CLINICAL REVIEW

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Established/Proper Name	Evolocumab
(Proposed) Trade Name	Repatha®
Applicant	Amgen Inc
Dosage Form(s)	Subcutaneous (SC) injection
Applicant Proposed Dosing Regimen(s)	420 mg once monthly or 140 mg every 2 weeks
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet, alone or in combination with other lipid-lowering therapy, for the treatment of pediatric patients aged 10 years and older with HeFH to reduce LDL-C/ HeFH patients, 10 years and older
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	HeFH: As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C/ HeFH patients, 10 years and older HoFH (clarify age limits of indication): As an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C/HoFH patients, 10 years and older

Table of Contents

Glossary 9

1. Executive Summary 12
   1.1. Product Introduction 12
   1.2. Conclusions on the Substantial Evidence of Effectiveness 12
   1.3. Benefit-Risk Assessment 15
   1.4. Patient Experience Data 22

2. Therapeutic Context 22
   2.1. Analysis of Condition 23
   2.2. Analysis of Current Treatment Options 25

3. Regulatory Background 37
   3.1. U.S. Regulatory Actions and Marketing History 37
   3.2. Summary of Presubmission/Submission Regulatory Activity 37
   3.3. Foreign Regulatory Actions and Marketing History 40

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 40
   4.1. Office of Scientific Investigations (OSI) 40
   4.2. Clinical Pharmacology 41

5. Sources of Clinical Data and Review Strategy 43
   5.1. Table of Clinical Studies 43
   5.2. Review Strategy 46

6. Review of Relevant Individual Trials Used to Support Efficacy 46
   6.1. Trial 20120123, HAUSER-RCT 46
      6.1.1. Study Design 46
      6.1.2. Study Results 58
   6.2. Trial 20120124, HAUSER-OLE 76
      6.2.1. Study Design 76
      6.2.2. Study Results 83

7. Integrated Review of Effectiveness 99
7.1. Assessment of Efficacy Across Trials 99
7.1.1. Primary Endpoints 99
7.1.2. Secondary and Other Endpoints 99
7.1.3. Subpopulations 99
7.1.4. Dose and Dose-Response 99
7.1.5. Onset, Duration, and Durability of Efficacy Effects 99
7.2. Additional Efficacy Considerations 102
7.2.1. Considerations on Benefit in the Postmarket Setting 102
7.2.2. Other Relevant Benefits 102
7.3. Integrated Assessment of Effectiveness 103

8. Review of Safety 104
8.1. Safety Review Approach 104
8.2. Review of the Safety Database 105
8.2.1. Overall Exposure 105
8.2.2. Relevant Characteristics of the Safety Population 107
8.3. Adequacy of Applicant's Clinical Safety Assessments 108
8.3.1. Issues Regarding Data Integrity and Submission Quality 108
8.3.2. Categorization of Adverse Events 108
8.3.3. Routine Clinical Tests 110
8.4. Safety Results 116
8.4.1. Deaths 117
8.4.2. Serious Adverse Events 117
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects 118
8.4.4. Significant Adverse Events 119
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions 121
8.4.6. Laboratory Findings 127
8.4.7. Electrocardiograms (ECGs) 141
8.4.8. Immunogenicity 142
8.5. Analysis of Submission-Specific Safety Issues 142

8.5.1. Adjudicated Clinical Endpoint Events 143
8.5.2. Hypersensitivity Events and Injection Site Reactions 143
8.5.3. Neurologic Development and Cognition 144
8.6. Safety Analyses by Demographic Subgroups 150
8.7. Specific Safety Studies/Clinical Trials 155
8.8. Additional Safety Explorations 159
8.8.1. Human Carcinogenicity or Tumor Development 159
8.8.2. Human Reproduction and Pregnancy 159
8.8.3. Pediatrics and Assessment of Effects on Growth 159
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound 164
8.8.5. 120-Day Safety Update 164
8.9. Safety in the Postmarket Setting 166
8.9.1. Safety Concerns Identified Through Postmarket Experience 166
8.9.2. Expectations on Safety in the Postmarket Setting 166
8.9.3. Additional Safety Issues From Other Disciplines 166
8.10. Integrated Assessment of Safety 166

9. Advisory Committee Meeting and Other External Consultations 168

10. Labeling Recommendations 168
10.1. Prescription Drug Labeling 168

11. Risk Evaluation and Mitigation Strategies (REMS) 171

12. Postmarketing Requirements and Commitments 171

13. Appendices 171
13.1. References 171
13.2. Financial Disclosure 171
13.3. Standardized MedDRA Query (SMQ) for Hypersensitivity 172
13.4. Amgen MedDRA Query (AMQ) for Injection Site Reactions 181

Table of Tables

Table 1 Drugs Currently Approved in the U.S. for the Treatment of HeFH in Pediatric Patients . 27
Table 2 Drugs Currently Approved in the U.S. for the Treatment of HoFH 32
Table 3 Listing of Clinical Trials Evaluating Evolocumab in the Treatment of Pediatric Patients with HeFH or HoFH 44
Table 4 Safety Stopping Rules for CK..... 53
Table 5 Schedule of Assessments for Trial 20120123..... 54
Table 6 Subject Disposition for Trial 20120123 (All Randomized Subjects)..... 59
Table 7 Important Protocol Deviations for Trial 20120123 (All Randomized Subjects)..... 61
Table 8 Randomization Stratifications for Trial 20120123 (Full Analysis Set)..... 61
Table 9 Demographic Characteristics of the Primary Efficacy Analysis Population for Trial 20120123 62
Table 10 Baseline Disease Characteristics of the Primary Efficacy Analysis Population for Trial 20120123 64
Table 11 Percent Change in Reflexive and Calculated LDL-C from Baseline to Week 24 Trial 20120123 (Full Analysis Set) 68
Table 12 Percent Change in Reflexive LDL-C from Baseline to Week 24 Trial 20120123 (Observed Data) 70
Table 13 Secondary Efficacy Endpoints for Trial 20120123 (Full Analysis Set-HeFH) 72
Table 14 Other Efficacy Endpoints for Trial 20120123 (Full Analysis Set-HeFH)..... 73
Table 15 Schedule of Assessments for Trial 20120124..... 80
Table 16 Subject Disposition for Trial 20120124 (All Enrolled Subjects) 85
Table 17 Demographic Characteristics of the Population for Trial 20120124 87
Table 18 Baseline Disease Characteristics of the Population for Trial 20120124 89
Table 19 Absolute Change and Percent Change from Baseline in Calculated LDL-C at Weeks 12, 48, and 80 for Subjects With <5% LDLR activity in Trial 20120124..... 93
Table 20. Overall Exposure to Evolocumab in Trials 20120123 and 20120124 (Full Analysis Set) 105
Table 21 Exposure to Investigational Product in Study 20120123 (Full Analysis Set)..... 106
Table 22 Tanner Stages (Sexual Maturity Ratings) for Trial 20120123 and Trial 20120124 111
Table 23. Analyte Listing[1] for Trial 20120123..... 114
Table 24 Laboratory Testing for Trial 20120124..... 115
Table 25 Summary of Treatment-emergent Adverse Events in Trial 20120123 (FAS-Actual Treatment)..... 116
Table 26 Summary of Treatment-emergent Adverse Events in Trial 20120124 (FAS-Actual Treatment)..... 116
Table 27 Summary of TEAEs, Grade ≥3, by Maximum Severity-Toxicity in Trial 20120123 119
Table 28 Subject 12463001001 Creatine Kinase Values..... 121

Table 29 Treatment-Emergent Adverse Events Reported by >1% of Patients in the Evolocumab Group by Preferred Term (where EvoMab>PBO) in Trial 20120123 (Full Analysis Set - Actual Treatment) 122
Table 30 Subject Incidence of Select Treatment-Emergent Adverse Events by System Organ Class, High Level Group Term and Preferred Term in Trial 20120123 (Full Analysis Set - Actual Treatment) 123
Table 31 Treatment-Emergent Adverse Events Reported by ≥ 4 Subjects Overall by Preferred Term in Descending Order of Frequency Trial 20120124 (Full Analysis Set - Actual Treatment) 124
Table 32 Subject Incidence of Select Treatment-Emergent Adverse Events by System Organ Class, High Level Group Term and Preferred Term in Trial 20120124 (Full Analysis Set - Actual Treatment) 125
Table 33 Changes in Glucose Parameters at Week 24 in Trial 20120123 128
Table 34 Changes in Steroid Hormones at Week 24 in Trial 20120123 129
Table 35 Missing Vitamin A Values in Trial 20120123 131
Table 36 Missing Vitamin K Values in Trial 20120123 132
Table 37 Changes in Vitamins at Week 24 in Trial 20120123 132
Table 38 Normalized Vitamin E in µmol/L by Scheduled Visit in Trial 20120123 (Full Analysis Set - Actual Treatment) 135
Table 39 Subject 12342001003 Creatine Kinase Values 137
Table 40 Subject 12342001013 Creatine Kinase Values 138
Table 41 Normalized Vitamin E in µmol/L by Scheduled Visit in Trial 20120124 (Full Analysis Set - Actual Treatment) 140
Table 42 Adverse Events of Special Interest Using Narrow SMQ and AMQ Search Strategy for Potential Hypersensitivity Events and Potential Injection Site Reaction Events in Trial 20120123 (Full Analysis Set - Actual Treatment) 143
Table 43 Summary of Change from Baseline to Week 24 in Cogstate Testing in Trial 20120123 (Full Analysis Set - Actual Treatment) 146
Table 44 Summary of Change from Baseline to Week 80 in Cogstate Testing in Trial 20120124 (Full Analysis Set - Actual Treatment) 147
Table 45 Subject Incidence of Neurological Examination Findings at Week 80 in Trial 20120124 (Full Analysis Set - Actual Treatment) 149
Table 46 Treatment-Emergent Adverse Events Reported by Subjects <14 Years of Age by Preferred Term (where the total count is ≥3) in Trial 20120123 (Full Analysis Set - Actual Treatment) 151
Table 47 Treatment-emergent Adverse Events Reported by Subjects ≥14 Years of Age by Preferred Term (where the total count is ≥ 3) in Trial 20120123 (Full Analysis Set - Actual Treatment) 151
Table 48 Treatment-Emergent Adverse Events Reported by Male and Female Subjects in the Evolocumab Treatment Group (where the total count is ≥ 3) in Trial 20120123 (Full Analysis Set - Actual Treatment) 152

Table 49 Subject Incidence of Treatment-Emergent Events by Race in Trial 20120124 where Total ≥6 Events 153
Table 50 Subject Incidence of Treatment-Emergent Events by Sex where Total ≥ 5 Events in Trial 20120124 153
Table 51 Subject Incidence of Treatment-Emergent Events by Age where Total ≥ 4 Events 154
Table 52 Change in Carotid Intima-Media Thickness from Baseline to Week 24 in Trial 20120123 157
Table 53 Tanner Staging at Baseline and Week 24 –Trial 20120123 (Full Analysis Set) 160
Table 54 Change in Growth Parameters at Week 24 –Trial 20120123 (Full Analysis Set) 161
Table 55 Summary of Subject Disposition Between the Original Pediatric Application and 120-Day Safety Update Trial 20120124 (All Enrolled Subjects) 164

Table of Figures

Figure 1 Serum Evolocumab Concentrations in Patients with HeFH, 10 to 17 Years of Age, in Trial 20120123 42
Figure 2 Trial Design and Treatment Schema for Trial 20120123 47
Figure 3 Forest Plot of Percent Change from Baseline in LDL-C at the Mean of Weeks 22 and 24 and Week 24 by Subgroups 75
Figure 4 Trial Design and Treatment Schema for Trial 20120124 78
Figure 5 Mean Percent Change from Baseline in Reflexive LDL-C by Scheduled Visit Trial 20120124 (Full Analysis Set) 98
Figure 6 Mean Percent Change from Baseline in Calculated LDL-C by Scheduled Visit and Treatment Group Trial 20120123 and 20120124 (Full Analysis Set for HeFH Subjects) 101
Figure 7 Vitamin K Levels at Week 24 in Trial 20120123 (Full Analysis Set) 133
Figure 8 BMI (kg/m^2) at Week 24 in Trial 20120123 (Full Analysis Set) 161
Figure 9 Height (cm) at Week 24 in Trial 20120123 (Full Analysis Set) 162
Figure 10 Weight (kg) at Week 24 in Trial 20120123 (Full Analysis Set) 162

Glossary

AC	advisory committee
AE	adverse event
ApoA1	apolipoprotein A-1
ApoB	apolipoprotein B
AR	adverse reaction
ASCVD	atherosclerotic cardiovascular disease
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
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
CVD	cardiovascular disease
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FH	familial hypercholesterolemia
FOURIER	Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk (FOURIER)
GCP	good clinical practice
GFR	glomerular filtration rate
GRMP	good review management practice

HAS	HoFH analysis set
HbA1c	hemoglobin A1c
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
hsCRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
iPSP	initial Pediatric Study Plan
IRB	Institutional Review Board
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
Lp(a)	lipoprotein (a)
LS	least squares
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
Non-HDL-C	non-high-density lipoprotein cholesterol
OCS	Office of Computational Science
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PCSK9	proprotein convertase subtilisin/kexin type 9
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	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome

PSUR	Periodic Safety Update report
Q2W	every 2 weeks
QM	once monthly
QTcB	Bazett's correction method for QTc
QTcF	Fridericia's correction method for QTc
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SAS	severe FH analysis set
SC	subcutaneous
SD	standard deviation
SGE	special government employee
SOC	standard of care
TAS	titration analysis set
TEAE	treatment emergent adverse event
TIA	transient ischemic attack
t_{max}	time at which C_{max} occurred
UC	ultracentrifugation
ULN	upper limit of normal
URTI	upper respiratory tract infection
US	United States
USPI	United States Prescribing Information

1. Executive Summary

1.1. Product Introduction

Repatha® (evolocumab) is a human monoclonal immunoglobulin G2 (IgG2) antibody directed at proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab binds and inhibits circulating PCSK9 from attaching to the low-density lipoprotein receptor (LDLR) on the liver cell surface. This action prevents PCSK9-mediated LDLR degradation, which leads to increases in LDLR and results in decreases in serum low-density lipoprotein cholesterol (LDL-C).

In 2015, evolocumab, 140 mg every 2 weeks or 420 mg once monthly 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. These two dosing regimens yield similar LDL-C reduction but provide patients a choice between an injection every 2 weeks or every month. Evolocumab, 420 mg once monthly, was also approved in 2015 as an adjunct to diet and other lipid lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

In 2017, evolocumab was approved in adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization based on the results of ra 27,564 person CVOT. 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 this application, the Applicant submits data to support their proposed indication for evolocumab as an adjunct to diet, alone or in combination with other lipid-lowering therapy, for the treatment of pediatric patients aged 10 years and older with HeFH to reduce LDL-C. They also provide data for pediatric patients, aged 11 years and older, with HoFH; previous HoFH trial data had included patients 13 years and older. The proposed dosing regimen for individuals with HeFH is 140 mg every 2 weeks or 420 mg once monthly, administered subcutaneously. The proposed dosing regimen for individuals with HoFH is 420 mg once monthly or, if LDL response is inadequate or on lipid apheresis, 420 mg every 2 weeks, administered subcutaneously.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Although FDA's evidentiary standard for effectiveness has been interpreted as evidence from two or more adequate and well-controlled trials, the regulations allow for flexibility and

scientific judgment in applying the standard. Given the challenge of studying a pediatric HeFH population due to the rarity of the condition, the seriousness of the underlying disease, and the strong, statistically persuasive results, a single adequate and well-controlled trial with confirmatory evidence is considered sufficient for pediatric HeFH. The single pivotal trial, 20120123: HAUSER-RCT, provides substantial evidence that evolocumab 420 mg administered subcutaneously every month, when used as an adjunct to diet and other LDL-C-lowering therapies, reduces LDL-C in pediatric patients aged 10 years and older with HeFH. The results of the trial were statistically significant after 24 weeks of treatment with evolocumab compared to placebo, and the magnitude of LDL-C lowering was clinically meaningful for this disease population. In addition, a reduction in LDL-C was observed in placebo-treated patients who entered the 80-week open-label period of this trial, representing additional evidence for evolocumab's treatment effect in this patient population. This single clinical investigation, for a new indication of an approved drug in the pediatric HeFH population, is supported by existing adequate and well-controlled trials that demonstrated the effectiveness and safety of evolocumab in adults with HeFH, approved with the original BLA in 2015.

This submission also provides data to lower the indicated age in pediatric patients with HoFH from age 13 to age 10 and older. The data constitute substantial evidence of effectiveness in this rare, serious condition with high unmet need. The primary source of data was an open-label extension trial (20120124: HAUSER-OLE) that enrolled 12 treatment-naive pediatric HoFH patients and 150 pediatric HeFH patients who previously completed trial 20120123: HAUSER-RCT. The observed treatment effect in these pediatric patients with HoFH cannot be attributed to other influences, such as spontaneous change, placebo effect, or biased observation. The approval decision for this younger age also relies on the previous finding of effectiveness for the 420 mg QM dose in the HoFH population, aged 13 years and older. This prior finding was based on a 12-week, randomized, controlled trial (Trial 20110233) that enrolled 39 adult and 10 pediatric patients, aged 13 to 17 years (7 evolocumab, 3 placebo), plus confirmatory evidence from an open-label 5-year extension trial (Trial 20110271). Trial 20110271 enrolled 106 patients with HoFH, of which 14 were aged 13 years and older. Trial 20110271 provides support (although limited, as this was open-label, uncontrolled data) on the durability of evolocumab's LDL-C lowering effect in patients with HoFH with continued treatment to at least 4 years.

Individuals with HeFH and HoFH have a similar pathogenesis – genetic mutations resulting in deficient or defective LDL receptor function, leading to elevated total cholesterol and LDL-C beginning in childhood. HeFH and HoFH are principally disorders of LDL-C metabolism. LDL-C is generally considered a surrogate of cardiovascular risk, and while a cardiovascular outcome trial in adults with primary hyperlipidemia and cardiovascular disease demonstrated CV risk reduction, a cardiovascular outcome trial in children or in the orphan population of HoFH is not feasible. Therefore, reduction of LDL-C is the therapeutically appropriate endpoint for clinical investigation in these populations.

Please see the Benefit-Risk Assessment for this reviewer's conclusions on the evolocumab

efficacy supplement application.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

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. LDL-C is a well-established surrogate of cardiovascular risk; thus, reduction of LDL-C is the central therapeutic goal for patients with FH. 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.

The pathophysiology of homozygous familial hypercholesterolemia (HoFH) derives from mutations to enzymes involved in LDL-C processing; in most cases, absent or severely reduced function of the LDLR, the primary mechanism responsible for clearance of LDL-C from blood, is responsible. Like HeFH, the treatment goal of HoFH is reduction in LDL-C to reduce CV risk. Evolocumab is currently approved for children aged 13 and older with HoFH. 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. Despite current pharmacologic and procedural interventions, many patients with HoFH remain at high risk for cardiovascular morbidity and mortality due to persistently elevated LDL-C levels. Additional effective and safe treatment options would benefit this patient population.

In support of the proposed indication "as an adjunct to diet, alone or in combination with other lipid-lowering therapy, for the treatment of pediatric patients aged 10 years and older with HeFH to reduce LDL-C," the Applicant conducted HAUSER-RCT (Trial 20120123), a 24-week, randomized, double-blind trial comparing evolocumab with placebo in 157 pediatric patients, aged 10 to <18 years, with HeFH. Following the Week 24 timepoint, 150 of 157 patients were treated with open-label evolocumab for up to an additional 80 weeks in Trial 20120124. 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; 66% of HeFH patients had genetic evidence of an FH-causing mutation. The primary endpoint in randomized, double-blind Trial 20120123 was the percent change from baseline to Week 24 in reflexive LDL-C. The primary endpoint in open-label extension Trial 20120124 was treatment emergent adverse events at Week 80 (end-of-study).

One hundred fifty-seven (157) patients with HeFH, with mean baseline LDL-C value of 184 mg/dL despite LDL-C-lowering therapies, were randomized 2:1 to evolocumab or placebo in Trial 20120123. Treatment with evolocumab 420 mg every month resulted in a least squares (LS) mean change in reflexive LDL-C from baseline to Week 24 of -44.5% in the evolocumab group and -6.2% in the placebo group with a mean treatment difference -38.3%, $p<0.0001$. At Week 80 of Trial 20120124, where all subjects were on evolocumab, the mean percent change from baseline (of parent Trial 20120123) in LDL-C was -36.3%

(n=96[1]). Secondary lipoprotein endpoints of ApoB, non-HDL-C, and total cholesterol in Trial 20120123 all demonstrated statistically significant reductions with evolocumab treatment (all p<0.0001).

In the HeFH trial, evolocumab 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, and there were no drug-related serious adverse events or adverse events leading to drug discontinuation. There were no instances of very low LDL-C (<25 mg/dL), new onset diabetes mellitus, anti-evolocumab antibodies, Hy's law, or serious allergic events in Studies 20120123 or 20120124. 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 evolocumab, compared to placebo, and evolocumab was well-tolerated.

Evolocumab is currently approved for children aged 13 and older with HoFH. The efficacy and safety of evolocumab for children aged 10 to <13 years was evaluated in a single, 80-week, open-label extension trial in pediatric patients with FH aged 10 years and older on optimized standard of care lipid-lowering therapy (Trial 20120124). Patients with either a genetic or clinical diagnosis of HoFH could be enrolled; all HoFH patients had genetic evidence of an FH-causing mutation. As noted previously, the primary endpoint in open-label extension Trial 20120124 was treatment emergent adverse events at Week 80 (end-of-study). The secondary endpoints included percent change from baseline to Week 80 in LDL-C and other lipid parameters (non-HDL-C, Apo B, total cholesterol/HDL-C ratio, ApoB/apolipoprotein A1 [ApoA1] ratio).

Twelve patients with HoFH, with mean and median baseline LDL-C values of 426 mg/dL and 398 mg/dL, respectively, despite LDL-C lowering therapies, were enrolled and received evolocumab. One patient discontinued treatment (subject request, discontinued after 28 weeks) during the 80-week treatment period. Treatment with evolocumab 420 mg every month resulted in a median percent change from baseline in LDL-C of -14.3% at Week 80; however, median LDL-C values remained high (309 mg/dL).

In the HoFH trial, evolocumab was generally 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, no patients had drug-related SAEs, and no patients discontinued during the open-label period because of adverse events.

[1] Not all subjects had reached Week 80 at the time of the submission of this supplement. Given the reassuring safety and efficacy data provided by the FOURIER trial (NCT01764633) in adults, FDA allowed submission of the supplemental application prior to the completion of Trial 20120124. The submission had to include 52 weeks of data (24 weeks from Part A and 28 weeks from Part B) to support a new indication in pediatric patients with HeFH.

In summary, patients with HoFH on background LDL-lowering therapy demonstrated a modest reduction in LDL-C with evolocumab compared to baseline, and the therapy was well-tolerated. Additional evidence to support lowering the HoFH indication age from 13 to 10 years in this single open-label extension trial is provided by a 12-week placebo-controlled trial and an open-label 5-year extension trial in adults and pediatric patients with HoFH. In addition, clinical trial 20120123 has established the effectiveness of evolocumab for pediatric patients, aged 10 years and older, with HeFH, a closely related genetic disorder of dysfunctional LDL clearance.

The safety profile of the 420 mg monthly dosing regimen in pediatric patients aged 10 years and older with FH in Trial 20120123 and Trial 20120124 was consistent with the safety data from adult clinical trials using the 420 mg QM or 140 mg Q2W dosing regimens. The safety data for these two studies in children does not suggest an increased risk or new safety findings in the pediatric population.

All review divisions support approval of this efficacy supplement.

The favorable benefit:risk profile of evolocumab supports the use of evolocumab in addition to statin ± ezetimibe therapy in pediatric patients with HeFH and HoFH to lower LDL-C levels and further reduce cardiovascular risk. Repatha should be approved for use as an adjunct to other LDL-C-lowering therapies for the treatment of pediatric patients aged 10 years and older with familial hypercholesterolemia to reduce LDL-C.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	**HeFH** • 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	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, unlike HoFH, typically respond well to statins and PCSK9 inhibitors, and therefore, can attenuate development of atherosclerosis and CVD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	artery disease) or through genetic testing. • LDL-C reduction with statins and PCSK9 inhibitors in adults is associated with improved CV outcomes in HeFH and non-familial hypercholesterolemia. ○ Meta-analysis of statin trials reported a 22% reduction in 5-year incidence of major vascular events per ~40 mg/dL (1 mmol/L) absolute reduction in LDL-C.[2] ○ 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.[3,4] ○ A CV outcome trial in adults with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering.[5] **HoFH** • Rare genetic disorder (1 in 160,000 to 1 in 1,000,000); estimated 330-2000 affected individuals in the U.S. • Absent or defective LDL receptor function results in extremely high levels of LDL-C, leading to very high risk for early and severe cardiovascular disease. • Persistent hyperlipidemia >400-500 mg/dL beginning in childhood. • Without treatment, clinical manifestations present before adulthood,	HoFH is a rare genetic condition that results in persistent severe hyperlipidemia, premature cardiovascular disease, and premature death. Patients with HoFH are treated with lipid-lowering therapies with the goal of reducing CV risk. However, patients with HoFH respond poorly to traditional lipid-lowering therapies as these treatments typically require a functional LDL-C receptor.

