1)	6.1 (-3.3, 15.5)	-	0 (0.0)	2 (3.8)	3.8 (-3.4, 11.1)	-	0 (0.0)	5 (5.0)	5.0 (-0.9, 10.8)	-
Pain and discomfort NEC	0 (0.0)	2 (4.1)	4.1 (-3.7, 11.8)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	2 (2.0)	0.1 (-4.6, 4.7)	1.0 (0.1, 11.1)
Chest pain	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Non-cardiac chest pain	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Investigations	0 (0.0)	2 (4.1)	4.1 (-3.7, 11.8)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Bacteria identification and serology (excl mycobacteria)	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Helicobacter test positive	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-

Vitamin analyses	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Vitamin D decreased	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Injury, poisoning and procedural complications	1 (4.0)	3 (6.1)	2.1 (-8.8, 13.0)	1.5 (0.2, 14.0)	1 (3.7)	2 (3.8)	0.1 (-8.7, 9.0)	1.0 (0.1, 10.9)	2 (3.8)	5 (5.0)	1.1 (-5.9, 8.1)	1.3 (0.3, 6.4)
Cerebral injuries NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Concussion	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Fractures and dislocations NEC	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Bone fissure	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Muscle, tendon and ligament injuries	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Ligament sprain	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Non-site specific injuries NEC	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Fall	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	2 (2.0)	2.0 (-1.8, 5.8)	-
Non-site specific procedural complications	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Procedural pain	0 (0.0)	1 (2.0)	2.0 (-3.5, 7.6)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Product administration errors and issues	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Accidental overdose	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Site specific injuries NEC	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	1 (1.9)	1 (1.0)	-0.9 (-4.7, 2.9)	0.5 (0.0, 8.1)
Head injury	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	0 (0.0)	1 (1.9)	1.9 (-3.3, 7.1)	-	0 (0.0)	1 (1.0)	1.0 (-1.7, 3.7)	-
Limb injury	1 (4.0)	0 (0.0)	-4.0 (-9.5, 1.5)	-	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Surgical and medical procedures	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-
Dental and gingival therapeutic procedures	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-

Tooth extraction	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)	-	1 (3.7)	0 (0.0)	-3.7 (-8.8, 1.4)	-	1 (1.9)	0 (0.0)	-1.9 (-4.6, 0.8)	-

Source: ADAE; Software R version 4.1.1.; MedDRA version 25.0

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/s/

EILEEN M CRAIG
02/09/2024 07:50:50 AM
This review serves as the primary clinical review by Craig Hales, MD as well as the secondary clinical review.