[2] Baigent, et al. Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170000 participants in 26 randomised trials. Lancet 2010;376:1670-1681.
[3] Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018; 379: 2097-107.
[4] Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22
[5] Cannon, CP, Blazing, MA, Giugliano, RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387–2397.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	including xanthomata, corneal arcus, atherosclerotic disease, and cardiovascular death. • Patients with HoFH are treated with aggressive lipid-lowering therapies starting in childhood to reduce CV risk, primarily based on extrapolation of evidence from LDL-C reduction in primary hyperlipidemia. Unknown how much this can be extrapolated to the extreme levels of LDL-C that characterize individuals with HoFH. • Patients with HoFH are typically unable to achieve LDL-C goals and respond poorly to many approved lipid-lowering therapies, since most therapies target the LDL-C receptor.	
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); no indication, data in Section 8.4 of PI in children 10 years and older (with simvastatin coadministration) • Colesevelam (-13% LDL-C reduction in HeFH) **Treatment options for pediatric patients with HoFH** • Statins (-14% to -30% LDL-C reduction in HoFH) • Ezetimibe (-21% LDL-C reduction in HoFH) • Evolocumab (-31% LDL-C reduction in HoFH); approved for ≥ 13 years • Evinacumab (-49% LDL-C reduction in HoFH); an ANGPTL3 inhibitor, administered as IV infusion every 4 weeks, approved for ≥ 12 years • Apheresis: limited availability, high patient burden and cost	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 ezetimibe, and colesevelam. HoFH: Currently approved lipid-lowering therapies, whether approved for HoFH or used off-label, do not adequately meet the need for LDL-C reduction in many patients with HoFH.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary efficacy endpoint in both populations was reduction in LDL-C, an accepted surrogate for cardiovascular risk. **HeFH** • 157 patients with genetic or clinical diagnosis of HeFH, with mean baseline LDL-C values of 184 mg/dL despite LDL-lowering therapy (99% on statin [17%, 62%, and 20% on high-, moderate-, or low-intensity statin, respectively]; 13% on ezetimibe), were randomized 2:1 to evolocumab 420 mg Q2W or placebo for 24 weeks. • After 24 weeks of treatment, the least squares (LS) mean treatment difference was -38.3% (95% CI -45.5 to -31.1), p<0.0001. Patients treated with evolocumab had a 44.5% reduction in LDL-C compared to a 6.2% reduction in LDL-C for patients treated with placebo. Mean absolute reflexive LDL-C values at Week 24 were 104 mg/dL in the evolocumab group and 172 mg/dL in the placebo group. • Statistically significant reductions in secondary endpoints: Treatment difference for ApoB (-32.5%), non-HDL-C (-35.0%), and total cholesterol (-26.8%) with evolocumab treatment compared to placebo treatment at Week 24 (all p<0.0001). • Patients treated with placebo who crossed over to open-label evolocumab treatment demonstrated an average 46% reduction in LDL-C from baseline after 12 weeks of treatment. **HoFH** • In patients with HoFH who took evolocumab as add-on to background lipid-lowering therapy (high-intensity statin, ezetimibe),	The submitted data provide substantial evidence of evolocumab's effectiveness in reducing LDL-C in pediatric patients with HeFH on background LDL-lowering therapy. The submitted data demonstrate that the treatment of pediatric patients with HoFH with evolocumab, in addition to background LDL-lowering therapy, led to a reduction in LDL-C; however, average LDL-C values remained high and individual treatment response may be variable.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	evolocumab lowered LDL-C by 14% at 80 weeks (open-label). • Evolocumab also lowered ApoB, non-HDL-C, and TC. • The effect of evolocumab on cardiovascular morbidity and mortality in a pediatric population with FH has not been assessed.	
Risk and Risk Management	• In the double-blind treatment period, the most frequently reported adverse events in the evolocumab group and greater than in placebo include: nasopharyngitis (11.5% evolocumab vs. 11.3% placebo), headache (10.6% evolocumab vs. 1.9% placebo), oropharyngeal pain (6.7% evolocumab vs. 0% placebo), upper respiratory tract infection (5.8% evolocumab vs. 1.9% placebo), and influenza (5.8% evolocumab vs. 3.8% placebo). • No patients died during the trial. One patient with HeFH discontinued during the placebo-controlled period because of a nonserious adverse event of arthropathy (of toes). This event improved but did not resolve with study drug discontinuation after 136 days. • No patients developed treatment emergent anti-drug antibodies (ADA). • Although the data were limited by incomplete collection of samples in all subjects, there does not appear to be an adverse effect of evolocumab on steroid hormone levels or on levels of Vitamin A, D, E, and K. • There was no signal of adverse effects in growth and development, cognition, or neurologic function with the use of evolocumab in this trial.	Potential risks of evolocumab 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, influenza and influenza-like illness, and injection site reactions. Risks associated with evolocumab are clinically manageable and can be adequately addressed through labeling.

1.4. Patient Experience Data

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

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[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 patient/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 patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	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 LDLR function, have elevated total cholesterol and LDL-C beginning in childhood and an increased risk of premature ASCVD.[6] 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.[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] 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. Diagnosis is either by phenotypic criteria (an elevated LDL-C level along with a family history of elevated LDL-C or premature coronary artery disease) or through genetic testing or cascade screening of families using a combined phenotypic and genotypic strategy. Untreated LDL-C levels in individuals with HeFH are significantly elevated compared to those without FH, and these individuals are at increased risk for CVD. Individuals with HeFH, unlike HoFH, typically respond well to statins and, therefore, can attenuate development of atherosclerosis and prevent CHD.[10] 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.[11] Identifying FH early in childhood allows for interventions to reduce LDL-C to start early in life and has a larger

[6] Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers 2017;3:17093-17093.
[7] Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. J Clin Invest. 2003;111:1795-1803.
[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 patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. Circulation 2020;141:1742-1759.
[10] 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.
[11] 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.

impact on reducing the increased risk for CVD.[12,13] Despite available therapies, guideline-recommended LDL cholesterol levels are not achieved in many pediatric patients with familial hypercholesterolemia.[14,15]

Homozygous Familial Hypercholesterolemia (HoFH)

HoFH is a rare genetic disorder that causes impaired clearing of LDL-C from the plasma and is characterized by extremely elevated LDL-C levels and accelerated atherosclerosis. The US prevalence of HoFH has long been estimated in the literature as ~1 in 1,000,000 persons,[16] but recent estimates, based on experience in other countries that have employed genetic screening of unselected populations, have suggested that HoFH may affect as many as 1 in 160,000 to 1 in 300,000 individuals.[17]

HoFH is caused by, in greater than 90% of the cases, mutations in which both LDL receptor (LDLR) alleles are defective. Mutations in other genes, such as gain of function mutations in proprotein convertase subtilisin/kexin type 9 (PCSK9), which regulates expression of the LDLR; APOB, which encodes apolipoprotein B-100; or LDLRAP1, affecting LDL receptor adaptor protein-1 (LDLRAP1) encoding, may cause a similar phenotype with varying severity.[18] Many individuals with HoFH may be compound heterozygotes with different mutations on each of the LDL receptor alleles.[19]

When patients with HoFH initially present for medical attention with a classic clinical phenotype, untreated individuals typically have very high concentrations of LDL-C, often in the

[12] 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.
[13] 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.
[14] 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.
[15] 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.
[16] Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial Hypercholesterolemias: Prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipid 2011; 5:S9-S17
[17] Cuchel M, Bruckert E, Ginsberg HN, et al; for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. ePub ahead of print, 22 Jul 2014.
[18] Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 223(2), 262–268 (2012).
[19] Goldstein J, Hobbs H, Brown, M. 2001. Familial hypercholesterolemia. In The metabolic and molecular bases of inherited disease. C. Scriver, A. Beaudet, W. Sly, and D. Valle, editors. McGraw-Hill. New York, New York, USA. 2863–2913.

range of 650 to 1000 mg/dL, cutaneous and tendinous xanthomata, corneal arcus, and premature coronary artery disease and aortic stenosis.[20] HoFH may be diagnosed by clinical criteria or confirmed via genetic testing. At academic centers, HoFH patients are often characterized by their degree of residual LDLR activity using ex vivo assays. Patients who are LDLR-negative (<2% of LDL receptor function in cultured fibroblasts) tend to have higher levels of LDL-C and a worse prognosis than those who are LDLR-defective (2-25% residual LDLR activity). Untreated LDLR-negative patients rarely survive beyond the second decade of life. Those who are LDLR-defective have a better prognosis, but still often develop clinically significant atherosclerotic vascular disease by the age of 30 years without treatment.[21]

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

2.2. Analysis of Current Treatment Options

Heterozygous Familial Hypercholesterolemia (HeFH)

US and European Union (EU) guidelines recommend pharmacologic treatment for pediatric patients ≥8 years of age with elevated LDL-C. US pediatric guidelines[22,23] recommend considering pharmacologic intervention after initial treatment with lifestyle modification has failed in patients ≥8 years of age with LDL-C that is:

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

[20] Goldstein AL, Brown MS. Molecular Medicine. The cholesterol quartet. Science. 2001;292(5520):1310-2.
[21] Raal FJ, Santos RD, Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment, Atherosclerosis 2012; 223: 262-68.
[22] Daniels SR, Greer FR. Committee on Nutrition. Lipid screening and cardiovascular health in childhood. Pediatrics. 2008;122:198-208.
[23] McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and pediatrics: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007;115:1948-1967.

Similarly, treatment guidelines from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS)[24] recommend starting a heart-healthy diet early in life and consideration of statin treatment at 6–10 years of age. The goal in children >10 years of age is an LDL-C <135 mg/dL and at younger ages a ≥50% reduction of LDL-C.

Statins are the standard of care for the treatment of HeFH in children and adolescents and have been shown to reduce LDL-C from 20 to 50% in pediatric patients and to reduce the risk of cardiovascular events in adults.

Non-statin treatment options, including ezetimibe and bile acid-binding resins (colesevelam), reduce LDL-C approximately 15%, in addition to background statin therapy.

Available therapies for the treatment of HeFH in pediatric patients are listed in the table below along with estimates of the treatment effect on LDL-C.

[24] 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

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	Reduce total-C, LDL-C, and ApoB in boys and postmenarchal girls, 10 to 17 years of age with HeFH after failing an adequate trial of diet therapy and: a. LDL-C ≥190 mg/dL or b. LDL-C ≥160 mg/dL and: • positive family hx of premature CVD or • ≥ 2 CVD risk factors in patient.	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	175 patients (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	Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events Adjunctive therapy to diet to reduce elevated total-C, LDL-C, ApoB, TG and increase HDL-C in patients with primary hyperlipidemia (HeFH) and mixed Dyslipidemia Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
Pravastatin (Pravachol) NDA 19898	Treat patients ≥ 8 years with HeFH after failing an adequate trial of diet therapy and: a. LDL-C ≥190 mg/dL or b. LDL-C ≥160 mg/dL and: • positive family hx	1991	20, 40 and 80 mg tablet; PO once daily Rec. dose in 8-13 yrs is 20mg; 14-18 yrs is 40 mg	214 patients (8-18 years); 65 on prava 20 mg; 41 on prava 40mg; 108 on Pbo; LDL-C change from baseline: -26% (prava 20 mg); -21% (prava 40 mg) vs -2% (pbo)	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of MI, revascularization, and cardiovascular mortality in hypercholesterolemic patients without clinically evident CHD Reduce the risk of total mortality by reducing coronary death, MI, revascularization, stroke/TIA, and the progression of coronary atherosclerosis in patients with clinically evident CHD Adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, and TG levels and to increase HDL-C in

	of premature CVD or • ≥ 2 CVD risk factors are present in the patient.					patients with primary hypercholesterolemia and mixed dyslipidemia Reduce elevated serum TG levels in patients with hypertriglyceridemia Treat patients with primary dysbetalipoproteinemia who are not responding to diet
Fluvastatin (Lescol, Lescol XL) NDA 20261, 21192	Reduce TC, LDL-C, and ApoB levels in boys and postmenarchal girls, 10 to 16 years of age, with HeFH after failing an adequate trial of diet therapy and: a. LDL-C ≥190 mg/dL or b. LDL-C ≥160 mg/dL and: • positive family hx of premature CVD or • ≥ 2 CVD risk factors are present in the patient.	1993	20, 40 and 80 mg tablet; PO once daily	85 patients (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 revascularization procedures in patients with clinically evident CHD Slow the progression of atherosclerosis in patients with CHD Adjunctive therapy to diet to reduce elevated TC, LDL-C, ApoB, and TG and increase HDL-C in adult patients with primary hyperlipidemia and mixed dyslipidemia
Atorvastatin (Lipitor) NDA 20702	Reduce total-C, LDL-C, and ApoB levels in patients, 10 to 17 years of age, with HeFH after failing an	1996	Tablets: 10, 20, 40, and 80 mg PO once daily Rec. dose in	187 patients (10 to 17 years); atorva 10 to 20 mg/day (N=140) and Pbo (N=47) LDL-C change from	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors

	adequate trial of diet therapy and: a. LDL-C ≥190 mg/dL or b. LDL-C ≥160 mg/dL and: • positive family hx of premature CVD or • ≥ 2 CVD risk factors are present in the patient.		10-17 yrs is 10-20mg;	baseline: -40% (atorva) vs 0% (pbo)		Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD Adjunct therapy to diet to reduce elevated total-C, LDL-C, ApoB, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (HeFH and nonfamilial) and mixed dyslipidemia Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia Reduce total-C and LDL-C in patients with HoFH as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable
Rosuvastatin (Crestor) NDA 21366	Pediatric patients 8 to 17 years of age with HeFH to reduce total-C, LDLC and ApoB after failing an adequate trial of diet therapy and: a. LDL-C ≥190 mg/dL or b. LDL-C ≥160 mg/dL and: • positive family hx of premature CVD or • ≥ 2 CVD risk factors are present in the patient.	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 patients (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	Adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDLC in patients with primary hyperlipidemia and mixed dyslipidemia Patients with hypertriglyceridemia Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) Reduce LDL-C, Total-C, and ApoB in patients ages 7 to adult with HoFH, either alone or with other lipid-lowering treatments (e.g., LDL apheresis). Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C Risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors
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
Simvastatin/ ezetimibe (Vytorin) NDA 21687	No indication. Study summarized in Section 8.4 Pediatric Use	2004	Tablets (ezetimibe mg/simvastat in mg): 10/10, 10/20, 10/40, 10/80; PO once daily	126 patients (10-17 years) on simva*/ezetimibe vs 122 patients 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 patients with primary (HeFH and non-familial) hyperlipidemia or mixed hyperlipidemia Reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.
Source: Individual drug prescribing information ApoB=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; HeFH=heterozygous familial hypercholesterolemia; HoFH= homozygous familial hypercholesterolemia; IV=intravenous; LDL-C=low-density lipoprotein cholesterol; Pbo=placebo; PO=by mouth; SC= subcutaneous; TG=triglycerides; total-C=total cholesterol (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)						

Homozygous Familial Hypercholesterolemia (HoFH)

Treatment of HoFH typically involves lipid-modifying medical therapy as well as extracorporeal removal of plasma LDL via LDL apheresis, typically once every 1-2 weeks. Since HoFH is a condition caused by either absent or deficient LDL receptor function resulting in reduced LDL-C clearance from plasma, therapies such as PCSK9 inhibitors and statins, which do not improve the function of individual LDL receptors but rather upregulate native (dysfunctional) LDL receptors, are not particularly effective. Evinacumab, approved in 2021, is a monoclonal antibody that inhibits angiopoietin-like 3 (ANGPTL3), an enzyme involved in lipid metabolism. Inhibition of ANGPTL3 allows enhanced lipoprotein lipase (LPL) activity leading to increased VLDL processing and a reduction in LDL-C, independent of the LDL-C receptor. Evinacumab, approved for patients 12 years and older, lowered LDL-C by 49% compared to placebo in patients with HoFH on maximally-tolerated lipid lowering therapy (defined as statin, ezetimibe, and PCSK9 inhibitor). LDL apheresis is FDA approved and indicated if the LDL-C is: >500 mg/dl in patients with homozygous FH, >300 mg/dl in patients without CAD, or >200 mg/dl in patients with CAD despite 6 months of treatment with maximal drug and dietary therapy. The reduction in LDL-C with apheresis is transient, as LDL cholesterol begins to reaccumulate after each session. While LDL apheresis significantly lowers LDL-C (50% time averaged) and is considered the standard of care for patients with HoFH, the limitations include limited availability, high cost, procedure duration, and the need to maintain adequate vascular access.[25]

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

Statins are considered first line therapy for patients with HoFH. Available therapies for HoFH are listed in the table below along with estimates of the treatment effect on LDL-C. Drugs that do not have any data in pediatric patients, for any hyperlipidemia condition, are denoted by the symbol †.

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

Table 2 Drugs Currently Approved in the U.S. for the Treatment of HoFH

Product Name	Relevant Indication	Year of 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	Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.	1991	5, 10, 20, 40 and 80 mg tablets, PO once daily	12 patients (15-39 years); simva 40 or 80mg/day; LDL-C reduction: -14% to -30%.	Skeletal muscle effects (myopathy/ rhabdomyolysis) with increased risk with 80 mg dose, liver enzyme abnormalities, hypersensitivity	Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events Adjunctive therapy to diet to reduce elevated total-C, LDL-C, ApoB, TG and increase HDL-C in patients with primary hyperlipidemia (HeFH) and mixed Dyslipidemia Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia Reduce elevated total-C, LDLC, and ApoB in boys and postmenarchal girls, 10 to 17 years of age with HeFH after failing an adequate trial of diet therapy
Atorvastatin (Lipitor) NDA 20702	Reduce total-C and LDL-C in patients with HoFH as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable	1996	Tablets: 10, 20, 40, and 80 mg PO once daily	29 patients (6 to 37 years); atorva 20 to 80 mg/day; LDL-C reduction: -18%	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD

						Adjunct therapy to diet to reduce elevated total-C, LDL-C, ApoB, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (HeFH and nonfamilial) and mixed dyslipidemia Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia Reduce elevated total-C, LDLC, and ApoB levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH after failing an adequate trial of diet therapy
Rosuvastatin (Crestor) NDA 21366	reduce LDL-C, Total-C, and ApoB in patients ages 7 to adult with HoFH, either alone or with other lipid-lowering treatments (e.g., LDL apheresis).	2003	5, 10, 20 and 40 tablets, PO once daily	40 patients (8-63 years) on rosuva 20 to 40 mg Mean LDL-C reduction: -22%. Pediatric study (N=14): Ages 7 to 15 years; -22%.	Skeletal muscle effects (myopathy/ rhabdomyolysis), liver enzyme abnormalities, hypersensitivity	Adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDLC in patients with primary hyperlipidemia and mixed dyslipidemia Patients with hypertriglyceridemia Patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) Slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C Pediatric patients 8 to 17 years of age with HeFH to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy Risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors
Available therapies for HoFH, *as add-on to statin*						
Ezetimibe (Zetia) Intestinal cholesterol/	Combination of ZETIA and atorvastatin or simvastatin is	2002	10 mg tablet PO once daily	LDL-C reduction: -21% at Wk 12 (N=50)	Elevations in liver enzymes, myopathy/ rhabdomyolysis	Reduce elevated total-C, LDLC, ApoB, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate

phytosterol absorption inhibitor NDA 21445	indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.					Adjunct to diet to reduce elevated total-C, LDL-C, ApoB, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with a statin Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)
Simvastatin/ ezetimibe (Vytorin) NDA 21687	Reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.	2004	Tablets (ezetimibe mg/simvastat in mg): 10/10, 10/20, 10/40, 10/80; PO once daily	LDL-C reduction: 10/40 and 10/80 pooled, n=14), -23% to -29%	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 patients with primary (HeFH and non-familial) hyperlipidemia or mixed hyperlipidemia
Lomitapide (Juxtapid)†	adjunct to diet and lipid-lowering treatments, including LDL apheresis, to reduce LDL-C, ApoB, TC, and non-HDL-C in patients with HoFH	2012	5, 10, 20, 30, 40 and 60 mg capsules, PO once daily	LDL-C reduction: At Wk 26 (N=29): Mean: -40%; Median: -50% (Single arm trial)	Hepatotoxicity with elevations in transaminases and increases in hepatic fat (hepatic steatosis); embryo-fetal toxicity	
Mipomersen (Kynamro)*	adjunct to lipid-lowering meds and diet to reduce	2013	200 mg once weekly as a subcutaneous	LDL-C reduction: At Wk 28 (N=51): Mean: -21%; Median: -19%	Hepatotoxicity with elevations in transaminases and	

	LDL-C, ApoB, TC, and non-HDL-C in patients with HoFH		injection		increases in hepatic fat (hepatic steatosis); injection site reaction; flu-like symptoms	
Atorvastatin/ ezetimibe (Liptruzet) *† NDA 200153	Reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.	2013	Tablets (ezetimibe mg/atorvastatin mg): 10/10, 10/20, 10/40, 10/80 PO once daily	LDL-C reduction: LIPTRUZET (10/40 and 10/80 pooled, n=24); -19%	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 patients with primary (HeFH and non-familial) hyperlipidemia or mixed Hyperlipidemia
Evolocumab (Repatha) PCSK9 inhibitor antibody BLA 125522	As an adjunct to other LDL-lowering therapies in patients with HoFH, to reduce LDL-C	2015	420 mg SC injection once monthly	LDL-C reduction: At Wk 12 (N=49) Mean -31% (placebo subtracted in combination with statins, ezetimibe)	Hypersensitivity reactions (angioedema, rash, urticaria)	In adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization Adjunct to diet, alone or in combination with other LDL-C-lowering therapies, in adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
Alirocumab (Praluent) † PCSK9 inhibitor antibody BLA 125559	As an adjunct to other LDL-C-lowering therapies in adult patients with HoFH to reduce LDL-C.	2015	150 mg SC injection every 2 weeks	LDL-C reduction: At Wk 12 (N=49) Mean -36% (placebo subtracted in combination with statins, ezetimibe, lomitapide)	Hypersensitivity reactions (angioedema, vasculitis, pruritus)	To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease Adjunct to diet, alone or in combination with other LDL-C-lowering therapies, in adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
Evinacumab (Evkeeza) Monoclonal antibody ANGPTL3 inhibitor	Adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged 12	2021	15 mg/kg every 4 weeks (Q4W) via IV infusion	LDL-C reduction: At Wk 24 (N=65) -49% (placebo subtracted in combination with other LLT – statins, ezetimibe, PCSK9	Hypersensitivity reactions (anaphylaxis), embryo-fetal toxicity	

BLA 761181	years and older, with HoFH			inhibitors, lomitapide apheresis		
LDL apheresis	To acutely remove LDL-C from the plasma of the following high risk patient population for whom diet has been ineffective or not tolerated: Group A – functional hypercholesterolemic homozygotes with LDL-C >500 mg/dL		2-5 hours Q1-2W	60-70% acutely; Approximately -50% time averaged	Thrombocytopenia infection, hypersensitivity, transient decrease in serum protein and albumin, hypotension, fainting, anemia, hemolysis	

Source: Individual drug prescribing information
ApoB=apolipoprotein B; HDL-C=high-density lipoprotein cholesterol; HeFH=heterozygous familial hypercholesterolemia; HoFH= homozygous familial hypercholesterolemia; IV=intravenous; LDL-C=low-density lipoprotein cholesterol; Pbo=placebo; PO=by mouth; SC= subcutaneous; TG=triglycerides; total-C=total cholesterol; QW=every week
*Marketing discontinued
†Drugs that do not have any data in pediatric patients, for any hyperlipidemia condition
(http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

In August 2015, evolocumab, 140 mg every 2 weeks or 420 mg once monthly subcutaneous (SC) dose, was approved in the US as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C. The initial marketing application for LDL-C lowering included approximately 1800 evolocumab-dosed subjects on study for at least 12 months and 600 evolocumab-dosed subjects on study for 2 years or more.

Evolocumab was also approved as an adjunct to diet and other lipid lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C in August 2015. A 420 mg Q2W dosing regimen for HoFH was approved in February 2021.

In 2017, based on the results of the FOURIER CVOT with over 13,700 subjects exposed to evolocumab, Repatha® was approved in adults with established cardiovascular disease to reduce the risk of myocardial infarction, stroke, and coronary revascularization. The original indication for the treatment of hyperlipidemia in adults with HeFH or CVD 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 based on favorable results in the CVOT.

Pediatric trials 20120123 and 20120124 were included in the US initial Pediatric Study Plan (iPSP) issued on September 16, 2014 and were included as postmarketing requirements (PMR) in the original Biologics License Application (BLA) approval letter issued by FDA on August 27, 2015. These trials evaluate evolocumab in children with HeFH and HoFH, 10 years and older.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pediatric Postmarketing Requirements

The August 27, 2015, approval for evolocumab contained the following Pediatric Postmarketing Requirement (PMR):

> 2946-1 Conduct an efficacy and safety study evaluating Repatha (evolocumab) in patients with heterozygous familial hypercholesterolemia (HeFH) ages 10 years to less

than 18 years. The study will be a randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety study (Part A) followed by an 18-month open-label extension in patients 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C ≥ 130 mg/dL (Part B).

Trial 20120123, entitled "Double-blind, Randomized, Multicenter, Placebo-Controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-Cholesterol (LDL-C) Reduction, as Add-On to Diet and Lipid-Lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH)" corresponds to Part A of the above PMR. The protocol was initially submitted December 12, 2014.

Trial 20120124, entitled "Open-label, Single-Arm, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-On to Diet and Lipid Lowering Therapy, in Pediatric Subjects From 10 to 17 Years of Age With Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH) corresponds to Part B of the above PMR. The protocol was initially submitted June 5, 2015.

<u>Excerpts of Pre-Submission Regulatory History</u>

Comments sent to Amgen on July 24, 2015 and Amgen responses dated September 21, 2015:

1. FDA clinical comment: We recommend revising the protocols to add an assessment of fat-soluble vitamins (A, D, E and K).
   Amgen: Amgen agrees to add assessments of vitamins A, D, E and K at day 1 and EOS (week 24) in Protocol 20120123, and at day 1 and EOS (week 80) in Protocol 20120124.

2. FDA clinical comment: We recommend revising the protocols to assess for the new onset of diabetes mellitus (through laboratory data, adverse events and initiation of anti-diabetic therapies) as was done in the adult population in BLA 125522 through the 3-component and 4-component analysis for new onset diabetes.
   Amgen: Amgen agrees to perform an analysis to assess for new-onset diabetes using the 4-component definition employed in the adult population in BLA 125522 and described in Amgen's response to the February 9, 2015 Question 9 that was submitted to the Agency on April 24, 2015 (SN 0037). The 4-component definition consists of the following:
   - 2 fasting blood glucose measurements ≥ 126 mg/dL
   - HbA1c ≥ 6.5%
   - diabetes adverse events, or
   - initiation of anti-diabetic medication in non-diabetic subjects who had normoglycemia, impaired fasting glucose, or both at baseline.

Since the 4-component definition includes all the components of the 3-component definition as well as HbA1c, and is consistent with the American Diabetes Association recommendations for the diagnosis of diabetes mellitus (ADA 2015), Amgen proposes that the analysis be limited to the more robust 4-component definition. Since the elements of the 4-component definition of new-onset diabetes (HbA1c, fasting glucose, diabetes medications and diabetes-related adverse events) are already specified in the protocol, no revision to the protocol is required; however, the details of this analysis will be included in the statistical analysis plan (SAP), which Amgen agrees to submit in advance of data unblinding.

3. FDA clinical comment: Please clarify if there will be additional safety monitoring by the DSMB for patients who have LDL-C values that are persistently ≤ 25 mg/dL.
   Amgen: The DMC will monitor safety in pediatric patients in Studies 20120123 and 20120124 with LDL-C ≤ 25 mg/dL. Standard safety tables will be provided to the DMC with various LDL-C cut-off levels.

On November 18, 2015, FDA advised the Applicant that the revised protocol for Trial 20120123 and the revised protocol for Trial 20120124 were acceptable.

In March 2018, FDA agreed with to a deferral extension request for the Pediatric Research Equity Act (PREA) PMR because of delays involving study participants and sites. The new dates were:

- Study Completion (Part A): June 2020 (revised)
- Study Completion (Part B): December 2021 (revised)
- Final Report Submission (Parts A and B): July 2022 (deferral extended)

In April 2020, Amgen asked if they could submit an efficacy supplement in support of a new indication in pediatric patients with HeFH, prior to completion of trial 20120124 (open-label extension). On April 8, 2020, the FDA issued a General Advice letter stating that given the reassuring safety and efficacy data provided by the FOURIER trial (NCT01764633) in adults, the Agency would allow submission of a supplemental application prior to the completion of trial 20120124. The submission should include 52 weeks of data (24 weeks from Part A and 28 weeks from Part B) to support a new indication in pediatric patients with HeFH. This duration of exposure is consistent with the data requested by FDA to support indications for HeFH in children and adolescents 10 to 17 years of age with other lipid-lowering agents. Upon the completion of trial 20120124, the applicant must submit the final study report to address the PMR.

Amgen now submits the final results from pediatric trial 20120123 and interim results from pediatric trial 20120124 to support a new indication in pediatric patients with HeFH and to support incorporating additional trial results in pediatric patients with HoFH into the label. The

final CSR for trial 20120124 will be submitted upon completion in mid-2021 to fulfill PMR 2946-1.

Amgen requests Priority Review Designation for this sBLA; however, FDA determined that the application will be reviewed under a standard review timeline as evolocumab does not appear to offer a significant improvement in the safety or effectiveness of the treatment of HeFH (i.e., it will likely be used in a minority of pediatric patients when LDL-C goals are not reached with the use of statin plus ezetimibe) and is already approved for HoFH.

3.3. Foreign Regulatory Actions and Marketing History

Evolocumab was first approved on July 17, 2015 in the European Union (EU) for the following 2 indications: hypercholesterolemia/mixed dyslipidemia and HoFH. The approved dose for the hypercholesterolemia and mixed dyslipidemia indication is 140 mg every 2 weeks or 420 mg once monthly. The approved dose for the HoFH indication is 420 mg once monthly, or in some regions or countries, 420 mg every 2 weeks.

Evolocumab was approved in the United States (US) on August 27, 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or ASCVD and as an adjunct to diet and other LDL-lowering therapies for the treatment of patients with HoFH. On December 1, 2017, evolocumab received approval in the US for the following additional indication: to reduce the risk of MI, stroke, and coronary revascularization in adults with established CVD. The approved dose for CV risk reduction is the same as that for hyperlipidemia: 140 mg every 2 weeks or 420 mg once monthly.

As of November 14, 2020, evolocumab has been approved in 77 countries. Evolocumab has not been withdrawn from marketing in any country for reasons related to safety and effectiveness.

In Europe, the evolocumab Paediatric Investigation Plan (PIP), initially agreed on May 28, 2013 prior to the original marketing authorization application (MAA), included pediatric trials 20120123 and 20120124 which are the focus of this submission.

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

4.1. Office of Scientific Investigations (OSI)

Cynthia Kleppinger, M.D. in the Division of Clinical Compliance Evaluation (DCCE) was consulted regarding the clinical site inspection of site 44144 for trials 20120123 and 20120124. The site

was chosen based on the risk rank score, number of subjects enrolled, and lack of previous inspection. As this is a non-mission critical application, DDLO is aware that the COVID-19 global pandemic has significantly limited the Office of Regulatory Affairs (ORA)'s ability to conduct on-site Good Clinical Practice (GCP) inspections. Inspections in support of applications not deemed mission critical will be prioritized to proceed when existing travel restrictions are lifted or alternative approaches to onsite inspections are established, if feasible prior to the user fee goal date.

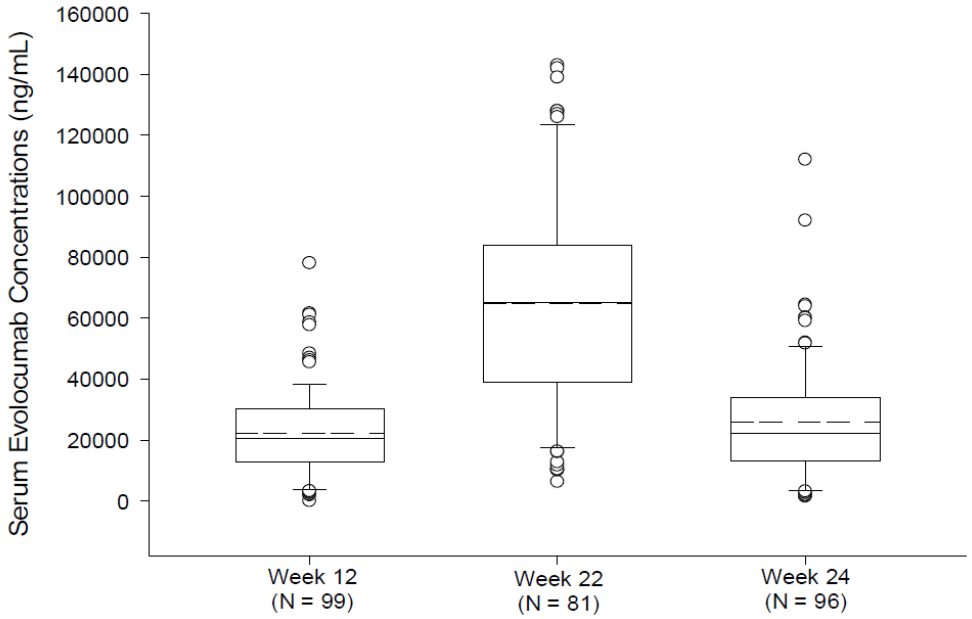
Dr. Kleppinger informed DDLO in July 2021 that, following guidelines to protect the safety and welfare of FDA employees and study staff, and with repeated evaluations of the current situation and mission-critical priorities, the planned inspection in support of BLA 125522/s029 has been cancelled (see memo in DARRTS dated July 13, 2021; Reference ID: 4825135).

4.2. Clinical Pharmacology

Patients in trial 20120123 randomized to the evolocumab group and all patients in trial 20120124 received 420 mg QM dosing with evolocumab. The Applicant reports that the pharmacokinetic data from trial 20120123 and 20120124 show that mean serum evolocumab values among pediatric patients with HeFH and HoFH were within the range of values observed in adult patients with primary hypercholesterolemia, including HeFH. The Applicant's proposed dosing regimens for pediatric patients with HeFH are the same as those currently approved for adult patients with HeFH (140 mg SC Q2W or 420 mg SC QM). The Applicant's proposed dosing regimens for pediatric patients with HoFH are the same as those currently approved for pediatric and adult patients with HoFH (420 mg SC QM and 420 mg SC Q2W).

In trial 20120123, pharmacokinetic data consisted of 405 samples from 103 subjects aged 10 to 17 years old who had at least 1 pharmacokinetic sample collected. Four pharmacokinetic samples were collected per subject; day 1, week 12, week 22 (peak) and week 24 (trough). Thirty-three (33) samples (8%) were excluded from the summary statistics; reasons cited included time deviations greater than 30% from nominal time, pre-dose samples collected after dose administration, dose reductions, and missed doses. According to the Applicant, following SC administration of 420 mg evolocumab QM, mean (SD) serum concentrations were 22.4 (14.7) mcg/mL, 64.9 (34.4) mcg/mL and 25.8 (19.2) mcg/mL over the week 12, week 22 and week 24 time points, respectively (see figure below). The FDA clinical pharmacology reviewer's analysis agrees with that of the Applicant.

Figure 1 Serum Evolocumab Concentrations in Patients with HeFH, 10 to 17 Years of Age, in Trial 20120123



Y-axis is in linear scale.
Note: Week 22=peak, Week 24=trough. Boxes display mean (dashed lines), median (solid lines), 25th (bottom) percentile), and 75th (top) percentile. Whiskers represent the 10th (bottom) and 90th (top) percentiles.
Source: CSR 20120123 Applicant's Figure 11-1

In trial 20120124, 3 pharmacokinetic samples were collected per subject on day 1, week 12, and week 80.

HeFH: Following SC administration of 420 mg evolocumab QM for subjects with HeFH, mean (SD) serum trough concentrations were 28900 (21100) ng/mL and 24000 (21600) ng/mL at week 12 and week 80, respectively.

HoFH: Following SC administration of 420 mg evolocumab QM for subjects with HoFH, median (coefficient of variation [CV]%) serum evolocumab trough concentrations were 16600 ng/mL (72%) and 9870 ng/mL (163%) at week 12 and week 80, respectively.

Anti-evolocumab antibodies were not detected post-baseline in this trial in pediatric patients treated with evolocumab.

The clinical-pharmacology review by Mohamad Kronfol, Ph.D. and Jaya Vaidyanathan, Ph.D. concludes that the data and proposed dosing in this submission are acceptable and

recommends approval of BLA125522 Supplement 29 (see review by Dr. Kronfol in DARRTS dated July 19, 2021; Reference ID: 4828187).

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 3 Listing of Clinical Trials Evaluating Evolocumab in the Treatment of Pediatric Patients with HeFH or HoFH

Trial Name/ NCT no.	Trial Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	Other Endpoints	# Enrolled/Analyzed
Controlled Studies to Support Efficacy and Safety in HeFH							
20120123 NCT 02392559	Pediatric subjects with HeFH on a stable low-fat diet and pre-existing, stable (at least 4 weeks) lipid-lowering therapy with LDL-C ≥130 mg/dL Age 10 to 17 years	Phase 3b, double-blind, randomized, PBO-controlled	PBO or EvoMab 420 mg SC QM AI/pen Randomized 2:1 EvoMab:PBO	24 weeks	Percent change from BL in LDL-C to Week 24.	• mean % change from BL to Weeks 22 and 24 in LDL-C • change from BL to Week 24 in LDL-C • % change from BL to week 24: −non-HDL-C −ApoB −TC/HDL-C ratio −ApoB/ApoA1 ratio	158/157
Uncontrolled Studies to Support Safety and Efficacy in HeFH and HoFH							
20120124 NCT 02624869	Pediatric subjects with HeFH or HoFH HeFH: completed trial 20120123 and no treatment-related SAE HoFH: genetic or clinical diagnosis, on a stable low-fat diet and stable (at least 4 weeks) lipid-lowering therapy with LDL-C ≥130 mg/dL Age 10 to 17 years	Phase 3b, open-label, long-term extension	EvoMab 420 mg SC QM AI/pen or AMD	80 weeks	Treatment emergent adverse events	• % change from BL to Week 80 in: - LDL-C - non-HDL-C - ApoB - TC/HDL-C ratio - ApoB/ApoA1 ratio • change from BL in LDL-C to Week 80	HeFH: 150/150 HoFH: 13/12
20110271[b] NCT	Pediatric and adult subjects with "severe" FH[a], previous completer or de novo	Phase 2/3, open-label, long-term extension	EvoMab 420 mg SC QM or SC Q2W (if eligible)	~5 years	Treatment emergent adverse events	• % change from BL to Week 80 in: - LDL-C - non-HDL-C	Total: 300 Severe HeFH: 194/194

Trial Name/ NCT no.	Trial Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	Other Endpoints	# Enrolled/Analyzed
01624142	Previous completer: completed a qualifying EvoMab protocol (without treatment-related SAE that led to IP discontinuation) and a diagnosis of "severe" FH De-novo: "severe" FH on stable (at least 4 weeks) background lipid-lowering therapy with LDL-C ≥100 mg/dL (with CHD or CHD risk equivalent) or ≥130 mg/dL (no CHD or CHD risk equivalent) Age 13 to 80 years		Vial and syringe, AI/pen, or AMD			- Lp(a) - ApoB - TC/HDL-C ratio - ApoB/ApoA1 ratio • response rate of subjects with 15% or greater reduction in LDL-C by scheduled visit	HoFH: 106/106 Ped HoFH: 14/14

[a] "severe" FH: Amgen's definition: diagnosis of familial hypercholesterolemia and taking pre-existing lipid-lowering therapies. Non-apheresis subjects were required to have elevated LDL-C (≥100 mg/dL for subjects with diagnosed coronary heart disease or risk equivalent, ≥130 mg/dL for subjects without diagnosed coronary heart disease or risk equivalent). There was no LDL-C entry requirement for apheresis subjects.
[b] This trial was reviewed under a Class 2 resubmission, submitted to FDA on August 31, 2020. Refer to clinical review by E. Craig in DARRTS dated February 25, 2021.
AI/pen=autoinjector/pen; AMD= automated mini-doser; ApoA1=apolipoprotein A1; ApoB= apolipoprotein B; BL=baseline; CHD=coronary heart disease; EvoMab =evolocumab; HDL-C =high-density lipoprotein cholesterol; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; hsCRP=high sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; Lp(a)= lipoprotein(a); non-HDL C= non high-density lipoprotein cholesterol; PBO=placebo; Q2W=once every 2 weeks; QM=once monthly; SC=subcutaneous; TC= total cholesterol; VLDL-C= very low density lipoprotein cholesterol; W=week.

5.2. Review Strategy

The primary focus of the clinical efficacy review is the placebo-controlled trial 20120123 in pediatric patients with HeFH and the OLE trial 20120124 in pediatric patients with HeFH and HoFH. Sections 6 and 7 of this review will present the results of the applicant's efficacy analyses with the clinical reviewer's commentary, where relevant.

Dr. Satyajit Ghosh, Office of Biometrics II, conducted an independent review of the efficacy of evolocumab. Please refer to his review for the FDA's statistical analysis of efficacy (in DARRTS dated September 9, 2021; Reference ID: 4854488). The statistical team concluded that the collective evidence from the submitted data demonstrated efficacy of evolocumab in the study population and recommend approval for the proposed indication based on findings from the submitted results.

Section 8 presents the safety review which focused on the pediatric safety data from the double-blind, randomized trial 20120123 and its open-label extension (OLE), trial 20120124. The applicant's analysis was verified and supplemented with the clinical reviewer's analysis, where applicable.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Trial 20120123, HAUSER-RCT: Double-blind, Randomized, Multicenter, Placebo-Controlled, Parallel Group Study to Characterize the Efficacy, Safety, and Tolerability of 24 Weeks of Evolocumab for Low Density Lipoprotein-Cholesterol (LDL-C) Reduction, as Add-On to Diet and Lipid-Lowering Therapy, in Pediatric Subjects 10 to 17 Years of Age with Heterozygous Familial Hypercholesterolemia (HeFH)

6.1.1. Study Design

Overview and Objective

Primary Objective: to evaluate the effect of 24 weeks of SC evolocumab compared with placebo, when added to standard of care, on percent change from baseline in LDL-C in pediatric subjects 10 to 17 years of age with HeFH.

Secondary Objectives:

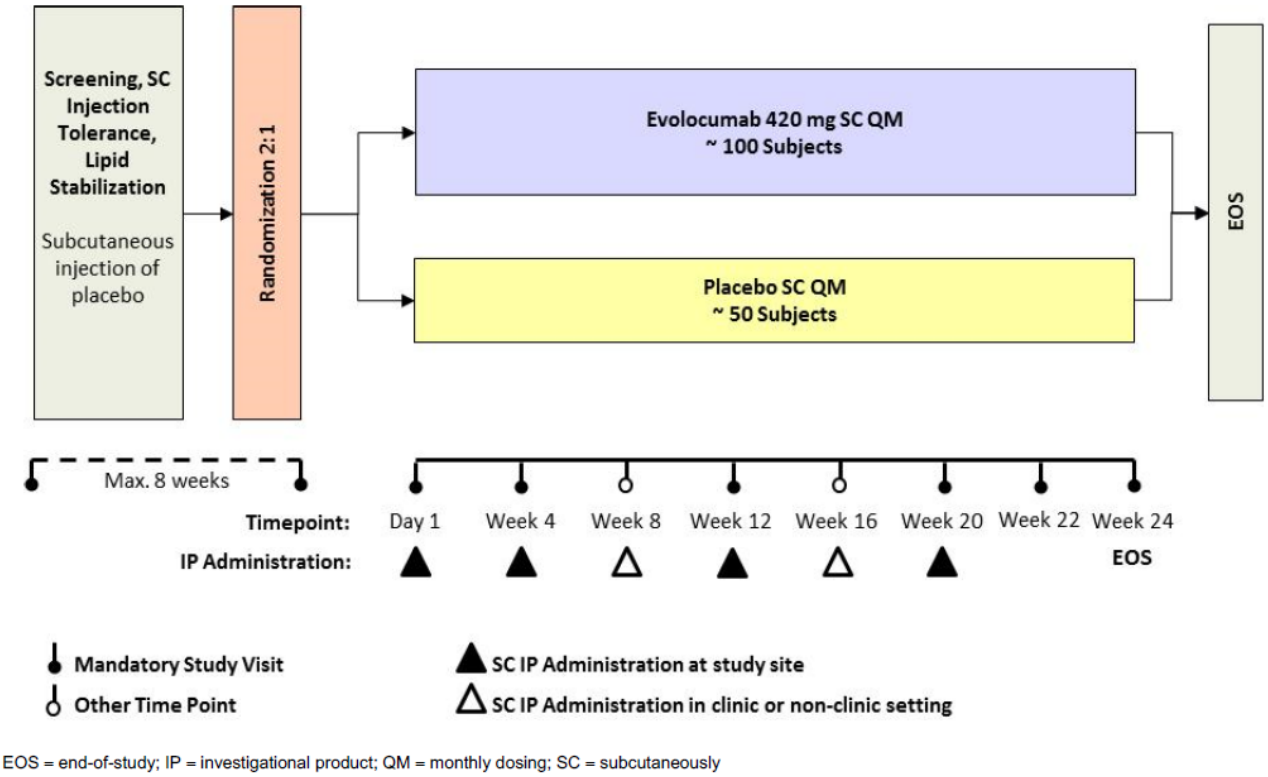
- In pediatric subjects 10 to 17 years of age with HeFH to assess the effects of SC evolocumab compared with placebo, when added to standard of care, on
    - mean percent change from baseline to Weeks 22 and 24 (time-averaged effect)

  - absolute change from baseline to Week 24 in LDL-C
  - percent change from baseline to Week 24 in non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, and ApoB/Apolipoprotein A-1 (ApoA1) ratio
- to evaluate the safety of SC evolocumab compared with placebo, when added to standard of care, in pediatric subjects 10 to 17 years of age with HeFH
- to characterize pharmacokinetic (PK) exposure

Trial Design

Trial 20120123 was a randomized, multicenter, placebo-controlled, double-blind, parallel group trial in approximately 150 (n=158) pediatric subjects, 10 to 17 years of age at time of randomization, who met the local applicable diagnostic criteria for HeFH. Subjects had to be on a low-fat diet and optimized background lipid-lowering therapy for ≥4 weeks prior to screening as determined by the subject's physician and not requiring up titration in the opinion of the investigator.

Figure 2 Trial Design and Treatment Schema for Trial 20120123



EOS = end-of-study; IP = investigational product; QM = monthly dosing; SC = subcutaneously

Source: Amgen's clin-over-peds CSR, Figure 3

Subjects received a one-time SC administration of placebo to evaluate tolerability of the SC injection via a prefilled autoinjector/pen (AI/pen) prior to randomization. Subjects were randomized in a 2:1 ratio to receive 24 weeks of evolocumab 420 mg SC QM or placebo SC QM (each delivered via 3 consecutively administered autoinjector/pens [AI/pen]). Randomization was stratified by screening LDL-C (<160 mg/dL vs. ≥160 mg/dL) and age (<14 years vs. ≥14 years). An interactive voice response system and/or interactive web response system assigned subjects to administration of investigational product.

Subjects visited the study site for assessments at Weeks 4, 12, 20, 22, and 24 (end-of-study [EOS]). Day 1 and Week 24 visits were to be scheduled at approximately the same time of day (8:00 a.m.) as several safety endpoints (hormones) have diurnal variation. Investigational product administration at Week 8 and Week 16 could be at the study site (optional visit) or at a non-clinic location (e.g., in the home) after competency with self-administration was demonstrated by the subject or caregiver/designee. Each QM administration of investigational product consisted of 3 injections of 140 mg evolocumab or placebo in 1.0 mL (administered by 3 AI/pens) for a total of 3.0 mL (placebo or 420 mg evolocumab) administered. The last administration of investigational product occurred at Week 20.

The dose of 420 mg QM was selected based on pharmacokinetic data from two studies with evolocumab that included adults and children 12 years and older (Studies 20110233 and 20110271). The results demonstrated that exposure among pediatric subjects was similar to adults of similar weight. Pharmacokinetic modeling was used to predict the dosing regimen for pediatric subjects 10 to 17 years of age; it showed that the exposure with 420 mg SC QM is expected to be within in the range observed in the evolocumab development program.

Blinding: The applicant states that evolocumab and placebo were identical in appearance and were administered via an identical AI/pen. Each AI/pen contained a 1.0 mL deliverable volume of 140 mg/mL evolocumab or 1.0 mL deliverable volume of placebo. Since some laboratory results could unblind investigators to treatment assignment to evolocumab, central laboratory results of the lipid panel; ApoA1; ApoB; Lp(a); fasting vitamins A, D, E, and K; PCSK9; and evolocumab were not available to the investigator (or study personnel) post-screening. Investigators were instructed not to perform non-protocol (i.e., local laboratory) testing of these analytes during a subject's participation from first administration of investigational product until at least 12 weeks after last investigational product administration, or the subject's end of study, whichever was later.

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

The Applicant made reasonable efforts to blind study medication from subjects and

investigators. However, if a patient wanted to unblind their treatment assignment and, for example, had an LDL-C assessment performed at a health fair, they may have been able to guess their treatment assignment based on test results.

After completion of Trial 20120123, patients were offered to participate in an extension study (Trial 20120124) in which they received open-label evolocumab for 80 weeks duration.

Key Inclusion Criteria:

- Males and females 10 to 17 years of age with a diagnosis of HeFH
    - Diagnosis of HeFH by local applicable diagnostic criteria for HeFH (i.e., criteria outlined by the Simon Broome Register Group [Scientific Steering Committee, 1991], the Dutch Lipid Clinic Network [World Health Organization, 1999], Make Early Diagnosis to Prevent Early Death (MEDPED) [Williams et al, 1993]), or by genetic testing.
- Provided informed consent or assent and parental/guardian consent
- On a low-fat diet and receiving optimized standard of care background lipid-lowering therapy, per local guidelines, including a statin at optimal dose (determined by the subject's managing physician) and not requiring uptitration (investigator determination)
- Stable (≥4 weeks prior to screening) lipid-lowering therapy
- Fasting LDL-C ≥130 mg/dL and fasting triglycerides ≤400 mg/dL by the central laboratory at screening

Reviewer Comment: There are several diagnostic tools used for identification of adult individuals with FH. These include the US MEDPED criteria, the UK Simon Broome system, and the Dutch Lipid Clinic Network criteria. The applicability of these diagnostic tools in pediatrics varies in clinical practice. The Dutch Lipid Clinic Network criteria do not have specific pediatric LDL-C thresholds, while the Simon Broome criteria have specific cut-offs for LDL-C in pediatric individuals <16 years old of 4 mmol/L (~155 mg/dL). The inclusion criteria for this program is consistent with other pediatric HeFH programs.

Key Exclusion Criteria:

- Homozygous familial hypercholesterolemia
- Type 1 diabetes, recently diagnosed (within 3 months of randomization) type 2 diabetes, poorly controlled (HbA1c >8.5%) type 2 diabetes, or newly diagnosed impaired glucose tolerance (within 3 months of randomization)
- Thyroid stimulating hormone (TSH) <lower limit of normal (LLN) or TSH >1.5x upper limit of normal (ULN) and free thyroxine (T4) levels that were outside normal range
- Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x ULN
- Creatine kinase (CK) >3x ULN

- Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction
- Received any cholesterylester transfer protein (CETP) inhibitor in the last 12 months, mipomersen or lomitapide in the last 5 months, lipid apheresis within the last 12 weeks, or if they have previously received evolocumab or any other investigational therapy to inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9)
- Enrollment in another investigational device or drug study, receive other investigational agent(s) or procedures, or be within less than 30 days since ending another investigational device or drug study
- Female subjects of childbearing potential cannot be pregnant, planning to become pregnant, breast feeding or planning to breastfeed and must be willing to use acceptable method(s) of effective contraception during treatment with IP (evolocumab or placebo) and for an additional 15 weeks after the end of treatment with IP (evolocumab or placebo).

Trial Endpoints

The primary endpoint in Trial 20120123 was the percent change from baseline to Week 24 in reflexive LDL-C.

Reflexive Approach for LDL-C
Since the Friedewald equation can return lower values (i.e., greater estimated reductions) when calculated LDL-C concentrations are <40 mg/dL or triglycerides are high, the primary analysis of LDL-C endpoints was assessed using a reflexive approach. For this method, calculated LDL-C was used unless LDL-C was <40 mg/dL or triglycerides were >400 mg/dL, in which case LDL-C by preparative ultracentrifugation (UC) was determined and utilized in the analysis.

Reviewer Comment: As LDL-C by UC is not widely available or routinely used in clinical practice, the calculated LDL-C 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.

The primary estimand was the treatment difference in mean percent change from baseline in LDL-C at Week 24 regardless of treatment adherence for pediatric subjects 10 to 17 years of age with HeFH in the full analysis set (FAS). The FAS included all randomized subjects who received at least 1 dose of investigational product and was used for both efficacy and safety analyses.

A secondary endpoint in the trial was mean percent change from baseline to Weeks 22 and 24 in LDL-C. The Applicant states that Week 22 reflects the peak and Week 24 the trough of the

QM dosing interval used in the trial and that the mean provides information about the time-averaged effect of evolocumab therapy over the entire dosing interval.

Other secondary endpoints included:

- absolute change from baseline to Week 24 in reflexive LDL-C
- percent change from baseline to Week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/apolipoprotein A1 [ApoA1] ratio
- subject incidence of treatment emergent adverse events
- safety laboratory values and vital signs at each scheduled assessment
- incidence of anti-evolocumab antibody (binding and neutralizing) formation
- serum concentration of evolocumab at each assessment

Exploratory endpoints included absolute and percent change from baseline at each scheduled assessment in LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, total cholesterol, VLDL-C, HDL-C, ApoA1, Triglycerides, Lp(a), and PCSK9.

Carotid intima-media thickness (cIMT) was measured by ultrasonography at Day 1 and Week 24/EOS. The cIMT test measured the thickness of the inner 2 layers of the carotid artery, the intima and media, and assessed for thickening over time. Lateral, anterior, and posterior measurements of the left and right common carotid arteries were assessed. Sonograms were sent to a core laboratory for analysis. The cIMT endpoint was not requested by FDA but was included by the Applicant to explore the hypothesis that additional lipid-lowering therapy may sufficiently reduce atherosclerosis to allow for intermittent treatment rather than continuous treatment during a patient's lifetime in situations where treatments are not available or need to be paused (e.g., pregnancy).[26]

Reviewer Comment: 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.

The secondary efficacy endpoint of mean percent change from baseline to Weeks 22 and 24 in LDL-C, which reflects the peak and the trough of the QM dosing interval, and, according to the Applicant, provides information about the time-averaged effect of evolocumab therapy over the entire dosing interval, is not an endpoint that DDLO has used as a regulatory standard to

[26] Gaudet D, Langslet G, Gidding SS, et al. Efficacy, safety, and tolerability of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia: rationale and design of the HAUSER-RCT study. J Clin Lipidol 2018;12:1199-1207.

support approval of LDL-C lowering therapies.

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).

The Applicant chose non-HDL-C, ApoB, the ratio of total cholesterol/HDL-C, the ratio of ApoB/ApoA1, and Lp(a) as secondary efficacy endpoints because these markers are known as useful markers of cardiovascular risk under certain circumstances [such as in patients 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. Additional tertiary endpoints included triglycerides and HDL-C because these endpoints are also used in predicting risk for cardiovascular disease.

While triglycerides, HDL-C, Lp(a), hsCRP and other biomarkers are included in the ACC/AHA ASCVD Risk Calculator, used to predict 10-year risk for cardiovascular disease, or as ASCVD Risk Enhancers in the 2018 AHA/ACC Guideline on the Management of Blood Cholesterol, observed drug-induced changes in such biomarkers are of unclear clinical significance, i.e., clinical trial or epidemiologic data have not directly demonstrated that reductions in these biomarkers reduce CV risk. Therefore, the Division does not typically include them in labeling if they represent potential claims not supported by substantial evidence.

Discontinuation from Trial: Withdrawal of consent for the study meant that the subject did not wish to receive further protocol-required therapies or procedures, and the subject did not wish to or was unable to continue further trial participation. Subject data up to withdrawal of consent was included in the analysis of the trial, and where permitted, publicly available data could be included after withdrawal of consent. Reasons for removal of a subject from the trial were: decision by sponsor, withdrawal of consent from trial, death, and lost to follow-up.

Discontinuation from Investigational Product: Subjects with abnormal hepatic laboratory values (i.e., alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin [TBL]) and/or international normalized ratio (INR) and/or signs/symptoms of hepatitis could meet criteria for withholding or permanent discontinuation of investigational product or other protocol-required therapies as specified in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. Subjects could also be discontinued from drug for other abnormal laboratory tests, including CK.

Table 4 Safety Stopping Rules for CK

CK at prior visit	CK on retest	Amgen Investigational Product and Non-Amgen Statin Background Therapy Administration
> 5x ULN	> 10x ULN	Discontinue statin and IP[a]. Contact Amgen Medical Monitor
	> 5x to ≤ 10x ULN	Discontinue statin and retest CK before statin administration. Consider continuing IP if alternative explanation
	≤ 5x ULN	Consider continuing IP and statin

[a] CK elevations >10x ULN that have been confirmed to be secondary to myocardial infarction do not require discontinuation of Amgen IP or non-Amgen statin background therapy.

Source: Trial 20120123 protocol; page 32 of 142

Table 5 Schedule of Assessments for Trial 20120123

Study Day / Week / Other Timepoint[a]	Screen	Rand D1	W4 (±3d)	W8 (±3d)	W12 (±3d)	W16 (±3d)	W20 (±3d)	W22 (±3d)	W24 (EOS) (±3d)
Study Day[a]		*D1*	*D29±3*	*D57±3*	*D85±3*	*D113±3*	*D141±3*	*D155±3*	*D169±3*
General Procedures									
Parental/guardian informed consent/permission & subject assent/consent	X								
Medical history	X								
Vital Signs (sitting BP, HR)	X	X	X		X		X	X	X
Review for AEs/SAEs/**ADEs/DREs**/CV events	X[e]	X	X	(X)[e]	X	(X)[e]	X	X	X
Concomitant therapy	X	X	X		X		X	X	X
Dietary instruction	X	X							
Physical exam (including neurologic examination; see Section 7.7.8)	X								X
Body weight, waist circumference, cIMT, Tanner staging		X							X
Body height		X							X
Cogstate neurocognitive assessment[c]	X	X							X
12 lead ECG		X			X				X
Randomization		X[d]							
Central Laboratory[e]									
Fasting lipids[e]	X	X			X			X	X
ApoA1, ApoB100, Lp(a)[f]		X			X			X	X
PK (evolocumab), PCSK9		X			X			X	X
Chemistry, including fasting glucose[e]	X				X				X
Hematology	X				X				X
HbA1c	X								X
Estradiol (females) / testosterone (males)		X							X
hsCRP, CK, FSH, LH, ACTH, DHEA-S, cortisol, **Fasting vitamins A/D/E/K**		X							X
TSH	X								
Biomarkers (blood)[g]		X							X
Anti-evolocumab antibodies		X			X				X
HCV testing[h]	X								
HCV viral load[h]		X							X
Serum pregnancy[i]	X								X
Urine pregnancy[i]		X			X				
Urinalysis, urine microalbumin		X			X				X
Investigational Product									
Screening placebo injection	X								
AI/Pen Instruction		X	X		X				
AI/Pen dispensation			X		X				
AI/Pen reconciliation					X		X		
IP (AI/Pen) administration on-site		X	X		X		X		
IP (AI/Pen) administration on-site or in non-investigator site setting				X		X			

a D1 = day of first administration of IP; a visit window of ± 3 days applies to all other visits. Note: Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.
b only AEs possibly related to study procedures and SAEs are collected during screening (from signing of ICF or subject assent, whichever is later); week 8 and week 16 AEs/SAEs/ADEs/DREs/CV events collection only if visit to study site. ADEs/Product Complaints are reported that occur after signing of the informed consent through 30 days after the last dose of IP or EOS, whichever is later.
c Cogstate cognitive battery tests
d randomization should be on day 1 or as close as possible to day 1 and must not be earlier than 5 days prior
e blood samples must be taken prior to IP administration, if applicable
f if subject is not fasting on day 1, reschedule; if subject is not fasting after day 1, do all procedures except fasting labs and IP administration, if applicable; schedule another visit, if possible within the visit window for fasting labs and IP administration
g if parental/guardian consent or permission and subject consent or assent to pharmacogenetics analyses has been provided, deoxyribonucleic acid (DNA) will be extracted from some of the blood samples, eg, biomarker samples
h HCV antibodies only in subjects at high risk for, or with history of, HCV infection or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV
i pregnancy testing in females of childbearing potential (additional pregnancy tests may be conducted if there is concern that a female subject has become pregnant).
Source: Applicant's Table 1; CSR 20120123 protocol

Statistical Analysis Plan

Sample Size: This trial was designed to evaluate evolocumab in approximately 150 pediatric subjects. Sample size calculations were based on the treatment effect from the phase 3 trial in adults with HeFH, in which evolocumab reduced LDL-C by approximately 55%. The Applicant states that a sample size of 150 pediatric subjects (100 randomized to evolocumab 420 mg QM and 50 randomized to placebo QM) provides approximately 99% power in testing the superiority of evolocumab 420 mg QM over placebo. The sample size calculation was performed using a two-sided t-test with a 0.05 significance level, assuming a treatment effect of 40% reduction in LDL-C, a common standard deviation (SD) of 20%, and a treatment discontinuation incidence of 20%.

Analysis Sets: Full analysis set (FAS) for Trial 20120123: all randomized subjects who received at least 1 dose of investigational product (IP). For efficacy analyses, subjects were analyzed according to their randomized treatment group assignment, regardless of the treatment received.
The completer analysis set (CAS) included subjects in the FAS who adhered to the scheduled IP and had observed values for the primary endpoints. The completer analysis set was used in sensitivity analyses of the primary endpoints.

Estimand: The estimand of primary interest is the difference in mean percent change from baseline in LDL-C at Week 24 regardless of treatment adherence for subjects in FAS. The superiority of evolocumab to placebo was assessed for all efficacy (lipid) endpoints using a repeated measures linear mixed effects model with unstructured covariance. The repeated

measures model included terms for treatment group, stratification factors, scheduled visit, and the interaction of treatment with scheduled visit. To account for the repeated LDL-C measurements within a subject across the visits, the repeated measures linear effects model used an unstructured covariance. This model was used to assess the efficacy of evolocumab in lowering LDL-C in previous submissions. Missing values were not imputed when the repeated measures linear mixed effects model was used. The analysis used LDL-C values measured, regardless of treatment adherence.

Sensitivity Analyses of Primary Efficacy Endpoints:

- The primary analysis was repeated using the CAS
- Non-parametric analyses (Quade test) were performed
- To evaluate the impact of missing data,
    - A sensitivity analysis under the assumption that subjects that discontinued IP and have missing endpoint data have a mean zero percent change from baseline was conducted using multiple imputation
    - If there are at least 25 subjects who discontinue IP but have non-missing week 24 endpoint data, the primary analysis model was repeated using FAS with missing values imputed for subjects who discontinued IP. Missing values were imputed using non-missing data from subjects who discontinued IP within the same treatment group.

Subgroup Analyses: Subgroup analyses on the primary and secondary LDL-C efficacy endpoints (at Week 24 and the mean of Weeks 22 and 24, respectively) were conducted. These included subgroups by age (<14, ≥14 years), screening LDL-C value (<160 mg/dL, ≥160 mg/dL), gender, region, baseline LDL-C < or ≥ median (173.0 mg/dL), baseline PCSK9 < or ≥ median (270.0 ng/mL), and statin intensity (high, moderate, low). Treatment interactions were also evaluated for the same variables.

Multiplicity: In order to preserve the familywise error rate at 0.05, multiplicity adjustment for the primary and secondary efficacy endpoints was performed using sequential gatekeeping and Hochberg procedures as follows:

1. If the treatment effect from the primary analysis of the primary endpoint was significant at a significance level of 0.05, statistical testing of the mean percent change from baseline to weeks 22 and 24 in LDL-C and change from baseline to week 24 in LDL-C proceeded using the sequential procedure with a significance level of 0.05.
2. If the treatment effect from change from baseline to week 24 in LDL-C was significant at a significance level of 0.05, statistical testing of the percent change from baseline to week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio and ApoB/ApoA1 ratio followed the Hochberg procedure at a significance level of 0.05.

Unless specified otherwise, all other hypothesis testing was 2-sided with a significance level of 0.05.

Protocol Amendments

Original, Date: December 9, 2014

- Amendment 1, Date: May 20, 2015: The following items were added to the protocol at the request of the FDA.
    - Hematology, urinalysis and anti-evolocumab antibody assessments at Week 12
    - Explicit exclusion of apheresis subjects added to synopsis
    - Documentation of historical lipid therapies
    - Assessments of cognitive function (added as an exploratory endpoint)
    - Clarification that the calculation of sample size accounts for 20% of randomized subjects discontinuing investigational product prior to completion of the trial

  The following change was also made:
    - The exploratory endpoint of "categorical change from baseline in high sensitivity C-reactive protein" was deleted.
- Amendment 2, Date: September 1, 2015: Purpose was to address regulatory feedback, clarify specific details of the statistical analysis and add safety assessments. No subjects enrolled under the original or Amendment 1; 158 subjects enrolled under Amendment 2.
    - added explicit exclusion of HoFH subjects
    - added adverse device effects (ADE) and disease-related events (DRE) as safety assessments
    - removed Cogstate neurocognitive battery as an exploratory endpoint and added it as another safety endpoint
    - added low-fat diet as background therapy to be maintained throughout the trial
    - added explicit exclusion subjects receiving lipid apheresis
    - added definition of product complaints to the schedule of assessments
    - added the primary estimands
    - added statistical methodology for reporting vital signs, antibody data, and pharmacokinetic data

On November 18, 2015 (DARRTS Reference ID: 3848355), FDA responded that the revised protocol for Trial 20120123 was acceptable. FDA recommended that Trial 20120123 use a multiple imputation approach for a sensitivity analysis, where subjects with missing values for the primary endpoint who do not adhere to therapy have their missing values represented by those subjects on the same treatment arm who were similarly non-adherent to therapy and were measured for the primary endpoint.

Reviewer Comment: The clinical team agreed with the applicant's protocol amendments and do

not believe that these modifications had a negative impact on the integrity of the trial or on our interpretation of the results, particularly since no changes were made after subject enrollment.

Publications:

- Gaudet D, Langslet G, Gidding SS, et al. Efficacy, Safety, and Tolerability of Evolocumab in Pediatric Patients with Heterozygous Familial Hypercholesterolemia: Rationale and Design of the Hauser-RCT Study. J. Clin. Lipidology. 2018;12:1199-1207.
- Santos RD, Ruzza A, Hovingh GK, et al. Evolocumab in pediatric heterozygous familial hypercholesterolemia. N Engl J Med 2020; 383: 1317-27.
- de Ferranti SD. Evolocumab in Children with Heterozygous Familial Hypercholesterolemia. N Engl J Med 2020; 383:1385-86.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the trial was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and Food and Drug Administration (FDA) regulations/guidelines.

Financial Disclosure

Refer to Appendix 13.2 for the financial disclosure overview.

Two investigators of (b) (6) in Trial 20120123/20120124 received a one-time funding grant of $95,000 to support a project (b) (6) in FH patients in 2016.

Three investigators participating in Trial 20120123 did not provide financial disclosure information because their affiliation end date was before the completion date for the financial form.

The applicant's efforts to minimize bias include:

- Use of multiple clinical sites
- Clinical site monitoring
- Clinical site audits
- Independent and centralized assessment of efficacy response data
- Use of multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurements of endpoints by someone other than the investigator.

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 and lack of disclosure despite due diligence do not

raise questions about the integrity of the data because of the study design (randomized, blinded, objective endpoints) and the small number of affected clinical investigators who provided minimal contribution to trial data. The disclosed financial interests/arrangements and lack of disclosure despite due diligence do not affect the approvability of the application.

Patient Disposition

This trial enrolled subjects at 47 centers in 23 countries in Asia Pacific, Europe, South America, and North America. The first subject was enrolled on March 24, 2016, and the last subject completed their last visit on November 25, 2019. A total of 202 subjects were screened for the trial; 158 subjects (105 evolocumab, 53 placebo) were enrolled and randomized. Of the 44 subjects that were screen failures, 36 did not meet inclusion criteria (the most common criterion not met was screening LDL cholesterol <130 mg/dL) and 8 declined to participate. One subject in the evolocumab group did not receive any investigational product (consent withdrawn). Thus, one hundred fifty-seven patients (104 evolocumab, 53 placebo) received at least 1 dose of investigational product and were included in the FAS. Four subjects (all in the evolocumab group) discontinued IP; 2 at the subjects' request, 1 because of an adverse event, and 1 because of "other" (subject missed the Week 20 visit; the final dose of investigational product for that subject was administered at Week 16). Overall, 153 (97%) patients completed investigational product; 157 (99%) patients completed the trial.

The completer analysis set (CAS) included 136 (86%) subjects who completed IP and who had LDL-C values for the primary endpoint. Of the 22 subjects excluded from the CAS, 5 missed doses of IP and 18 were missing the primary endpoint.

Table 6 Subject Disposition for Trial 20120123 (All Randomized Subjects)

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 105) n (%)	Total (N = 158) n (%)
Investigational Product Assessment			
Subjects who never received IP	0	1 (1.0)	1 (0.6)
Subjects who received IP: Full Analysis Set	53 (100.0)	104 (99.0)	157 (99.4)
Subjects who completed IP	53 (100.0)	100 (95.2)	153 (96.8)
Subjects who discontinued IP	0	4 (3.8)	4 (2.5)
Adverse event	0	1 (1.0)	1 (0.6)
Pregnancy	0	0	0
Death	0	0	0
Subject request	0	2 (1.9)	2 (1.3)
Decision by sponsor	0	0	0

Lost to follow-up	0	0	0
Other	0	1 (1.0)	1 (0.6)
Trial Completion Assessment			
Subjects who completed trial	53 (100.0)	104 (99.0)	157 (99.4)
Subjects who discontinued trial	0	1 (1.0)	1 (0.6)
Withdrawal of consent from	0	1 (1.0)	1 (0.6)
Death	0	0	0
Decision by sponsor	0	0	0
Lost to follow-up	0	0	0
Completers analysis set inclusion	44 (83.0)	92 (87.6)	136 (86.1)
Completers analysis set exclusion	9 (17.0)	13 (12.4)	22 (13.9)
Did not complete IP doses	0	5 (4.8)	5 (3.2)
Missing primary endpoint	9 (17.0)	9 (8.6)	18 (11.4)

N = Number of subjects randomized; EvoMab = Evolocumab; QM = monthly; IP= Investigational Product
Number of subjects screened: 202; First subject enrolled: March 24, 2016; Last subject completed trial: November 25, 2019.
Source: Reviewer modified from CSR 20120123 Tables 14-1.1.1 and Table 14-1.2.1.

Protocol Violations/Deviations

Eight percent of subjects in the evolocumab group and in the placebo group had an important protocol deviation. Some subjects had more than one such protocol deviation. As shown in the below table, there were 8 subjects in the evolocumab group with important protocol deviations: four subjects with "other" deviations (3 did not have a pregnancy test during screening and 1 who did not have a CK measurement at screening, although the CK at day 1 was normal), three subjects who received expired or compromised IP (one of these subjects also had an issue with no legally acceptable representative consent where the mother signed the consent form at screening and the father signed later), one subject received prohibited lipid regulating medications, one subject received the wrong IP box, and one subject was missing eligibility labs.

There were 4 subjects in the placebo group with important protocol deviations: one subject received expired or compromised IP, one subject with "other" deviation (stopped statin therapy for ~30 days because of AEs of jaundice and abdominal pain which subsequently resolved), one subject with no informed consent or subject assent (assent was not collected at screening but was completed at the next visit), and one subject, identified after the database lock, who received prohibited medication (amphetamines [Vyvanse]) during the trial that could affect lipid levels. Protocol deviations were similar between the treatment groups and were not believed to have a negative impact on study results.

Table 7 Important Protocol Deviations for Trial 20120123 (All Randomized Subjects)

Stratification Element	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 105) n (%)	Total (N = 158) n (%)
Number of subjects with ≥1 important protocol deviation	4 (7.5)	8 (7.6)	11 (7.0)
Important protocol deviations			
Missing eligibility labs	0	1 (1.0)	1 (0.6)
No informed consent or subject assent	1 (1.9)	0	1 (0.6)
No legally acceptable representative consent	0	1 (1.0)	1 (0.6)
Other	1 (1.9)	4 (3.8)	5 (3.2)
Received expired or compromised IP	1 (1.9)	3 (2.9)	4 (2.5)
Received prohibited lipid regulating medications	1 (1.9)	1 (1.0)	1 (0.6)
Received wrong IP box	0	1 (1.0)	1 (0.6)

N = number of subjects randomized; EvoMab = Evolocumab; IP = Investigational Product; QM = monthly (subcutaneous)
Multiple deviations within the same category are counted once per subject.
Source: datasets adam.adsl, adam.addv and CSR 20120123 Table 14-3.1.1.

Demographic Characteristics

As noted in Section 6.1.1, randomization was stratified by age and baseline LDL-C. As shown below, this was reasonably balanced between the two groups.

Table 8 Randomization Stratifications for Trial 20120123 (Full Analysis Set)

Stratification Element	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)	Total (N = 157) n (%)
Age Group			
< 14 years	25 (47)	48 (46)	73 (47)
≥ 14 years	28 (53)	56 (54)	84 (54)
Screening LDL-C Level			
< 160 mg/dL	16 (30)	33 (32)	49 (31)
≥ 160 mg/dL	37 (70)	71 (68)	108 (69)

In Trial 20120123, 56% of patients were female, 85% were white, 1% black, 1% Asian, 13% other, and 8% were Hispanic. The mean age at enrollment was 13.7 years (range 10-17 years). Thirty-nine (25%) patients were 10 to 11 years of age, and 119 (75%) patients were 12 to 17 years of age.

Reviewer Comment: As shown in detail in Table 9, baseline demographic characteristics for the placebo and evolocumab group were reasonably similar. The trial primarily enrolled white subjects so there is very limited representation of non-white or Hispanic patients. The trial population included appropriate representations of male and female sex.

Table 9 Demographic Characteristics of the Primary Efficacy Analysis Population for Trial 20120123

Demographic Parameters	**Placebo QM** (N=53) n (%)	**Evolocumab 420 mg QM** (N=104) n (%)	**Total** (N=157) n (%)
Sex			
Male	26 (49.1)	43 (41.3)	69 (43.9)
Female	27 (50.9)	61 (58.7)	88 (56.1)
Age			
Mean years (SD)	13.7 (2.5)	13.7 (2.3)	13.7 (2.4)
Median (years)	14.0	14.0	14.0
Min, max (years)	10, 17	10, 17	10, 17
Age Group			
< 14 years	25 (47.2)	48 (46.2)	73 (46.5)
≥ 14 years	28 (52.8)	56 (53.8)	84 (53.5)
10-11 years	14 (26.4)	25 (23.8)	39 (24.7)
≥ 12 years	39 (73.6)	80 (76.2)	119 (75.3)
Race			
White	44 (83.0)	89 (85.6)	133 (84.7)
Black or African American	0	2 (1.9)	2 (1.3)
Asian	0	2 (1.9)	2 (1.3)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	9 (17.0)	11 (10.6)	20 (12.7)
Ethnicity			
Hispanic	7 (13.2)	6 (5.8)	13 (8.3)
Not Hispanic	46 (86.8)	98 (94.2)	144 (91.7)
Region			
North America	10 (18.9)	12 (11.5)	22 (14.0)
United States	4 (7.5)	1 (1.0)	5 (3.2)

Canada	6 (11.3)	11 (10.5)	17 (10.8)
Europe	35 (66.0)	68 (65.4)	103 (65.6)
Austria	4 (7.5)	3 (2.9)	7 (4.4)
Belgium	1 (1.9)	3 (2.9)	4 (2.5)
Czech Republic	0	5 (4.8)	5 (3.2)
Greece	1 (1.9)	0	1 (0.6)
Hungary	4 (7.5)	6 (5.7)	10 (6.3)
Italy	7 (13.2)	19 (18.1)	26 (16.5)
Netherlands	7 (13.2)	15 (14.3)	22 (13.9)
Norway	3 (5.7)	5 (4.8)	8 (5.1)
Poland	2 (3.8)	2 (1.9)	4 (2.5)
Portugal	0	1 (1.0)	1 (0.6)
Russian Federation	1 (1.9)	0	1 (0.6)
Slovenia	0	1 (1.0)	1 (0.6)
Spain	1 (1.9)	4 (3.8)	5 (3.2)
Switzerland	2 (3.8)	2 (1.9)	4 (2.5)
Turkey	1 (1.9)	1 (1.0)	2 (1.3)
United Kingdom	1 (1.9)	2 (1.9)	3 (1.9)
South America	8 (15.1)	18 (17.3)	26 (16.6)
Brazil	4 (7.5)	16 (15.2)	20 (12.7)
Colombia	4 (7.5)	2 (1.9)	6 (3.8)
Asia Pacific	0	6 (5.8)	6 (3.8)
Australia	0	3 (2.9)	3 (1.9)
Malaysia	0	1 (1.0)	1 (0.6)
South Africa	0	2 (1.9)	2 (1.3)

ApoB = Apolipoprotein B; CHD = Coronary Heart Disease; CVD= cardiovascular Disease; DBP = Diastolic Blood Pressure; FH = Familial Hypercholesterolemia; HDL-C = High-density lipoprotein cholesterol; HeFH = Heterozygous Familial Hypercholesterolemia; LDL-C = Low-density lipoprotein cholesterol; PCSK9 = Proprotein Convertase Subtilisin/kexin type 9; QM = monthly (subcutaneous); SBP = Systolic Blood Pressure
N = number of subjects randomized and dosed in the full analysis set.
Family history of premature coronary heart disease (CHD) was CHD in first degree relative male at less than or equal to 55 years or female at less than or equal to 65 years of age.
[a] low HDL-C defined as baseline HDL-C < 40 mg/dL for both males and females with age 10 to <16 years; < 40 mg/dL in male and < 50 mg/dL in female with age ≥ 16 years.
Source: adsl.xpt; Software: JMP Clinical and reviewer created from CSR 20120123 Tables 14-2.1.1, 14-1.7.1, 14-1.4.1.

Disease Characteristics

Per 20120123 entry criteria, subjects in the FAS had a genetic or known clinical diagnosis of HeFH. Sixty-six percent of patients had documented genetic evidence of an FH-causing mutation (64% in the LDL receptor); 34% of patients enrolled based on clinical criteria alone (Simon-Broome, Dutch Lipid Clinic Network, or Make Early Diagnosis to Prevent Early Deaths [MEDPED] criteria).

Mean LDL-C levels were nearly identical between placebo and evolocumab (183 vs 185 mg/dL, respectively). Statin usage (high, moderate, and low intensity) was also similar between the two groups. In the overall population, the mean LDL-C at baseline was 184 mg/dL, total cholesterol was 250 mg/dL, non-high-density lipoprotein cholesterol (non-HDL-C) was 203 mg/dL, PCSK9 was 283 ng/mL, and hsCRP was 0.94 mg/L. The mean concentrations of vitamins A, D, E, and K were within normal reference ranges.

No patient had CAD or CHF, but one (2%) placebo patient had a history of stroke at baseline. The most common CHD risk factors at baseline (evolocumab, placebo) were low HDL-C (39%, 34%), family history of premature CHD (30%, 40%), and hypertension (2%, 6%).

All 157 (100%) patients were taking lipid-lowering medication, and 156 (99%) were on a statin at baseline. Twenty-six patients (17%) were on high-intensity statins, 98 patients (62%) were on moderate-intensity statins, and 31 (20%) were on low-intensity statins at baseline. Twenty patients (13%) were on a statin plus ezetimibe; 1 (0.6%) patient took only ezetimibe.

Table 10 Baseline Disease Characteristics of the Primary Efficacy Analysis Population for Trial 20120123

Baseline Characteristics	**Placebo QM** (N=53) n (%)	**Evolocumab 420 mg QM** (N=104) n (%)	**Total** (N=157) n (%)
Systolic blood pressure (mmHg)			
Mean (SD)	112.0 (12.1)	110.8 (11.5)	111.2 (11.7)
Min, max	90, 140	86, 144	86, 144
Diastolic blood pressure (mmHg)			
Mean (SD)	67.2 (8.7)	66.3 (7.7)	66.6 (8.1)
Min, max	49, 89	47, 89	47, 89
Heart rate (beats/min)			
Mean (SD)	74.3 (11.7)	74.5 (11.1)	74.4 (11.2)
Min, max	53, 96	55, 127	53, 127
Body mass index (kg/m^2)			
Mean (SD)	21.3 (4.2)	22.6 (5.5)	22.1 (5.1)
Min, max	14, 33	14, 46	14, 46
Screening LDL-C level			
< 160 mg/dL	16 (30)	33 (32)	49 (31)
≥ 160 mg/dL	37 (70)	71 (68)	108 (69)
LDL-C [a] (mg/dL)			
Mean (SD)	183.0 (47.2)	185.0 (45.0)	184.3 (45.6)
Min, max	122, 326	118, 368	118, 368
LDL-C, calculated (mg/dL)			
Mean (SD)	182.9 (47.2)	184.8 (44.9)	184.2 (45.6)

Min, max	122, 326	118, 368	118, 368
Total cholesterol (mg/dL)			
Mean (SD)	247.3 (49.5)	250.7 (47.0)	249.6 (47.7)
Min, max	181, 392	173, 445	173, 445
HDL-C (mg/dL)			
Mean (SD)	47.2 (11.9)	46.8 (12.0)	46.9 (11.9)
Min, max	26, 89	26, 82	26, 89
Triglycerides (mg/dL)			
Median (Q1, Q3)	78.0 (62.5, 101.0)	86.8 (63.8, 117.0)	84.0 63.0, 108.0
Min, max	47, 220	44, 281	44, 281
ApoB (mg/dL)			
Mean (SD)	119.4 (27.9)	123.3 (27.1)	122.0 (27.3)
Min, max	82, 206	75, 220	75, 220
Non-HDL-C (mg/dL)			
Mean (SD)	200.2 (48.2)	203.8 (47.3)	202.6 (47.5)
Min, max	139, 344	132, 406	132, 406
Lp(a) (nmol/L)			
Mean (SD)	88.7 (99.7)	88.7 (97.4)	88.7 (97.8)
Min, max	2, 360	5, 443	2, 443
hsCRP (mg/L)			
Mean (SD)	0.94 (1.5)	0.94 (1.2)	0.94 (1.3)
Min, max	0.1, 8.6	0.1, 6.7	0.1, 8.6
PCSK9 (ng/mL)			
Mean (SD)	294.2 (101.3)	277.2 (92.1)	283.1 (95.4)
Min, max	127, 665	18, 503	18, 665
CVD			
Coronary artery disease	0	0	0
Stroke/cerebral infarction	1 (1.9)	0	1 (0.6)
Congestive heart failure	0	0	0
CHD risk factors			
Current cigarette smoking	2 (3.8)	1 (1.0)	3 (1.9)
Hypertension	3 (5.7)	2 (1.9)	5 (3.2)
Type II diabetes mellitus	0	1 (1.0)	1 (0.6)
Family history of premature CHD	21 (39.6)	31 (29.8)	52 (33.1)
Low HDL-C [b]	18 (34.0)	40 (38.5)	58 (36.9)
Diagnosis of HeFH			
Genetic	32 (60.4)	72 (69.2)	104 (66.2)
LDL receptor mutation	30 (56.6)	70 (67.3)	100 (63.7)
ApoB mutation	1 (1.9)	2 (1.9)	3 (1.9)
PCSK9 gain of function	1 (1.9)	0	1 (0.6)
Clinical	21 (39.6)	32 (30.8)	53 (33.8)
Simon-Broome	7 (13.2)	9 (8.7)	16 (10.2)

Definite HeFH	4 (7.5)	5 (4.8)	9 (5.7)
Possible HeFH	3 (5.7)	4 (3.8)	7 (4.5)
Dutch Lipid Clinic Network	10 (18.9)	22 (21.2)	32 (20.4)
Definite HeFH	6 (11.3)	12 (11.5)	18 (11.5)
Possible HeFH	4 (7.5)	10 (9.6)	14 (8.9)
MEDPED	4 (7.5)	1 (1.0)	5 (3.2)
Statin usage at baseline[c]			
High intensity statin usage	7 (13.2)	19 (18.3)	26 (16.6)
Moderate intensity statin usage	35 (66.0)	63 (60.6)	98 (62.4)
Low intensity statin usage	10 (18.9)	21 (20.2)	31 (19.7)
Statins	52 (98.1)	104 (100.0)	156 (99.4)
Atorvastatin	26 (49.1)	42 (40.4)	68 (43.3)
Pravastatin	6 (11.3)	13 (12.5)	19 (12.1)
Rosuvastatin	12 (22.6)	39 (37.5)	51 (32.5)
Simvastatin	8 (15.1)	10 (9.6)	18 (11.5)
Other Lipid modifying agents	9 (17.0)	17 (16.3)	26 (16.6)
Ezetimibe	8 (15.1)	13 (12.5)	21 (13.4)
Fish oil	2 (3.8)	5 (4.8)	7 (4.5)
Phytosterols	0	1 (1.0)	1 (0.6)
Colesevelam	1 (1.9)	0	1 (0.6)

N = number of subjects randomized and dosed in the full analysis set; QM = monthly (subcutaneous); ACC = American College of Cardiology; AHA = American Heart Association; CHD = Coronary Heart Disease; FH = Familial Hypercholesterolemia; HeFH = Heterozygous Familial Hypercholesterolemia; LDL-C=Low-density lipoprotein; HDL-C = High-density lipoprotein; Non-HDL-C = Non-High-density lipoprotein cholesterol; ApoB = Apolipoprotein B; Lp(a) = Lipoprotein (a); PCSK9 = Proprotein convertase subtilisin/kexin type 9; hsCRP = High-sensitivity C-reactive Protein
a When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C and calculated VLDL-C will be replaced with ultracentrifugation VLDL-C from the same blood sample, if available.
b low HDL-C defined as baseline HDL-C < 40 mg/dL for both males and females with age 10 to < 16 years; < 40 mg/dL in male and < 50 mg/dL in female with age >= 16 years.
c Statin usage at baseline per American College of Cardiology/American Heart Association (ACC/AHA) definition: High-intensity: atorva ≥ 40 mg QD, rosuva ≥ 20 mg QD; Moderate-intensity: atorva 10 to < 40 mg QD, rosuva 5 to < 20 mg QD, simva 20-80 mg QD, prava ≥ 40 mg QD; Low-intensity: atorva <10 mg QD, rosuva <5 mg QD, simva <20 mg QD, prava < 40 mg QD
Source: Reviewer modified from datasets adam.adsl, adam.adslbl and CSR 20120123 Tables 14-2.2.1., 14-2.3.1., 14-2.5.1, 14-2.6.1., 14-2.8.1., 14-2.8.2., 14-2.8.3., and 14-8.4.1.

Reviewer Comment: As detailed in Table 10, the baseline characteristics were mostly balanced between the two treatment groups, especially for LDL-C level, CVD, and intensity of statin dose at baseline. There were small differences between placebo and evolocumab for CHD risk factors with a higher incidence of current cigarette smoking, hypertension, and family history of premature CHD in the placebo group. The differences are unlikely to impact efficacy results, particularly as the baseline LDL-C values are similar between groups.

One of the inclusion criteria for this protocol stated that subjects were required to be receiving optimized background lipid-lowering therapy, defined as a statin at optimal dose (as determined by the subject's managing physician) and not requiring uptitration in the opinion of the investigator. A total of 156 (99%) patients were on a statin at baseline and most (124 [79%]) were on moderate- or high-intensity statins at baseline, based on adult classifications. Of these, only 16 (13%) were also taking ezetimibe. Of the 31 (20%) patients who were on low-intensity statins at baseline, 27 (87%) were on statins alone and 4 (13%) were also taking ezetimibe. While the recommended statin dose for pediatric patients is lower than that for adults, it seems that some of these trial patients may not have been on maximized therapy (i.e., statin plus ezetimibe) prior to entering Trial 20120123.

Santos et al.[27] commented that background lipid-lowering treatment in this trial "reflected the diversity of the real-life management of pediatric familial hypercholesterolemia in the 23 countries from which the patients originated". The authors noted that only a minority of children with FH are receiving adequate treatment[28], and there are differences between high-income and low-income areas.[29]

In the US, data from the Cascade Screening for Awareness and Detection-FH Registry show that only 77% of children eligible for lipid-lowering therapy were receiving treatment, and only 39% of those treated met their LDL-C goal. Statins, particularly atorvastatin and simvastatin, are the most commonly prescribed lipid-lowering drugs in pediatric FH patients. Of patients aged ≥10 years, 261 (67%) were taking statins but only 27 (7%) were taking ezetimibe. And in children less than 10 years, 16 (16%) were on a statin and only 1 (1%) were taking ezetimibe.[30] Thus, a small percentage of pediatric patients using ezetimibe in addition to statin therapy in this trial is consistent with real-world practice.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

With the exception of one placebo patient who stopped statin background therapy for approximately 30 days during the trial because of adverse events of jaundice and abdominal pain which subsequently resolved, there was no change in concomitant statin use or intensity during the trial.

[27] Santos RD, Ruzza A, Hovingh GK, et al. Evolocumab in pediatric heterozygous familial hypercholesterolemia. N Engl J Med 2020; 383: 1317-27.
[28] Bogsrud MP, Langslet G, Wium C, Johansen D, Svilaas A, Holven KB. Treatment goal attainment in children with familial hypercholesterolemia: a cohort study of 302 children in Norway. J Clin Lipidol 2018; 12: 375-82.
[29] Representatives of the Global Familial Hypercholesterolemia Community. Reducing the clinical and public health burden of familial hypercholesterolemia: a global call to action. JAMA Cardiol 2020; 5: 217-29.
[30] de Ferranti SD, Shrader P, Linton MF, et al. Children with Heterozygous Familial Hypercholesterolemia in the United States: Data from the Cascade Screening for Awareness and Detection-FH Registry. J Pediatr. 2021;229:70-77.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint in double-blind, placebo-controlled Trial 20120123 was percent change from baseline to Week 24 in reflexive LDL-C. The least squares (LS) mean (SE) change in reflexive LDL-C from baseline to Week 24 was -44.5% (2.2%) in the evolocumab group and -6.2% (3.1%) in the placebo group with a mean treatment difference (95% CI) of -38.3% (-31.1, -45.5), p<0.0001. Mean absolute reflexive LDL-C values at Week 24 were 104 mg/dL in the evolocumab group and 172 mg/dL in the placebo group.

Analysis of the primary endpoint using calculated LDL-C values produced almost identical results to those using reflexive LDL-C values. At Week 24, the LS mean (SE) change in calculated LDL-C from baseline was -44.4% (2.2%) in the evolocumab group and -6.2% (3.1%) in the placebo group with a mean treatment difference (95% CI) of -38.2% (-31.0, -45.5). Mean absolute calculated LDL-C values at Week 24 were 104 mg/dL in the evolocumab group and 172 mg/dL in the placebo group.

At Week 12, there was data on all 53 patients in the placebo group and 101 out of 104 of the patients in the evolocumab group. The mean (SD) percent change from baseline to Week 12 in calculated LDL-C was -45.7% (25.9) in the evolocumab group and -5.0% (19.2) in the placebo group. The LDL-C changes at Week 12 were similar to those at Week 24.

No patient had an LDL-C level of 25 mg/dL or less during Trial 20120123. The lowest LDL-C level was 30 mg/dL (reflexive) at Week 22.

Mean investigational product exposure was similar between the evolocumab (5.5 months) and placebo (5.5 months) groups. Overall, 98 (94%) patients in the evolocumab group and 51 (96%) patients in the placebo group received all 6 doses of investigational product. Trial exposure was also similar between the 2 treatment groups at 5.6 months in the evolocumab group and 5.7 months in the placebo group.

Table 11 Percent Change in Reflexive and Calculated LDL-C from Baseline to Week 24 Trial 20120123 (Full Analysis Set)

	Placebo QM (N=53)	**EvoMab 420 mg QM (N=104)**
Week 24 (reflexive LDL-C)		
n	44	96
Mean (SD)	-6.7 (18.3)	-44.2 (22.4)
Median	-6.2	-46.9
Min, Max	-69.1, 30.9	-83.9, 43.8

Mean absolute reflexive LDL-C values (mg/dL) at Week 24	171.9 mg/dL	103.9 mg/dL
Median and (min, max) absolute reflexive LDL-C values (mg/dL) at Week 24	158.5 mg/dL (71, 302)	90.5 mg/dL (31, 343)
LS Mean[a] (95% CI)	-6.2 (-12.3, -0.2)	-44.5 (-48.8, -40.3)
Treatment difference (95% CI)		-38.3 (-45.5, -31.1)
Adjusted p-value[b]		<0.0001
Week 24 (calculated LDL-C)		
n	44	96
Mean (SD)	-6.7 (18.3)	-44.1 (22.5)
Median	-6.2	-46.9
Min, Max	-69.1, 30.9	-80.3, 43.8
LS Mean[a] (95% CI)	-6.2 (-12.3, -0.1)	-44.4 (-48.7, -40.2)
Treatment difference (95% CI)		-38.2 (-45.5, -31.0)
Adjusted p-value[b]		<0.0001

[a] Least squares mean is from the repeated measures model which includes treatment group, stratification factor of screening LDL-C level and age, scheduled visit and the interaction of treatment with scheduled visit as covariates. The model uses an unstructured covariance.
[b] Adjusted p-value was based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value was compared to 0.05 to determine statistical significance.
Values are observed data. The results do not include imputed data for missing values.
N=number of subjects randomized and dosed in the full analysis set; n=number of subjects with observed data; EvoMab=Evolocumab; QM=monthly (subcutaneous); CI=Confidence Interval; LDL-C=low-density lipoprotein cholesterol
Source: Reviewer modified from datasets adam.adsl, adam.adlb and CSR 20120123 Tables 14-4.7.1 and 14-4.7.3

Missing Primary Efficacy Endpoint Data at Week 24

Nine patients (17%) in the placebo population and 8 patients (8%) in the evolocumab group (for a total of 17 patients [11%]), missed the primary endpoint assessment at Week 24. The reasons for the missing assessment of LDL-C at Week 24 are as follows:

- Thirteen patients had Week 24 assessments that were outside of the analytical time window pre-specified in the statistical analysis plan (SAP) for that visit (Week 24 analytical time window was day 162 to 175, inclusive); 1 assessment was early and was assigned to the week 22 analysis visit and 12 assessments (6 in the evolocumab group

and 6 in the placebo group) occurred after the Week 24 analytical time window (range: day 176 to 186).
- Three patients had samples that were considered outside of stability, and therefore, were not tested.
- One patient did not have a sample taken.

The Applicant states that a sensitivity analysis of the primary endpoint using multiple imputation could not be conducted because too few subjects (<25 subjects) had missing primary endpoint data.

The Applicant was asked to re-do the analysis of the primary endpoint of percent change in LDL-C from baseline to Week 24 removing the upper bound of the analytical window, and thus including the 12 patients whose Week 24 assessments were past the pre-specified analytical window. The results were similar to the primary analysis of the primary endpoint. The mean treatment differences (95% CI) in these analyses were -40.0% (-32.9, -47.1) and -39.9% (-32.8, -47.0) for reflexive and calculated LDL-C, respectively, compared with -38.3% (-31.1, -45.5) for reflexive LDL-C for the FAS in the primary analysis of the primary endpoint.

The applicant was also asked to re-do the analysis of the primary endpoint of percent change in LDL-C from baseline to Week 24 using only the patients that had a baseline LDL value and a Week 24 LDL value (44 in the placebo group and 96 in the evolocumab group). In this analysis that excluded 17 patients with missing data for the primary endpoint, the LS mean (95% CI) change in LDL-C from baseline at Week 24 was -44.2% (-39.8, -48.6) in the evolocumab group and -7.0% (-0.6, -13.5) in the placebo group based on reflexive LDL-C values (see table below). The mean treatment difference (95% CI) was -37.2% (-29.6, - 44.8). The results for this analysis were also similar to the primary analysis of the primary endpoint. Therefore, the missing data from these 17 patients had minimal effect on the primary endpoint results.

Table 12 Percent Change in Reflexive LDL-C from Baseline to Week 24 Trial 20120123 (Observed Data)

	Placebo QM (N=44)	**EvoMab 420 mg QM (N=96)**
Week 24 (reflexive LDL-C), % change		
n	44	96
Mean (SD)	-6.7 (18.3)	-44.2 (22.4)
Median	-6.2	-46.9
Min, Max	-69.1, 30.9	-83.9, 43.8
LS Mean[a] (95% CI)	-7.0 (-13.5, -0.6)	-44.2 (-48.6, -39.8)

Treatment difference (95% CI)		-37.2 (-44.8, -29.6)
Adjusted p-value	-	< 0.0001

[a] Least squares mean is from the repeated measures model which includes treatment group, stratification factor of screening LDL-C level and age, scheduled visit and the interaction of treatment with scheduled visit as covariates. The model uses an unstructured covariance.
Values are observed data. The results do not include imputed data for missing values.
N=number of subjects randomized and dosed in the full analysis set with an observed LDL-C value at Week 24; n=number of subjects with observed data; EvoMab=Evolocumab; QM=monthly (subcutaneous); CI=Confidence Interval; LDL-C=low-density lipoprotein cholesterol
Source: Applicant's Response to FDA Information Request dated March 1, 2021

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 excellent as 97% of patients completed investigational product and 99% of patients completed the trial. Although only 86% of patients who completed IP had LDL-C values for the primary endpoint, the missing data did not have a meaningful effect on the results. 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

The secondary endpoint of mean percent change from baseline to the mean of Weeks 22 and 24 in LDL-C was analyzed using calculated LDL-C values. The LS mean change in calculated LDL-C from baseline to the mean of Weeks 22 and 24 was -48.0% (1.9%) in the evolocumab group and -5.9% (2.7%) in the placebo group with a treatment difference [95%CI]) at the mean of Weeks 22 and 24 of -42.1% (-48.4, -35.9).

This secondary endpoint information reflects the peak concentration of evolocumab at Week 22 to the trough concentration at Week 24 and is supposed to represent a 'time-averaged effect'. This time-averaged percentage change in LDL-C from baseline over the dosing interval confirms how we expect the treatment to work over time. DDLO has not used this endpoint of mean percent change in LDL-C over a peak to trough interval as a regulatory standard to support approval of LDL-C lowering therapies. We have recommended using the baseline to trough concentration to reflect a more conservative and reproducible estimate of the drug-induced LDL-C lowering.

As shown in the table below, use of evolocumab led to statistically significant reductions in all secondary lipid endpoints including change in reflexive and calculated LDL-C from baseline to

Week 24, and the percent changes from baseline to Week 24 in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/apolipoprotein A1 (ApoA1) ratio.

Table 13 Secondary Efficacy Endpoints for Trial 20120123 (Full Analysis Set-HeFH)

	Treatment Difference[b] EvoMab 420 mg QM vs Placebo QM
Calculated LDL-C	
LS Mean[c] % change from BL to Wks 22 and 24 (95% CI)	-42.1 (-48.4, -35.9)[d]
Calculated LDL-C	
Change from baseline to Week 24 (95% CI) - mg/dL	-68.3 (-82.9, -53.8)[d]
Reflexive LDL-C[a]	
LS Mean[c] % change from BL to Wks 22 and 24 (95% CI)	-42.1(-48.3, -35.8)[d]
Reflexive LDL-C[a]	
Change from baseline to Week 24 (95% CI) - mg/dL	-68.6 (-83.1, -54.0)[d]
Non-HDL-C	
% change from baseline to Week 24 (95% CI)	-35.0 (-41.8, -28.3)[d]
ApoB	
% change from baseline to Week 24 (95% CI)	-32.5 (-38.8, -26.1)[d]
Total cholesterol/HDL-C ratio	
% change from baseline to Week 24 (95% CI)	-30.3 (-36.4, -24.2)[d]
ApoB/ApoA1 ratio	
% change from baseline to Week 24 (95% CI)	-36.4 (-43.0, -29.8)[d]

[a] When the calculated LDL-C was < 40 mg/dL or triglycerides were > 400 mg/dL, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available.
[b] Treatment difference used placebo group as the reference. Treatment difference was from the repeated measures model which included treatment group, stratification factor of age and screening LDL-C, scheduled visit and the interaction of treatment with scheduled visit as covariates.
[c] Least squares mean is from the repeated measures model which includes treatment group, stratification factor of screening LDL-C level and age, scheduled visit and the interaction of treatment with scheduled visit as covariates. The model uses an unstructured covariance.
[d] Adjusted p-value <0.0001; Adjusted p-value was based on a combination of sequential testing and the Hochberg procedure to control the overall significance level for all primary and secondary endpoints. Each individual adjusted p-value was compared to 0.05 to determine statistical significance.

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; BL=baseline; CI=Confidence Interval; EvoMab= Evolocumab; HDL-C=high-density lipoprotein cholesterol; LDL-C= low-density lipoprotein cholesterol; QM =monthly (subcutaneous).
Source: Reviewer modified from CSR 20120123 Table 14-4.5.1; Tables 5 and 6 of Module 2.7.3, Summary of Clinical Efficacy Appendix

Table 14 Other Efficacy Endpoints for Trial 20120123 (Full Analysis Set-HeFH)

	Treatment Difference[a] EvoMab 420 mg QM vs Placebo QM
HDL-C	
% change from baseline to Week 24 (95% CI)	6.8 (1.2, 12.4), p=0.019
Total cholesterol	
% change from baseline to Week 24 (95% CI)	-26.8 (-32.4, -21.2), p-value <0.0001
Triglycerides	
% change from baseline to Week 24 (95% CI)	-3.8 (-13.9, 6.3), p=0.46
Lp(a)	
% change from baseline to Week 24 (95% CI)	-9.2 (-31.6, 13.3), p=0.42

EvoMab = Evolocumab; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; Lp(a) = lipoprotein (a); QM = monthly (subcutaneous).
[a] Treatment difference used placebo group as the reference. Treatment difference was from the repeated measures model which included treatment group, stratification factor of age and screening LDL-C (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates.
Source: Reviewer modified from Trial 20120123 CSR Tables 14-4.6.11, 14-4.6.13, 14-4.6.14, and 14-4.6.15,

Dose/Dose Response

There was only one dose of evolocumab, 420 mg SC QM, used in this trial.

Durability of Response

Reductions in LDL-C were seen at the first post-baseline assessment at Week 12 timepoint and were maintained throughout the trial (Week 24).

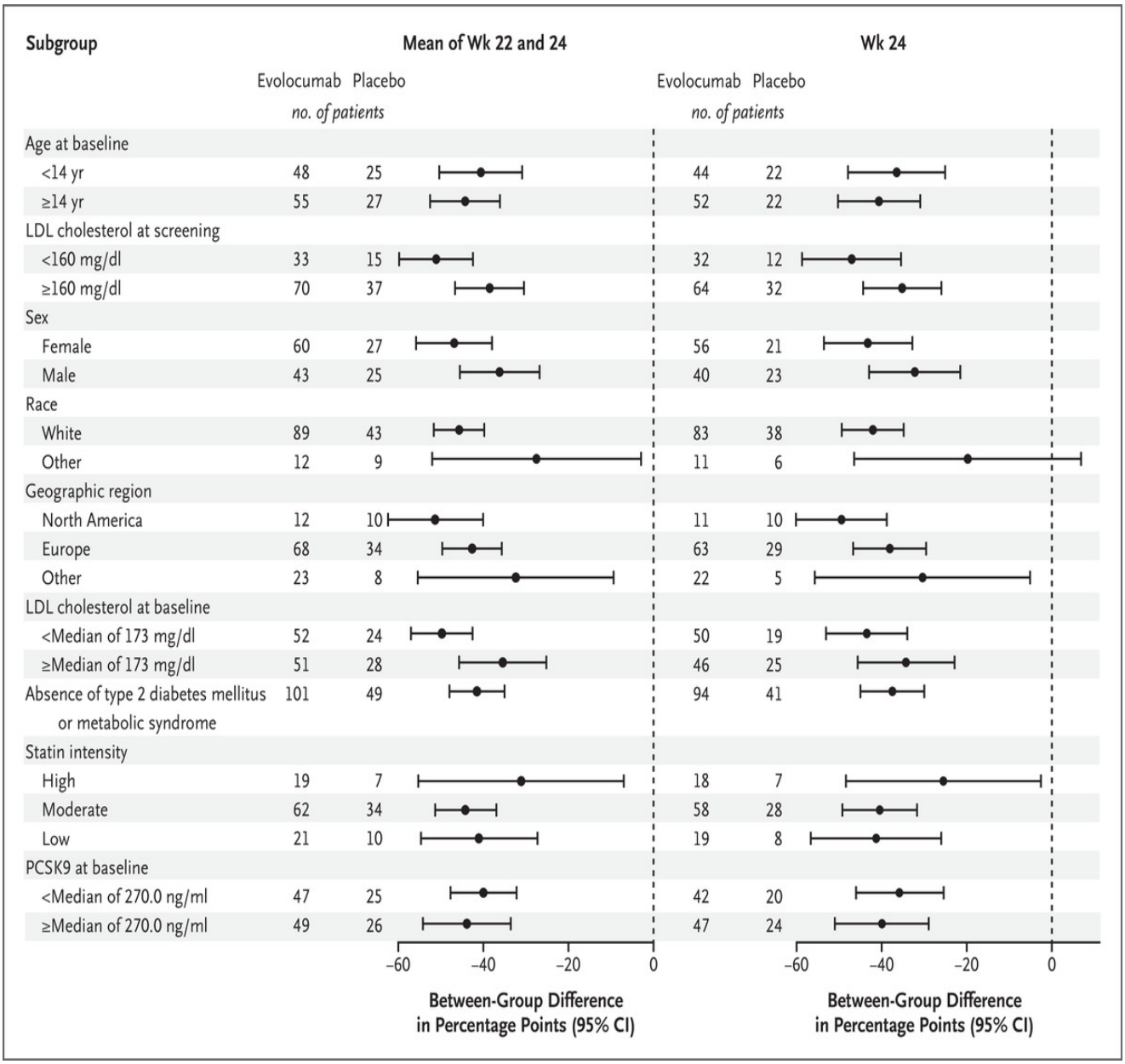
Persistence of Effect

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

Additional Analyses Conducted on the Individual Trial

Subgroup Analyses:
As shown in the figure below, subgroup analyses for efficacy showed that evolocumab's LDL-C reduction ability was similar regardless of subject age, gender, race, region, baseline LDL-C, or background LLT. Several subgroups were too small to meaningfully assess for differences (Black, only 2 subjects in the evolocumab group; Other race, 6 in placebo group and 11 in evolocumab group, resulting in an imprecise primary endpoint [wide CI]; metabolic syndrome, 4 subjects total; and type 2 diabetes, 1 subject total).

Figure 3 Forest Plot of Percent Change from Baseline in LDL-C at the Mean of Weeks 22 and 24 and Week 24 by Subgroups



Least squares mean differences and 95% CI were from the repeated measures model. No imputation was used for missing values.
Source: Figure 2; RD Santos et al. N Engl J Med 2020;383:1317-1327

Reviewer Comment: In this trial of pediatric patients with HeFH, evolocumab demonstrated a clinically meaningful reduction in LDL-C relative to placebo.

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

6.2. Trial 20120124, HAUSER-OLE: Open-Label, Single-Arm, Multicenter, Study to Evaluate the Safety, Tolerability and Efficacy of Evolocumab for LDL-C Reduction, as Add-On to Diet and Lipid Lowering Therapy, in Pediatric Subjects from 10 to 17 Years of Age with Heterozygous Familial Hypercholesterolemia (HeFH) or Homozygous Familial Hypercholesterolemia (HoFH)-Interim Analysis

6.2.1. Study Design

Overview and Objective

Primary Objective: to describe the safety and tolerability of 80 weeks of subcutaneous (SC) evolocumab when added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH.

Secondary Objectives (assessed after 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH):

- percent change and absolute change from baseline in LDL-C, and on percent change from baseline in non-HDL-C, ApoB, total cholesterol/HDL-C ratio, and ApoB/ ApoA1 ratio
- change from baseline in steroid hormones and the subject incidence of abnormal muscle and liver enzyme levels
- changes from baseline in carotid intima-media thickness (cIMT)
- change from baseline in growth and pubertal development parameters at measured timepoints

Other Objectives (assessed after or with 80 weeks of SC evolocumab, added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH):

- incidence of abnormal neurological examination findings
- assess cognitive function, using the change from baseline in the components of the Cogstate battery at each scheduled administration
- absolute change and percent change at measured timepoints in LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, lipoprotein(a) [Lp(a)],

- change at measured timepoints in proprotein convertase subtilisin/kexin type 9 (PCSK9) and high sensitivity C-reactive protein (hsCRP)
- investigate the relationship between novel and established biochemical cardiovascular and lipid biomarkers and effects of evolocumab in pediatric subjects 10 to 17 years of age with HeFH
- in subjects consenting to the optional pharmacogenetics analysis, to investigate potential correlations of trial data including the subject response to evolocumab with genetic variation in markers of (PCSK9) signaling, low-density lipoprotein receptor (LDLR) turnover, cholesterol metabolism, inflammation, and plaque stability

Trial Design

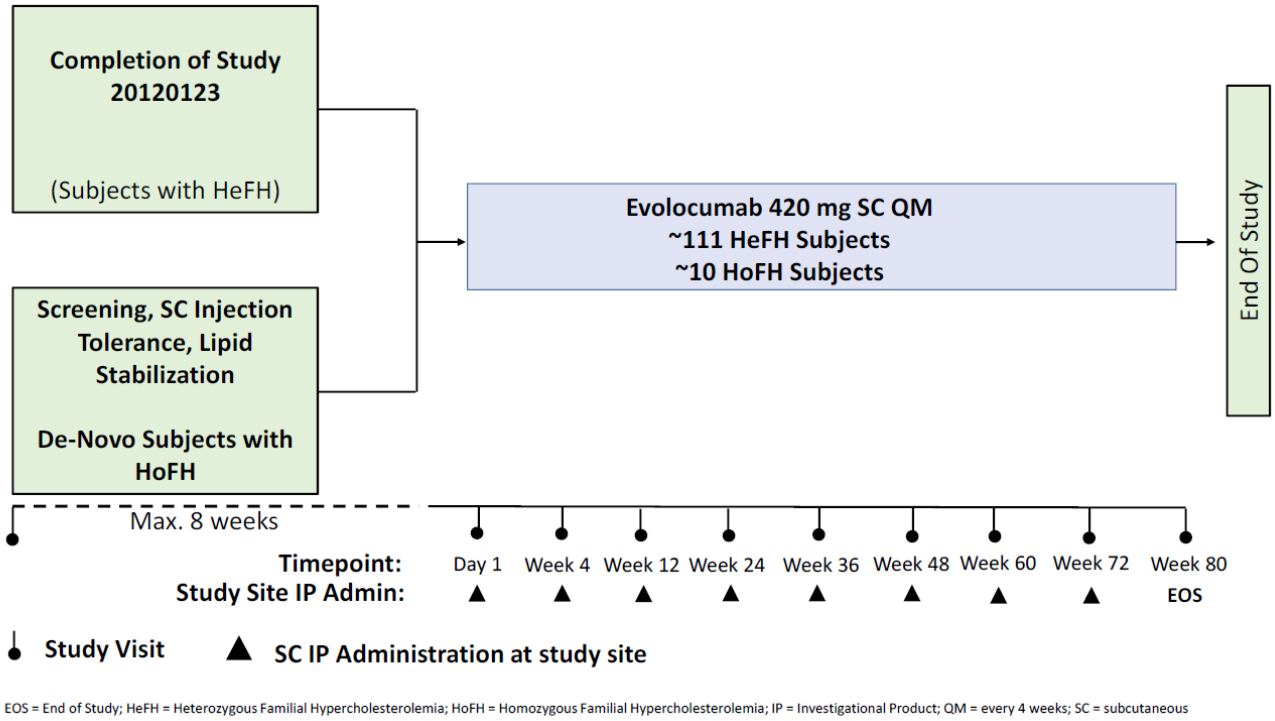
Trial 20120124 was an open-label, single-arm, multicenter trial of evolocumab in pediatric subjects 10 to 17 years of age with HeFH or HoFH to evaluate the safety, tolerability, and efficacy of evolocumab for LDL-C reduction, as add-on to diet and other LDL-C lowering therapy. Patients with HeFH who completed Trial 20120123 (and did not experience a treatment-related serious adverse event) and patients with HoFH, 10 to 17 years of age, receiving optimized standard of care lipid-lowering therapy, were eligible for this trial. Subjects underwent screening laboratory assessments, including a one-time SC administration of placebo in subjects with HoFH only, to evaluate tolerability of the SC injection. Subjects were instructed to maintain their diet, lipid-lowering therapy, and exercise regimen throughout screening and all phases of trial participation.

Evolocumab was administered as 420 mg SC QM using either 3 AI/pen injections or 1 automated mini-doser (AMD) administration. Subjects could switch between the AI/pen and AMD at any scheduled time point where evolocumab was supplied to the subject, provided the appropriate supply was available. The planned trial duration was approximately 80 weeks; interim data from a minimum of 28 weeks of evolocumab exposure (data cutoff date of June 8, 2020) for all subjects who did not discontinue the trial is included in this submission.

Day 1 was defined as the day of first administration of evolocumab in this trial. Subsequent study visits were at Weeks 4, 12, 24, 36, 48, 60, 72, and 80 (EOS, end-of-study). Subjects who discontinued evolocumab early for any reason were asked to return for all other study procedures and measurements until the end of the trial.

The first subject was enrolled on September 10, 2016. The last subject last visit prior to data cutoff date (June 8, 2020) was May 28, 2020.

Figure 4 Trial Design and Treatment Schema for Trial 20120124



EOS = End of Study; HeFH = Heterozygous Familial Hypercholesterolemia; HoFH = Homozygous Familial Hypercholesterolemia; IP = Investigational Product; QM = every 4 weeks; SC = subcutaneous

Source: Amgen's clin-over-peds CSR, Figure 4

Key Inclusion Criteria:

- HeFH: Males and females who provided informed consent and completed Trial 20120123 (and did not experience a treatment-related serious adverse event)
- HoFH: Males and females 10 to 17 years of age with a diagnosis of HoFH receiving optimized standard of care lipid-lowering therapy per locally applicable guidelines. The diagnosis of HoFH was by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C >500 mg/dL along with either xanthoma before 10 years of age or evidence of HeFH in both parents. At screening, HoFH subjects had to be on a low-fat diet and had to be receiving background lipid-lowering therapy (such as statins, cholesterol absorption inhibitors, bile acid sequestrants, nicotinic acid, or combinations thereof). Lipid-lowering therapy must have been stable for at least 4 weeks prior to screening with a fasting LDL-C ≥130 mg/dL and fasting triglycerides ≤400 mg/dL by the central laboratory at screening.

Key Exclusion Criteria:

- For patients with HeFH: same as those listed for trial 20120123
- For patients with HoFH:
    - Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2

- CK >3x upper limit of normal (ULN)
- AST or ALT >2x ULN
- Known active infection or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction
- Administered a cholesterylester transfer protein (CETP) inhibitor in the last 12 months prior to screening, mipomersen or lomitapide in the last 5 months prior to LDL-C screening, or any therapy to inhibit PCSK9 within 12 weeks prior to screening
- Female subjects of childbearing potential cannot be pregnant or breast feeding or planning to become pregnant or planning to breast feed and must be willing to use acceptable method(s) of effective birth control (may include true sexual abstinence) during treatment with evolocumab and for an additional 15 weeks after the end of treatment with evolocumab.

Withholding of evolocumab:

- CK elevations: Section 6.4 of the protocol states that if CK is >5x ULN, CK must be retested before evolocumab is administered. Investigators were to ask trial subjects to promptly report muscle pain, cramps, or weakness especially if accompanied by malaise or fever. If such symptoms occurred, the subject's CK levels was to be measured and if CK is >5x ULN, the subject was instructed to discontinue statin background therapy and evolocumab. CK must be retested before any statin or evolocumab is re-started.
- Abnormal hepatic laboratory values discovered during trial participation may meet the criteria for withholding or permanent discontinuation of Amgen investigational product or other protocol-required therapies as specified in the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Table 15 Schedule of Assessments for Trial 20120124

Study Day / Week / Other Timepoint[a]	Screening HoFH	Screening HeFH[b]	D1/Parent Study EOS	W4[c] (±3d)	W12 (±7d)	W24 (±7d)	W36 (±7d)	W48 (±7d)	W60 (±7d)	W72 (±7d)	W80 (EOS) (±7d)
General Procedures											
Informed parental/guardian consent/permission and subject consent/assent – HoFH subjects	X										
Informed parental/guardian consent/permission and subject consent/assent – HeFH subjects		X	X								
Enrollment			X[d]								
Medical history	X										
Vital Signs (sitting BP, HR)	X	X	X	X	X	X		X			X
Review for AEs/SAEs/ADEs	X[e]	X[e]	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Dietary instruction	X	X	X		X	X	X	X	X	X	
Physical exam (including neurologic examination)	X										X
Height, weight, cIMT, Tanner staging			X[f]			X		X			X
Neurocognitive assessment (Cogstate battery)	X		X[g]			X		X[g]			X
12 lead ECG			X								X
Central Laboratory[h]											
Fasting lipids[h]	X	X[i]	X		X			X			X
ApoA1, ApoB100, Lp(a)[h]			X		X						X
PK (evolocumab), PCSK9			X		X						X
Chemistry, including fasting glucose[h]	X	X			X			X			X
Hematology	X	X						X			X
Estradiol (females) / testosterone (males)		X[i]	X								X
HbA1c, FSH, LH, ACTH, DHEA-S, cortisol, hsCRP, fasting vitamins A/D/E/K[j]		X[i]	X								X
CK	X	X[i]	X		X			X			X
Biomarkers (blood)[k]			X								X
Anti-evolocumab antibodies			X								X
HCV testing[l]	X										
HCV viral load[l]			X					X			X
Serum pregnancy[m]	X	X									X
Urine pregnancy[m]			X[n, o]	X	X	X	X	X	X	X	
Urinalysis, urine microalbumin, urine creatinine, urine albumin/creatinine ratio			X								X

Study Day / Week / Other Timepoint[a]	Screening HoFH	Screening HeFH[b]	D1/Parent Study EOS	W4[c] (±3d)	W12 (±7d)	W24 (±7d)	W36 (±7d)	W48 (±7d)	W60 (±7d)	W72 (±7d)	W80 (EOS) (±7d)
Investigational Product											
Screening placebo AI/Pen (HoFH subjects only)	X										
IP administration on-site / instruction as needed			X	X	X	X	X	X	X	X	
AI/Pen or AMD dispensation[p]			X[q]	X	X	X	X	X	X	X	
AI/Pen or AMD reconciliation					X	X	X	X	X	X	X

ACTH = adrenocorticotropic hormone, ADE = adverse device effect, AE = adverse event, AI/Pen = autoinjector/pen, ALT = alanine aminotransferase, AMD = automated mini-dose, ApoA1 = apolipoprotein A-1, ApoB100 = apolipoprotein B100, AST = aspartate aminotransferase, BP = blood pressure, cIMT = Carotid Intima-Media Thickness, CK = creatine kinase, D = day, DHEA-S = dehydroepiandrosterone sulfate, ECG = electrocardiogram, EOS = end-of-study (for the individual subject), FSH = follicle-stimulating hormone, HbA1c = hemoglobin A1C, HCV = hepatitis C virus, HeFH = heterozygous familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia, HR = heart rate, hsCRP = high sensitivity C-reactive protein, ICF = informed consent form, IP = investigational product, LH = luteinizing hormone, Lp(a) = lipoprotein(a), PCSK9 = proprotein convertase subtilisin/kexin type 9, PK = pharmacokinetic, SAE = serious adverse event, ULN = upper limit of normal, W = week

[a] D1 = day of first administration of IP; this visit should also coincide with EOS visit for parent study in subjects rolling over from Study 20120123; procedures NOT conducted as part of EOS visit for parent study should be completed at this visit.
[b] For rollover subjects only, when time between Study 20120123 EOS visit and Study 20120124 day 1 visit exceeds 4 weeks.
[c] Week 4 training visit applies to HoFH subjects only (due to lack of prior experience of in-home use of IP).
[d] Enrollment should be on day 1 or as close as possible to day 1 and must not be earlier than 5 days prior.
[e] Only AEs possibly related to study procedures, SAEs, and ADEs (placebo injections for HoFH subjects) are collected during the screening period (from signing of ICF).
[f] Study 20120124 day 1 cIMT is not required for rollover subjects completing the 20120123 EOS cIMT (regardless of time between Study 20120123 EOS and Study 20120124 day 1).
[g] HoFH subjects only.
[h] Blood samples must be taken prior to IP administration and apheresis, if applicable. Note: apheresis is permitted only for subjects with HoFH.
[i] For rollover subjects that have performed the screening visit will not have to repeat the labs that were performed at screening at day 1: fasting lipids, hormones, HbA1, FSH, LH, ACTH, DHEA-S, CK, Cortisol, hsCRP, fasting vitamins A,D,E,K.
[j] If a subject with HoFH is not fasting on day 1, reschedule. All other subjects or timepoints: if the subject is not fasting, do all procedures except fasting labs and IP administration, if applicable; schedule another visit, if possible within the visit window for fasting labs and IP administration.
[k] If the subject consented to pharmacogenetics analyses, deoxyribonucleic acid (DNA) will be extracted from some of the blood samples, eg, biomarker samples.
[l] HCV antibodies only in subjects at high risk for or with history of HCV infection (see Section 7.2.1.2) or if ALT or AST > 2x ULN at any time during screening; viral load only in subjects positive for HCV.
[m] Pregnancy testing in females of childbearing potential; if urine test is positive, perform confirmatory serum pregnancy test.
[n] For rollover subjects: urine pregnancy test at day 1 is not required in lieu of serum pregnancy at Study 20120123 EOS visit if completed within 7 days of initiation of evolocumab in Study 20120124.
[o] For rollover subjects that have performed the screening visit: urine pregnancy test at day 1 is not required in lieu of serum pregnancy at screening visit if completed within 7 days of day 1.

[p] Subjects will have the opportunity to switch between the AI/Pen and AMD at any scheduled time point where evolocumab is supplied to the subject, provided the appropriate supply is available. The first self-administration after switching the device should be done at a regularly scheduled visit under the supervision of the investigator or qualified study center staff.
[q] HeFH subjects only.

Source: Applicant's Table 2; CSR 20120124 protocol

Publication(s): None

Trial Endpoints

The primary endpoint in open-label extension Trial 20120124 was treatment emergent adverse events at Week 80 (end-of-study).

Secondary endpoints included

- percent change from baseline to Week 80 in LDL-C, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/apolipoprotein A1 [ApoA1] ratio
- change from baseline in LDL-C at Week 80
- change from baseline in steroid hormones (estradiol in females, testosterone in males; follicle-stimulating hormone [FSH], luteinizing hormone [LH], adenocorticotropic hormone [ACTH], dehydroepiandrosterone sulfate [DHEA-S], cortisol in all subjects) at Week 80
- abnormal muscle and liver enzyme levels (creatine kinase [CK], aspartate aminotransferase [AST], or alanine aminotransferase [ALT]) at Week 80
- change in cIMT from baseline tot Week 80
- change from baseline in growth (height and weight) and pubertal development (Tanner staging) to Weeks 24, 48, and 80

Other exploratory endpoints include:

- Change from baseline and percent change from baseline at each scheduled assessment for LDL-C, total cholesterol, non-HDL-C, ApoB, total cholesterol/HDL-C ratio, ApoB/ApoA1 ratio, triglycerides, VLDL-C, HDL-C, ApoA1, Lp(a)
- Change from baseline at each scheduled assessment for PCSK9 and hsCRP

Statistical Analysis Plan

FAS for Trial 20120124: all subjects with HeFH from parent Trial 20120123 who entered and were dosed in Trial 20120124 as well as all de novo subjects with HoFH who were enrolled and dosed in this trial. The interim analysis of Trial 20120124 was conducted when all subjects in the trial completed 28 weeks of evolocumab exposure or had early termination from the trial. The interim data were summarized separately by cohort (HeFH or HoFH).

For open-label Trial 20120124, where all subjects received evolocumab, results were descriptive in nature. No statistical hypothesis was tested, and no missing value imputation was

planned. Median values were presented for HoFH results because of the small sample size and non-normal distribution. For efficacy analyses, the baseline value was defined as:

- Subjects that participated in parent Trial 20120123 and with baseline data from the parent trial: the baseline was defined as the baseline of the qualifying parent trial.
- Subjects not enrolling from a parent trial or without baseline data from the parent trial: the baseline was defined as the baseline in this trial.

Analysis of Primary Efficacy Endpoint: The primary analysis of LDL-C endpoints was assessed using a reflexive approach. For this method, calculated LDL-C was used unless LDL-C was <40 mg/dL or triglycerides were >400 mg/dL, in which case LDL-C by preparative ultracentrifugation (UC) was determined and utilized in the analysis.

Interim Analysis
The interim analysis was conducted when all enrolled subjects had 28 weeks of evolocumab exposure or had withdrawn from the trial.

Protocol Amendments

Original**,** Date: May 27, 2015
Amendment 1, Date: September 10, 2015 (0 subjects enrolled between this date and the date of the next amendment)

- Added safety assessments:
    - evaluate the incidence of abnormal neurological examination findings after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
    - assess cognitive function by change from baseline in the components of the Cogstate battery at each scheduled administration, after 80 weeks of SC evolocumab added to standard of care in pediatric subjects 10 to 17 years of age with HeFH or HoFH
    - collection of samples for assessment of fasting vitamins A, D, E, and K levels.

Amendment 2, Date: June 22, 2016 (42 subjects enrolled under this amendment)

- Clarified primary endpoint language on TEAEs subject incidence at Week 80.
- Added language that defines baseline lab values for rollover and de novo subjects.
- Clarified/updated eligibility criteria: Rollover subjects should not have experienced treatment-related serious adverse events in Trial 20120123.
- Updated Schedule of Assessments and Trial Procedures:
    - Allowed for a 4-week screening window for rollover subjects and for those subjects who exceed the 4-week window, clarified which procedures must be redone.
    - Updated collection points for creatinine kinase.
    - Removed thyroid stimulating hormone (TSH) as an analyte.

  - Clarified when lipid panel results will be unblinded.
  - Clarified that blood draw procedures must be performed before apheresis (if applicable).

Amendment 3, Date: April 26, 2017 (121 subjects enrolled under this amendment)

- Clarified that investigational product (IP) will be administered using either an autoinjector/pen (AI/Pen) or automated mini-doser (AMD).
- Clarified apheresis is only permitted for subjects with HoFH.
- Added QM administration by AMD, to consist of 1 injection of 420 mg / 3.5 mL deliverable volume of evolocumab.

Amendment 4, Date: May 27, 2020 (0 subjects enrolled under this amendment)

- Added interim analysis for all enrolled subjects that will be conducted when all the enrolled subjects in the trial have had 28 weeks of investigation product exposure or have early termination from the trial.
- Updated number of subjects expected to roll over from trial 20120123 into trial 20120124 to approximately 111 subjects and 10 subjects with HoFH with an expected total enrollment of approximately 124 subjects.

There were no changes to statistical methods detailed in the SAP.

Reviewer Comment: The protocol amendments were reasonable and unlikely to have had a negative impact on the integrity of the trial or on our interpretation of the results.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant asserts that the trial was conducted in accordance with ICH GCP and FDA regulations/guidelines.

Financial Disclosure

One investigator in Trial 20120124 has a long-term investment in Amgen. One investigator participating in Trial 20120124 did not provide financial disclosure information because their affiliation end date was before the completion date for the financial form. Refer to Appendix 13.2 for the financial disclosure overview.

Patient Disposition

A total of 150 pediatric patients with HeFH who participated in Trial 20120123 and 13 de novo pediatric patients with HoFH (12 of whom received evolocumab) entered open-label extension

Trial 20120124. This trial was conducted at 46 centers in 23 countries[31] in the regions of Asia Pacific (7%), Europe (64%), South America (16%), and North America (12%).

The first subject was enrolled on September 10, 2016, and the last subject visit on or prior to data cutoff was May 28, 2020. The data cutoff for this interim analysis was June 8, 2020.

HeFH: A total of 150 patients with HeFH rolled over from the parent Trial 20120123; 101 received evolocumab in the parent trial and 49 received placebo in the parent trial. All 150 patients received evolocumab in Trial 20120124. At the time of data cutoff (June 8, 2020), all patients completed a minimum of 28 weeks of evolocumab exposure unless they terminated early from the open-label extension trial.

- For the trial: As of the data cutoff, 105 (70%) subjects have completed the trial, 42 (28%) subjects are still on trial, and 3 (2%) have discontinued the trial by withdrawing consent.
- For the trial drug (evolocumab): As of the data cutoff, 40 (27%) subjects were still on evolocumab and 104 (69%) subjects completed evolocumab in the trial. Six (4%) subjects discontinued evolocumab; all discontinued evolocumab at the subject's request.

HoFH: Thirteen de novo patients with HoFH were enrolled; 1 did not receive any evolocumab (subject request) and was not included in the FAS. At the time of data cutoff, all patients had either completed the trial (11 [85%]) or discontinued the trial (2 [15%]). Eleven (85%) subjects have completed evolocumab and 1 (8%) discontinued evolocumab.

Overall, as shown in the following table, 162 subjects received at least 1 dose of evolocumab and were included in the FAS. One (0.6%) subject (HoFH subject described above) was excluded from the FAS as this subject did not receive any dose of evolocumab.

[31] Australia, Austria, Belgium, Brazil, Canada, Colombia, Czech Republic, Greece, Hungary, Italy, Malaysia, Netherlands, Norway, Poland, Portugal, Russia, Slovenia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and United States.

Table 16 Subject Disposition for Trial 20120124 (All Enrolled Subjects)

	HeFH			HoFH	Total HeFH + HoFH
	Placebo QM in 20120123 (N = 49) n (%)	EvoMab 420 mg QM in 20120123 (N = 101) n (%)	Total HeFH (N = 150) n (%)	EvoMab 420 mg QM (N = 13) n (%)	EvoMab 420 mg QM (N = 163) n (%)
Investigational Product Assessment					
Subjects who did not receive IP:	0	0	0	1 (8)	1 (0.6)
Subjects who received IP:	49 (100)	101 (100)	150 (100)	12 (92)	12 (99)
Subjects who completed IP	32 (65)	72 (71)	104 (69)	11 (85)	115 (71)
Subjects still on IP	15 (31)	25 (25)	40 (27)	0	40 (25)
Subjects who discontinued IP	2 (4)	4 (4)	6 (4)	1 (8)	7 (4)
Adverse event	0	0	0	0	0
Pregnancy	0	0	0	0	0
Death	0	0	0	0	0
Subject request	2 (4)	4 (4)	6 (4)	1 (8)	7 (4)
Decision by sponsor	0	0	0	0	0
Lost to follow-up	0	0	0	0	0
Other	0	0	0	0	0
Trial Completion Assessment					
Subjects who completed trial	33 (67)	72 (71)	105 (70)	11 (85)	116 (71)
Subjects still on trial	15 (31)	27 (27)	42 (28)	0	42 (26)
Subjects who discontinued trial	1 (2)	2 (2)	3 (2)	2 (15)	5 (3)
Withdrawal of consent from trial	1 (2)	2 (2)	3 (2)	1 (8)	4 (3)
Death	0	0	0	0	0
Decision by sponsor	0	0	0	0	0
Lost to follow-up	0	0	0	1 (8)	1 (0.6)

N = number of subjects with HeFH enrolled from parent trial 20120123 and number of subjects with HoFH enrolled in this trial; EvoMab = Evolocumab; QM = monthly (subcutaneous); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia
Interim analysis data cutoff date: June 8, 2020
Source: adam.adsl; software: JMP Clinical 7.1 and reviewer modified from CSR 20120124 Table 14-1.1.1

Protocol Violations/Deviations

HeFH:
Nine (6%) patients with HeFH had at least 1 important protocol deviation (IPD):

- 4 (3%) subjects had IPDs reported as 'other'. One subject enrolled into the trial 2 days prior to completing all procedures for the parent Trial 20120123; 3 instances of incomplete consent/assent forms in which either the subject, investigator, or both had not signed the appropriate sections of the consent form. These instances of incomplete consent/assent were resolved.
- 2 (1%) subjects received prohibited lipid-regulating medications: one subject started ezetimibe and one subject started omega-3 fatty acids.
- 2 (1%) subjects received wrong IP box.
- 1 (<1%) subject had an eligibility deviation for not having a legally acceptable representative consent (resolved prior to initiation of trial-specific procedures).

Thirty-seven (25%) subjects had at least one protocol deviation due to COVID-19. These deviations included:

- 25 (15%) were alternative site visits
- 25 (15%) were partial missed visit
- 21 (15%) were alternative evolocumab administration
- 5 (3%) were other alternative procedures
- 4 (3%) were missed visit
- 1 (<1%) were missed IP dispensing

HoFH:
No patient with HoFH had an IPD or protocol deviation due to COVID-19.

Reviewer Comment: The protocol violations/deviations were unlikely to have a significant impact on trial results.

Demographic Characteristics

HeFH: 150 of 157 HeFH patients rolled over from the parent Trial 20120123; refer to Table 9 and Table 10 for details on baseline demographics and characteristics of this group that are not already described in Table 17 and Table 18.

In summary, 55% of patients were female, 84% were white, 1% black, 1% Asian, 13% other and 9% were Hispanic. The mean age at enrollment was 14.1 years (range 10-18 years); 8 patients, who were 17 years of age at enrollment in parent Trial 20120123, were 18 years of age at the start of Trial 20120124. In the HeFH study population, mean (SD) LDL-C at baseline was 184 (46) mg/dL, total cholesterol was 250 (48) mg/dL, non-HDL-C was 203 (48) mg/dL, ApoB was 122 (28) mg/dL, Lp(a) was 89 (97) nmol/L, PCSK9 was 283 (96) ng/mL, and hsCRP was 0.96 (1.31) mg/L. One (0.7%) patient had a history of stroke. Ninety-nine (66%) patients had genetic evidence of an FH-causing mutation, of which 96 (97%) had a mutation in the LDL receptor. All 150 (100%) patients were taking lipid-regulating medication at baseline including statins (149 [99%]) and ezetimibe (21 [14%]). For statin use, 43% were on atorvastatin, 33% on rosuvastatin, 13% on pravastatin, and 11% on simvastatin. Twenty-six (17%) HeFH patients were on high-intensity statin by ACC/AHA definition at baseline, 91 (61%) were on moderate-intensity statin, 31 (21%) were on low-intensity statin, and 1 (<1%) was on an unknown statin regimen at baseline.

HoFH: For the 13 patients with HoFH who were new enrollees to Trial 20120124, 12 received evolocumab. Eighty-three percent of patients with HoFH were male and 75% were white, 17% Asian and 8% other; none were Hispanic. The median age at enrollment was 11.5 years (range 11 to 17 years); 6 (46%) patients were 11 to <12 years old and 7 (54%) were 12 to 17 years of age. Fifty percent of patients were from Europe and 50% from Asia Pacific. All 12 patients with HoFH who received evolocumab in the trial had documented genetic evidence of HoFH. At baseline, median LDL-C was 398 mg/dL, total cholesterol was 448 mg/dL, non-HDL-C was 411 mg/dL, ApoB was 227 mg/dL, Lp(a) was 77 nmol/L, PCSK9 was 472 ng/mL, hsCRP was 0.28 mg/L and median concentrations of vitamin A, D, E, and K were within normal reference ranges. As expected, at baseline, patients with HoFH had some lipid parameters levels that were increased compared to patients with HeFH, particularly for LDL-C, ApoB, TC, non-HDL-C, Lp(a), and PCSK9 levels. All 12 (100%) were taking high-intensity statins + ezetimibe; 9 were on atorvastatin and 3 on rosuvastatin. None of the HoFH subjects in Trial 20120124 were on lipid apheresis during the trial.

Table 17 Demographic Characteristics of the Population for Trial 20120124

Demographic Parameters	**HeFH** (N=150) n (%)	**HoFH** (N=12) n (%)	**Total FH** (HeFH + HoFH) (N=162) n (%)
Sex			
Male	67 (45)	10 (83)	77 (47.5)
Female	83 (55)	2 (17)	85 (52.5)
Age			
Mean years (SD)	14 (3)	12 (2)	14 (2.5)
Median (years)	14	12	14

Min, max (years)	10, 18	11, 17	10, 18
Age Group			
< 14 years	62 (41)	10 (83)	72 (44)
≥ 14 years	88 (59)	2 (17)	90 (56)
Race			
White	126 (84)	9 (75)	135 (83)
Black or African American	2 (1)	0	2 (1)
Asian	2 (1)	2 (17)	4 (2)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	20 (13)	1 (8)	21 (13)
Ethnicity			
Hispanic or Latino	13 (9)	0	13 (8)
Not Hispanic or Latino	137 (91)	12 (100)	149 (92)
Region			
North America	20 (13)	0	20 (12)
Canada			17 (10.5)
US			3 (1.9)
Europe	98 (65)	6 (50)	104 (64)
South America	26 (17)	0	26 (16)
Asia Pacific	6 (4)	6 (50)	12 (7)

Interim analysis data cutoff date: June 8, 2020
N = number of subjects with HeFH enrolled and dosed from parent trial 20120123 and number of subjects with HoFH enrolled and dosed in this trial; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia
Source: adam.adsl; Software: JMP Clinical 7.1 and reviewer modified from CSR 20120124 Table 14-2.1.1

Disease Characteristics

Table 18 Baseline Disease Characteristics of the Population for Trial 20120124

Baseline Characteristics	**HeFH** (N=150) n (%)	**HoFH** (N=12) n (%)	**Total FH** (HeFH + HoFH) (N=162) n (%)
Systolic blood pressure (mmHg)			
Mean (SD)	111 (12)	111 (14)	111 (12)
Min, max	86, 144	80, 134	80, 144
Diastolic blood pressure (mmHg)			
Mean (SD)	67 (8)	66 (7)	67 (8)
Min, max	47, 89	57, 83	47, 89
Heart rate (beats/min)			
Mean (SD)	75 (11)	74 (12)	75 (11)
Min, max	53, 127	62, 89	53, 127
Body mass index (kg/m^2)			
Mean (SD)	22 (5)	20 (4)	22 (5)
Min, max	14, 46	16, 26	14, 46
Screening LDL-C level			
< 160 mg/dL	16 (30)	33 (32)	49 (31)
≥ 160 mg/dL	37 (70)	71 (68)	108 (69)
LDL-C [a] (mg/dL)			
Mean (SD)	184 (46)	426 (166)	202 (89)
Median	173	398	176
Min, max	122, 326	161, 785	118, 785
LDL-C, calculated (mg/dL)			
Mean (SD)	184 (46)	426 (166)	202 (89)
Median	173	398	176
Min, max	122, 326	161, 785	118, 785
Total cholesterol (mg/dL)			
Mean (SD)	250 (48)	481 (167)	267 (88)
Median	238	448	242
Min, max	173, 445	214, 851	173, 851
HDL-C (mg/dL)			
Mean (SD)	47 (12)	37 (13)	46 (12)
Median	45	36	44
Min, max	26, 89	21, 71	21, 89
Triglycerides (mg/dL)			
Median	81	78	81
Min, max	44, 281	47, 150	44, 281
ApoB (mg/dL)			
Mean (SD)	122 (28)	250 (85)	132 (49)

Baseline Characteristics	**HeFH** (N=150) n (%)	**HoFH** (N=12) n (%)	**Total FH** (HeFH + HoFH) (N=162) n (%)
Median	118	227	119
Min, max	75, 220	116, 435	75, 435
Non-HDL-C (mg/dL)			
Mean (SD)	203 (48)	444 (171)	221 (90)
Median	192	411	194
Min, max	132, 406	171, 815	132, 815
Lp(a) (nmol/L)			
Mean (SD)	89 (97)	115 (112)	91 (98)
Median	47	77	50
Min, max	2, 443	16, 353	2, 443
hsCRP (mg/L)			
Mean (SD)	0.96 (1.3)	0.80 (0.9)	0.94 (1.3)
Median	0.40	0.28	0.40
Min, max	0.1, 8.6	0.1, 2.5	0.1, 8.6
PCSK9 (ng/mL)			
Mean (SD)	283 (96)	502 (196)	297 (118)
Median	269	472	282
Min, max	18, 665	251, 841	18, 841
CVD			
Coronary artery disease/CABG	0	1 (8)	1 (<1)
Cerebrovascular Disease/Stroke	1 (<1)	0	1 (<1)
Congestive heart failure	0	0	0
CHD Risk Factors			
Current cigarette smoking	3 (2)	0	3 (2)
Hypertension	5 (3)	0	5 (3)
Type II diabetes mellitus	1 (<1)	0	1 (<1)
Family history of premature CHD	51 (34)	5 (42)	56 (35)
Low HDL-C [b]	57 (38)	9 (75)	66 (41)
Diagnosis of HeFH or HoFH			
Genetic evidence of an FH-causing mutation	99 (66)	12 (100)	
LDL receptor	67 (45)	12 (100)	
ApoB	3 (2)	0	
PCSK9 gain of function	0	0	
ARH	0	0	
LDLR activity in homozygosis[c]			
< 5% (null mutation)		3 (25)	
5-99% (defective mutation)		6 (50)	
Unknown		6 (50)	

Baseline Characteristics	**HeFH** (N=150) n (%)	**HoFH** (N=12) n (%)	**Total FH** (HeFH + HoFH) (N=162) n (%)
Genotype			
Homozygous		9 (75)	
Compound heterozygous		3 (25)	
Statin usage at baseline[d]			
High intensive statin usage	26 (17)	12 (100)	38 (24)
Moderate intensive statin usage	91 (61)	0	91 (56)
Low intensive statin usage	31 (21)	0	31 (19)
Unknown statin intensity	1 (<1)	0	1 (<1)
No statin usage	1 (<1)	0	1 (<1)
Statins	149 (99)	12 (100)	161 (99)
Atorvastatin	64 (43)	9 (75)	73 (45)
Pravastatin	19 (13)	0	19 (12)
Rosuvastatin	49 (33)	3 (25)	52 (32)
Simvastatin	17 (11)	0	17 (11)
Other Lipid Modifying Agents	26 (17)	12 (100)	38 (24)
Ezetimibe	21 (14)	12 (100)	33 (20)
Fish oil	7 (5)	1 (8)	8 (5)
Phytosterols NOS	1 (<1)	0	1 (<1)

Interim analysis data cutoff date: June 8, 2020
N = number of subjects with HeFH enrolled and dosed from parent trial 20120123 and number of subjects with HoFH enrolled and dosed in this trial; ACC = American College of Cardiology; AHA = American Heart Association; CHD = Coronary Heart Disease; FH = Familial Hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C=Low-density lipoprotein; HDL-C= High-density lipoprotein; Non-HDL-C = Non-High-density lipoprotein cholesterol; ApoB = Apolipoprotein B; Lp(a) = Lipoprotein (a); PCSK9 = Proprotein convertase subtilisin/kexin type 9; hsCRP = High-sensitivity C-reactive Protein; ARH = autosomal recessive hypercholesterolemia; LDLR = low-density lipoprotein Receptor
For subjects with HeFH rolling over from parent trial 20120123, baseline lipid and lipid-related parameters are defined as parent trial baseline lipid and lipid-related parameters; for de novo subjects with HoFH, the baseline values are defined as the mean of the two most recent non-missing concentrations measured through central lab prior to or on Trial Day 1.
a When the calculated LDL-C is < 40 mg/dL or triglycerides are > 400 mg/dL, calculated LDL-C will be replaced with ultracentrifugation LDL-C and calculated VLDL-C will be replaced with ultracentrifugation VLDL-C from the same blood sample, if available.
b low HDL-C defined as baseline HDL-C < 40 mg/dL for both males and females with age 10 to < 16 years; < 40 mg/dL in male and < 50 mg/dL in female with age >= 16 years.
c Subjects may have multiple mutations. The subcategories are not mutually exclusive.
d Statin usage at baseline per American College of Cardiology/American Heart Association (ACC/AHA) definition: High-intensity: atorva ≥ 40 mg QD, rosuva ≥ 20 mg QD; Moderate-intensity: atorva 10 to < 40 mg QD, rosuva 5 to < 20 mg QD, simva 20-80 mg QD, prava ≥ 40 mg QD; Low-intensity: atorva <10 mg QD, rosuva <5 mg QD, simva <20 mg QD, prava < 40 mg QD
Source: Reviewer modified from datasets adam.adsl, adam.adslbl and CSR 20120124 Applicant's Tables 14-2.2.1., 14-2.3.1., 14-2.5.1, 14-2.7.1., 14-8.4.1

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most subjects remained on the same statin intensity throughout the trial; 2 HeFH subjects who were on low intensity statin at baseline increased to moderate intensity statin usage post-baseline. In addition, 2 HeFH subjects modified their background lipid-regulating medications post-baseline: one subject started ezetimibe and one subject started omega-3 fatty acids.

Efficacy Results – Secondary Endpoints

HeFH:

- Mean (SE) change in reflexive LDL-C from baseline of parent Trial 20120123 during the trial:
    - Week 12 (n=146): -44.4% (1.7)
        - Patients treated with placebo in Trial 20120123 who crossed over to the open-label evolocumab treatment period, demonstrated a mean 46.1% reduction in LDL-C from baseline after 12 weeks of treatment (n=47).
        - Patients treated with evolocumab in Trial 20120123 who continued on open-label evolocumab, demonstrated a mean 43.6% reduction in LDL-C from baseline (in the parent trial) after 12 weeks of treatment (n=99).
    - Week 48 (n=121): -40.6% (2.2)
    - Week 80 (n=96): -36.3% (2.5)
- Mean (SE) change in calculated LDL-C from baseline of parent Trial 20120123 during the trial:
    - Week 12 (n=146): -44.4% (1.7)
    - Week 48 (n=121): -40.5% (2.2)
    - Week 80 (n=96): -36.2% (2.5)
- Mean (SE) absolute reflexive LDL-C was 184.3 (3.8) mg/dL at baseline and 120.0 (5.9) mg/dL at Week 80. Mean absolute change (mg/dL) from baseline was
    - Week 12 (n=146): -80.8 mg/dL (3.3)
    - Week 48 (n=121): -74.8 mg/dL (4.3)
    - Week 80 (n=96): -66.9 mg/dL (4.7)

HoFH:

All 12 patients with HoFH in Trial 20120124 who received evolocumab either completed the trial (Week 80) or terminated participation in the trial prior to the interim analysis data cut-off date (June 8, 2020). Thus, the following results describe the final efficacy results for HoFH subjects.

- Median (Q1, Q3) absolute reflexive (calculated results were identical) LDL-C in patients with HoFH was 397.5 mg/dL (342.5, 475.0) at baseline and 309.0 mg/dL (219.0, 468.0) at Week 80. Median absolute change (mg/dL) from baseline was
    - Week 12 (n=12): -46.3 mg/dL (-172.0, 8.8)
    - Week 48 (n=11): -54.5 mg/dL (-147.0, 6.0)

    - Week 80 (n=11): -36.5 mg/dL (-180.5, 16.0)
- Median (Q1, Q3) percent change from baseline in reflexive (calculated results were identical) LDL-C during the trial:
    - Week 12 (n=12): -12.2% (-32.5, 2.6)
    - Week 48 (n=11): -14.5% (-38.6, 3.7)
    - Week 80 (n=11): -14.3% (-40.6, 3.5)
- For the 6 HoFH subjects 11 to <12 years, the median (Q1, Q3) percent change from baseline in calculated LDL-C was:
    - Week 12: -12.2% (-26.2, 0.6)
    - Week 48: -4.6% (-41.3, 3.7)
    - Week 80: -19.2% (-37.2, 1.2)

Three subjects with HoFH (subject # (b) (6)) in Trial 20120124 showed <5% LDLR activity (null mutation) upon testing at baseline. Two of the 3 subjects ((b) (6)) had a response to evolocumab treatment. One subject ((b) (6)) had consistent and substantial reductions from baseline in LDL-C; the other subject ((b) (6)) had reductions that were smaller and more variable. In contrast, Subject (b) (6) did not have a meaningful response; LDL-C values increased from baseline at Week 12 and Week 80, with a minor reduction of <4% at Week 48 (see table below; reflexive LDL-C changes were nearly identical to calculated LDL-C changes).

Table 19 Absolute Change and Percent Change from Baseline in Calculated LDL-C at Weeks 12, 48, and 80 for Subjects With <5% LDLR activity in Trial 20120124

Subject ID	Analysis Visit	Trial Day	LDL-C (mg/dL)	Change from Baseline (mg/dL)	Percent Change from Baseline
(b) (6)	Baseline	≤ -1	392	--	
	Week 12	92	485	+93.5	+23.9%
	Week 48	331	377	-14.5	-3.7%
	Week 80	555	420	+28.5	+7.3%
(b) (6)	Baseline	≤ -1	785	--	
	Week 12	84	618	-167	-21.3%
	Week 48	337	749	-36	-4.6%
	Week 80	567	634	-151	-19.2%
(b) (6)	Baseline	≤ -1	498	--	
	Week 12	82	260	-238	-47.8%
	Week 48	334	263	-235	-47.2%
	Week 80	566	292	-206	-41.4%

Source: Applicant Response to FDA Information Request, dated April 16, 2021

Reviewer Comment:
In a small subgroup of HoFH patients with <5% LDL receptor activity, efficacy was highly variable. Thus, continued evolocumab treatment may not be appropriate for some patients in this subgroup who do not exhibit a clinical response to treatment.

Reviewer Conclusions:
HeFH: In Trial 20120124, the treatment response to evolocumab as measured by LDL-C values in this pediatric HeFH population was consistent with the results from the placebo-controlled parent trial, 20120123. In this trial of pediatric patients with HeFH, evolocumab demonstrated a clinically meaningful reduction in LDL-C relative to baseline levels in children 10 years of age and older.

HoFH:
In Trial 20120124, the treatment response to evolocumab was notably modest and variable in this pediatric HoFH population as compared to the pediatric HeFH population. This HoFH population had a high LDL-C at baseline despite high-intensity statin therapy and is likely not very responsive to therapies such as statins and PCSK9 inhibitors whose mechanism of action is dependent on adequate LDL receptor function. The results from the OLE trial 20120124 in pediatric patients with HoFH are in line with the LDL-C reductions seen in pediatric patients with HoFH in other studies with evolocumab. The Applicant has provided sufficient clinical data to demonstrate evidence that evolocumab 420mg QM dosing reduces LDL-C in pediatric patients with HoFH, 11 years of age and older, when added to other LDL-C-lowering therapies.

Data Quality and Integrity

The trial was well executed and largely adhered to the protocol. For subjects with HoFH, 11 of 12 subjects completed use of evolocumab over 80 weeks. For subjects with HeFH, the trial is on-going. To date, subject retention and trial completion is very good. 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 – Additional Secondary and Other Relevant Endpoints

HeFH: Mean (SE) change from baseline during the trial in:

- non-HDL-C:
    - Week 12 (n=147): -40.7% (1.5)
    - Week 48 (n=121): -37.4% (2.1)
    - Week 80 (n=96): -33.0% (2.4)
- Total cholesterol:

    - Week 12: -32.0% (1.3)
    - Week 48: -29.0% (1.7)
    - Week 80: -25.7% (1.9)
- ApoB:
    - Week 12: -33.9% (1.6)
    - Week 80: -26.0% (2.3)
- ApoB/ApoA1 ratio:
    - Week 12: -36.0% (1.6)
    - Week 80: -30.6% (2.5)
- Total cholesterol/HDL-C ratio:
    - Week 12: -34.8% (1.4)
    - Week 48: -33.1% (2.0)
    - Week 80: -28.0% (2.3)
- Triglycerides:
    - Week 12: 1.2% (4.0)
    - Week 48: -4.7% (2.6)
    - Week 80: -2.1% (3.3)
- HDL:
    - Week 12: 5.9% (1.3)
    - Week 48: 8.6% (1.5)
    - Week 80: 7.5% (2.0)
- ApoA1:
    - Week 12: 4.5% (1.1)
    - Week 80: 9.5% (1.8)
- Lp(a):
    - Week 12: -9.2% (3.0)
    - Week 80: 26.4% (13.1)
- PCSK9 (ng/mL):
    - Week 12: -131.7 (21.5)
    - Week 80: -111.7 (13.6)
- hsCRP (mg/L):
    - Week 80: 0.68 (0.3)

HoFH: Median (Q1, Q3) change from baseline during the trial in:

- non-HDL-C:
    - Week 12 (n=12): -11.1% (-31.1, 2.2)
    - Week 48 (n=11): -14.3% (-34.8, 7.3)
    - Week 80 (n=11): -13.0% (-40.7, 2.7)
- Total cholesterol:
    - Week 12: -8.9% (-30.4, 1.2)
    - Week 48: -13.9% (-31.0, -0.9)

    - Week 80: -13.6% (-38.4, 2.0)
- ApoB:
    - Week 12: -5.8% (-22.5, -1.0)
    - Week 80: -19.2% (-33.3, 11.6)
- ApoB/ApoA1 ratio:
    - Week 12: -3.1% (-23.2, 7.2)
    - Week 80: -3.0% (- 35.7, 9.3)
- Total cholesterol/HDL-C ratio:
    - Week 12: -6.2% (-29.1, 12.8)
    - Week 48: -5.5% (-28.2, 6.6)
    - Week 80: +3.7% (-41.2, 7.8)
- Triglycerides:
    - Week 12: 2.0% (-23.9, 23.5)
    - Week 48: 1.5% (-16.0, 23.9)
    - Week 80: -15% (-43.9, 6.4)
- HDL:
    - Week 12: -1.3% (-3.9, 8.2)
    - Week 48: -8.1% (-16.1, 6.3)
    - Week 80: 0% (-7.0, 10.8)
- ApoA1:
    - Week 12: 2.5% (-5.6, 5.6)
    - Week 80: -2.4% (-13.7, 16.4)
- Lp(a):
    - Week 12: -14.5% (-22.8, -0.8)
    - Week 80: -4.4% (-13.9, 4.6)
- PCSK9 (ng/mL):
    - Week 12: -159.6 (-362.0, 91.0)
    - Week 80: -161.5 (-266.0, 2.5)
- hsCRP (mg/L):
    - Week 80: 0.90 (-0.09, 2.20)

Reviewer Comment:
HeFH Subjects
Evolocumab improved lipid parameters at each study assessment with the following exceptions, no reduction in percent change from baseline was observed in triglycerides at Week 12 and Lp(a) at Week 80.

HoFH Subjects
In general, evolocumab modestly improved lipid parameters at each study assessment with the following exceptions, no reduction in percent change from baseline was observed in

TC/HDL-C ratio at Week 80 and triglycerides at Week 12 or 48, and no increase in percent change from baseline was observed in ApoA1 at Week 12 or HDL-C at any timepoint.

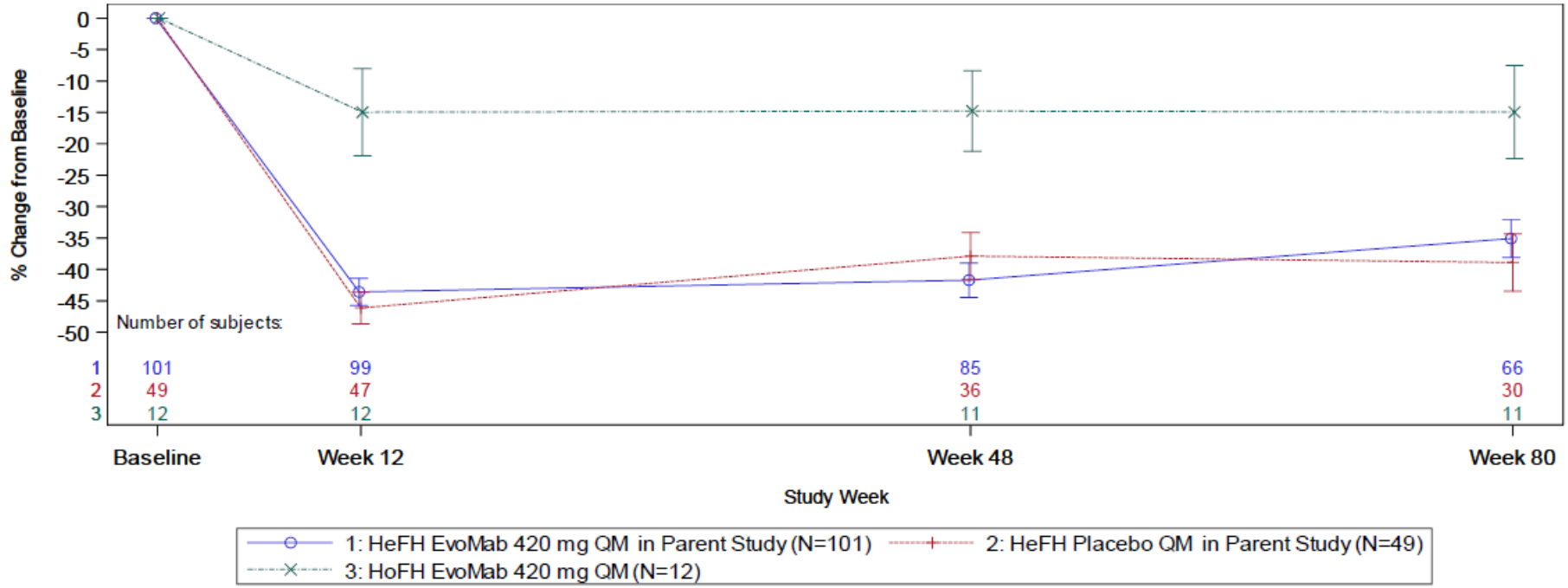
Dose/Dose Response

Not applicable as there was just one dose.

Durability of Response

As shown in the following figure, the reductions in calculated LDL-C for these subjects were maintained throughout the extension trial (up to Week 80).

Figure 5 Mean Percent Change from Baseline in Reflexive LDL-C by Scheduled Visit Trial 20120124 (Full Analysis Set)



N=number of subjects with HeFH enrolled and dosed from parent trial 20120123 and number of subjects with HoFH enrolled and dosed in this trial.
EvoMab=Evolocumab; QM=monthly (subcutaneous); LDL-C=low-density lipoprotein cholesterol; HeFH=heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values.
When calculated LDL-C is <40 mg/dL or triglycerides are > 400 mg/dL, the ultracentrifugation LDL-C value from the same blood sample will be used instead, if available.
Source: CSR_SCE-peds_Figure 1

Persistence of Effect

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

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This submission includes final data from Trial 20120123 and interim data with a data cut-off date of June 8, 2020 from open-label extension Trial 20120124. For Trial 20120124, the data cut-off date was chosen to allow all subjects who did not discontinue evolocumab early to complete a minimum of 28 weeks of evolocumab exposure. These data include 2 years of evolocumab exposure and lipid-lowering data for 72 subjects with HeFH randomized to receive evolocumab in Trial 20120123 who subsequently entered and completed evolocumab administration in open-label extension Trial 20120124 by the interim database cut-off date. These data also include 18 months of evolocumab exposure and lipid-lowering data for 11 de novo patients with HoFH enrolled in Trial 20120124 who completed evolocumab administration.

7.1.1. Primary Endpoints

There is only one placebo-controlled trial in this submission. Refer to Section 6.1.2 for a discussion of these results.

7.1.2. Secondary and Other Endpoints

There is only one placebo-controlled trial in this submission. Refer to Section 6.1.2 for a discussion of these results. Results of the OLE trial are described in Section 6.2.2.

7.1.3. Subpopulations

Subgroup analyses on the primary and secondary LDL-C efficacy endpoints for the placebo-controlled Trial 20120123 are discussed in Section 6.1.2 and displayed in Figure 3.

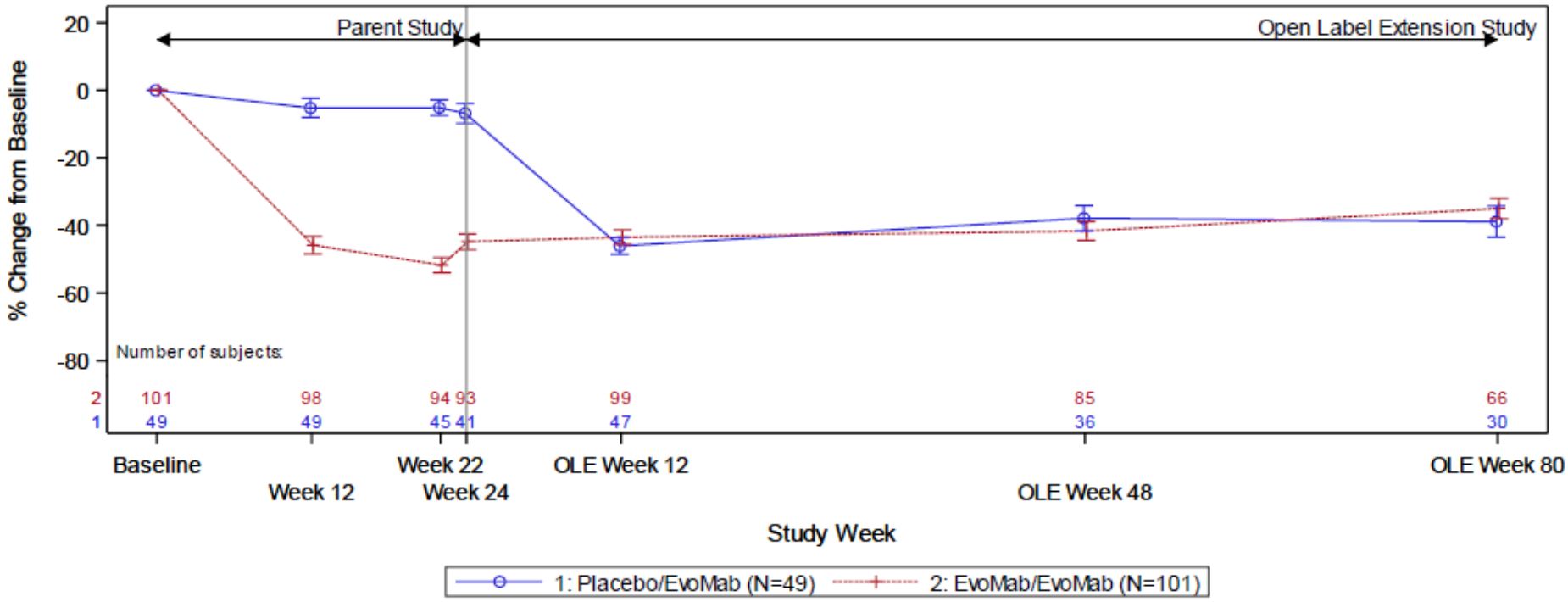
7.1.4. Dose and Dose-Response

Not applicable. Only one dose of evolocumab was studied in Studies 20120123 and 20120124.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

For patients with HeFH, the percent reduction in calculated LDL-C from baseline of parent Trial 20120123 through the end of open-label extension Trial 20120124 is shown in the figure below. Reductions in LDL-C in the evolocumab group were seen by the first post-baseline assessment at the Week 12 and were maintained until Week 24. For those who entered the open-label extension Trial 20120124, LDL reductions continued throughout the extension trial (up to Week 80). Patients in the placebo treatment group in the parent trial, who entered the extension trial, achieved similar LDL-C reductions by Week 12 of the open label extension trial and reduction was maintained throughout the extension trial (up to Week 80).

Figure 6 Mean Percent Change from Baseline in Calculated LDL-C by Scheduled Visit and Treatment Group Trial 20120123 and 20120124 (Full Analysis Set for HeFH Subjects)



Source: Amgen's clin-over-peds CSR, Figure 6
Based on the final database snapshot date (Feb 25, 2020) data for 20120123 and the interim analysis data cut-off date (June 8, 2020) data for 20120124.
Number of subjects: number of subjects with HeFH from parent trial 20120123 who are entered and dosed in trial 20120124.
EvoMab=Evolocumab; HeFH=heterozygous familial hypercholesterolemia; LDL-C=Low-density lipoprotein cholesterol; OLE=open-label extension
Vertical lines represent the standard error around the mean. Plot is based on observed data and no imputation is used for missing values. Baseline is defined as the parent trial 20120123 baseline.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Evolocumab, for this pediatric HeFH indication, was administered as a 420 mg monthly subcutaneous injection during the clinical trials and will be administered monthly as a 420 mg subcutaneous injection in the postmarketing setting. Thus, other than patients being non-compliant with their monthly injections, there should not be significant potential differences in how the drug was administered and used in the clinical trial and its expected use in the postmarket setting. The benefit demonstrated in the clinical trials can reasonably be expected to be achieved in the postmarket setting.

In the 2 pediatric trials, the entry criteria and exclusions were appropriate for the population that might receive the drug in clinical practice. Of the 162 pediatric patients treated with evolocumab in the OLE trial 20120124, the mean and median age was 14 years with an age range of 10 to 18 years. Non-white individuals and Hispanic individuals were underrepresented in the enrolled population; however, the prevalence of FH is more common in the white population which is generally attributed to a founder effect.[32] Overall, patients studied in 20120123 and 20120124 adequately represent the intended target population for evolocumab treatment in pediatric patients 10 years and older with HeFH or HoFH as an adjunct to optimized statin therapy.

7.2.2. Other Relevant Benefits

Evolocumab and statins have CV outcome data in adults that confirms a reduction in CV morbidity and mortality. This data is obtained from CVOTs that are several years in duration and enroll thousands of patients.

Evolocumab has a robust pharmacodynamic effect on LDL-C levels and a longer half-life than

[32] Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol. 2004;160(5):407–20

statins, which allows for less frequent dosing. It is possible, but not proven, that less frequent, monthly dosing with evolocumab may improve a patient's adherence to medication. Evolocumab may be a benefit in some pediatric patients struggling with adherence to daily oral therapy.

7.3. Integrated Assessment of Effectiveness

In pediatric patients with HeFH, results from Trial 20120123 and Trial 20120124 show that:

- Evolocumab was superior to placebo ($p < 0.0001$) in lowering LDL-C. At Week 24, the LS mean reduction in calculated LDL-C from baseline was 44.4% in the evolocumab group and 6.2% in the placebo group with a mean treatment difference (95% CI) of 38.2% (31.0, 45.5). Mean absolute calculated LDL-C values at Week 24 were 104 mg/dL in the evolocumab group and 172 mg/dL in the placebo group.
- For patients who received evolocumab in Trial 20120123 and who completed open-label extension Trial 20120124 by the interim data cut-off date (n=72), reductions in LDL-C were observed by the first assessment at Week 12 in the parent trial and were maintained over a period of 2 years (through Week 80 of open-label extension trial).
- Evolocumab was superior to placebo in improving other lipid parameters, including reductions in non-HDL-C, ApoB, and total cholesterol.

In pediatric patients with HoFH, results from Trial 20120124 show that:

- Median (Q1, Q3) reductions from baseline in calculated LDL-C were modest but consistent during the trial up to Week 80; 12% at Week 12, 15% at Week 48, and 14% at Week 80.
- For the 6 patients with HoFH <12 years of age, median reductions from baseline in calculated LDL-C were consistent with results from the overall population: 12% at Week 12, 5% at Week 48, and 19% at Week 80.
- For the 3 patients with <5% LDLR activity (null mutation), 2 had a response to evolocumab treatment. One patient had consistent and substantial reductions from baseline in LDL-C and the other had reductions that were smaller and more variable. The third patient did not have a meaningful response.

Results from these two studies demonstrated clinically meaningful and statistically significant reductions in LDL-C and improvements in other lipid parameters for subjects with HeFH. The treatment of most pediatric patients with HeFH is likely adequately managed with statins with or without ezetimibe and will not involve additional treatment. However, LDL-C goals are not achieved in some patients because of reduced drug response to therapies involving the LDLR, poor treatment adherence, or side effects. Evolocumab, as an adjunct to diet and other LDL-C-

lowering therapies, can help these pediatric patients achieve their LDL-C goals and potentially reduce their risk for cardiovascular disease.

In patients with HoFH, reductions in LDL-C from therapies like evolocumab, whose mechanism of action necessitates a functional LDLR, have been modest and variable based on genotype and LDLR function. However, overall results in pediatric patients with HoFH enrolled in Trial 20120124 support the efficacy of evolocumab to lower LDL-C in pediatric HoFH patients 11 years and older.

In conclusion, the data presented in this submission support the use of evolocumab in pediatric patients 10 years of age and older with heterozygous and homozygous familial hypercholesterolemia who do not achieve sufficient LDL cholesterol lowering with a healthy lifestyle, optimal statin therapy, and, possibly, 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, particularly in the HeFH population, and an acceptable safety profile, this reviewer recommends approval of evolocumab for the following indications:

- As an adjunct to diet and other LDL-C-lowering therapies to reduce LDL-C in pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
- As an adjunct to other LDL-C-lowering therapies to reduce LDL-C in pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).

8. Review of Safety

8.1. Safety Review Approach

The primary demonstration of safety comes from placebo-controlled data from 157 pediatric patients with HeFH in the 24-week trial 20120123. Supportive safety data was obtained from the open-label extension trial 20120124 which included 150 subjects with HeFH (rolled over from trial 20120123) and 12 subjects with HoFH on evolocumab. In Trial 20120124, safety results are presented for the HoFH and HeFH populations separately and combined. The dose of evolocumab for both studies was 420 mg administered subcutaneously every month.

The safety data included all data available after the last patient completed the Week 24 visit of trial 20120123, as well as all data from the OLE trial available at the time of the data cut-off date (June 8, 2020). All pediatric patients with HoFH had completed or discontinued the trial by this interim analysis timepoint.

The four-month safety update provided information from patients with HeFH in the open-label extension Trial 20120124 collected through the 120-day data cutoff date of December 9, 2020.

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 study drug) were analyzed. Adverse events of special interest, based on the known safety profile of evolocumab, theoretical concerns in pediatric populations, and standard safety review practices, included hypersensitivity events, injection site reactions, immunogenicity, skeletal muscle related adverse events, hepatic related adverse events, and neurocognitive related adverse events.

Safety endpoints included the subject incidence of all-cause death by any cause, CV death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, hospitalization for heart failure, transient ischemic attack [TIA],) and non-coronary revascularization. All safety endpoints, except non-coronary revascularization, were adjudicated. Safety assessments included adverse event and laboratory changes as well as assessments of puberty, and cognition (by change from baseline score in the components of the Cogstate battery test).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

This submission, which contains interim data from trial 20120124, includes at least 52 weeks of data (24 weeks from Part A [trial 20120123] and at least 28 weeks from Part B [trial 20120124]).

The exposure to evolocumab across parent trial 20220123 and the OLE trial 20120124 as of the data cutoff is summarized in the table below. As of the data cutoff date, 149 HeFH subjects had exposure to evolocumab ≥ 6 months, 135 had evolocumab exposure ≥ 12 months, and 72 had evolocumab exposure ≥ 24 months.

Table 20. Overall Exposure to Evolocumab in Trials 20120123 and 20120124 (Full Analysis Set)

Number of subjects on IP exposure (months)[a]	Evolocumab HeFH 420 mg QM (N = 153) n (%)	Evolocumab HoFH 420 mg QM (N = 12) n (%)	Evolocumab Total 420 mg QM (N = 165) n (%)
≥ 6 months	149 (97.4)	12 (100)	161 (97.6)
≥ 12 months	135 (88.2)	11 (91.7)	146 (88.5)

≥ 24 months	72 (47.1)	0	72 (43.6)

HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; IP = investigational product
Based on the final database snapshot date (February 25, 2020) data for 20120123 and the interim analysis data cutoff date (June 8, 2020) data for 20120124.
a % calculation based on total number of subjects who ever received evolocumab in Study 20120123 or 20120124 within each of HeFH and HoFH as well as total.
Source: Modified from CSR 20120124 Table 14-5.1.1 and Summary of Clinical Safety, Table 2

Trial 20120123 (HeFH):

In Trial 20120123, patients with HeFH were randomized 2:1 to 24 weeks of QM evolocumab 420 mg or placebo for a total of 6 doses. Mean investigational product exposure was 5.5 months for both the evolocumab and placebo groups. Ninety-eight patients (94%) in the evolocumab group and 51 (96%) in the placebo group received all 6 doses of investigational product.

Table 21 Exposure to Investigational Product in Study 20120123 (Full Analysis Set)

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
Duration of IP exposure (months)[a]		
Mean (SD)	5.5 (0.1)	5.5 (0.4)
Median	5.6	5.6
Min, Max	5.1, 5.7	1.9, 5.8
Duration of Trial exposure (months)[b]		
Mean (SD)	5.7 (0.3)	5.6 (0.1)
Median	5.6	5.6
Min, Max	5.1, 7.0	5.4, 6.5

EvoMab = Evolocumab; IP=investigational product; QM = monthly (subcutaneous).
N = Number of subjects randomized and dosed in the full analysis set.
a IP exposure (Months) = [min (Last IP dose date + 28 days, End of Study Date) -First IP dose date +1] /365.25 * 12.
b Trial exposure (Months) = (End of Study date - Randomization Date +1)/365.25 * 12
Source: Reviewer created from CSR 20120123 Table 14-5.1.1

Trial 20120124 (HeFH):

In ongoing Trial 20120124, enrolled patients will receive 80 weeks of 420 mg evolocumab QM administered subcutaneous (SC). At the time of data cut-off, the mean (SD) evolocumab exposure for the subjects receiving placebo in trial 20120123 was 15.7 (4.4) months and was 16.4 (3.9) months for those receiving evolocumab. The mean (SD) evolocumab exposure across the 2 trials was 16.1 (4.1) months and median evolocumab exposure was 18.4 months.

Trial 20120124 (HoFH):

For pediatric patients with HoFH in Trial 20120124, 12 patients were treated with at least 1 dose of 420 mg evolocumab QM administered SC: 11 patients received 80 weeks of evolocumab 420 mg QM, and 1 patient discontinued the trial early after 28 weeks. Mean (SD) evolocumab exposure was 17.5 (3.2) months and median evolocumab exposure was 18.4 months. As of the interim analysis data cut-off date of June 8, 2020, all 12 patients with HoFH (100%) had evolocumab exposure ≥28 weeks, and 11 subjects (92%) had evolocumab exposure of 80 weeks, which represents a total of 17 patient-years of exposure.

8.2.2. Relevant Characteristics of the Safety Population

Trial 20120123 (HeFH): 56% of patients with HeFH were female, 85% were white, and 8% were of Hispanic/Latino ethnicity. The mean (SD) age at time of enrollment was 13.7 (2.4) years with a range of 10 to 17 years of age. Thirty-nine (25%) subjects were 10 to 11 years of age and 119 (75%) were 12 to 17 years of age. Mean reflexive LDL-C at baseline was 184 mg/dL, total cholesterol was 250 mg/dL, and non-HDL-C was 203 mg/dL. One (2%) placebo subject had a history of stroke at baseline. No patients had congestive heart failure or clinically diagnosed coronary artery disease at baseline. The most common coronary heart disease (CHD) risk factors at baseline (evolocumab, placebo) were low HDL-C (39%, 34%), family history of premature CHD (30%, 40%), and hypertension (2%, 6%). Sixty-six percent of patients had documented genetic evidence of an FH-causing mutation (64% in the LDL receptor), while 34% of subjects qualified on clinical criteria alone. One hundred and fifty-six (99%) patients were on a statin at baseline; 1 (1%) patient was on ezetimibe only. Twenty-six patients (17%) were on high-intensity statins, 98 patients (62%) were on moderate-intensity statins and 31 (20%) were on low-intensity statins at baseline. Twenty patients (13%) were on a statin plus ezetimibe; 1 (0.6%) patient took only ezetimibe. Twenty patients (13%) were on a statin plus ezetimibe. Refer to Section 6.1.2 for additional details.

Trial 20120124 (HeFH): Trial 20120124 was the OLE trial for pediatric patients with HeFH enrolled in Trial 20120123. Demographic and baseline characteristics for HeFH patients in this trial were similar with those provided above for Trial 20120123.

Trial 20120124 (HoFH): 13 pediatric patients with HoFH were enrolled, and 12 of these received evolocumab. Eighty-three percent (83%) of patients were male and 75% were white; none were of Hispanic ethnicity. Fifty percent of patients were from Europe and 50% from Asia Pacific. The median age at the time of enrollment was 11.5 years; 6 (46%) patients were <12 years of age and 7 (54%) were between 12 and 17 years of age. All 12 patients with HoFH who received evolocumab in the trial had documented genetic evidence of HoFH. Median reflexive LDL-C at baseline was 398 mg/dL, total cholesterol was 448 mg/dL, and non-HDL-C was 411 mg/dL. The most common CHD risk factors were low HDL-C (75%) and family history of premature CHD (42%). One (8%) patient had a history of coronary artery bypass graft (CABG). All 12 (100%) patients in the FAS were taking LDL-lowering therapy at baseline including statins (100%) and

ezetimibe (100%). Refer to Section 6.2.2, Table 18 for additional details.

Reviewer Comment: While no subjects from the US were enrolled, the data in the HoFH population is relevant for the US population given the rarity of the disease, the uniformity of the genetic disease worldwide, and similar global medical management of HoFH. In addition, the trial was conducted in accordance with Good Clinical Practice (GCP) and under a US IND.

Adequacy of the Safety Database

The evolocumab clinical development program has an extensive safety database, primarily in adults, including a cardiovascular outcome trial, from which the safety profile of evolocumab has been previously evaluated.

The Applicant submitted an adequate exposure to assess the safety of evolocumab in the pediatric HeFH population. Across trials 20120123 and 20120124, 149 pediatric patients with HeFH were exposed to evolocumab for 6 months, 135 were exposed for 1 year, and 72 were exposed for 2 years.

For pediatric patients with HoFH, 12 patients had a median evolocumab exposure of 18.4 months. The safety database for this application is small but adequate given the rarity of the HoFH population. Additional pediatric HoFH safety data was previously reviewed from a 12-week trial in 10 patients ages 13 to 17 years (TESLA trial, NCT01588496) and in an OLE trial involving 14 adolescent patients with HoFH exposed to evolocumab for a median of 54 months (TAUSSIG trial, NCT01624142).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Applicant states that trial centers were monitored by Amgen contract research organizations at regular intervals and a visit log was maintained. Monitors were responsible for reviewing adherence to the protocol; compliance with GCP; and the completeness, accuracy, and consistency of data.

In general, the submission was high-quality, complete, and well-organized. As discussed in more detail in Section 8.4.6, some data (approximately 20% depending on the analyte) were missing for the analysis of change from baseline to Week 24 for chemistry, HbA1c, hematology, and vitamin assessments. While there were no safety concerns raised on review of the laboratory data, the missing data does limit the completeness of the assessment.

8.3.2. Categorization of Adverse Events

For the completed Trial 20120123 and for ongoing Trial 20120124 (data cut-off date of June 8, 2020), safety assessments included treatment-emergent adverse events, adverse device events, laboratory parameters, vital signs, neurologic examinations, Cogstate battery tests, anti-evolocumab antibodies, and electrocardiograms. Treatment-emergent adverse events were defined as events with an onset after the administration of the first dose of investigational product and up to and including 30 days after the last dose of investigational product, or the EOS date, whichever was earlier.

Subject incidence of treatment-emergent adverse events, serious adverse events, and adverse events leading to withdrawal of investigational product were summarized by system organ class, high level group term, and preferred term. Adverse events associated with injectable protein therapies (i.e., potential hypersensitivity events and potential injection site reactions) were evaluated using narrow and broad Standard MedDRA Queries (SMQs) or Amgen MedDRA queries (AMQs).

An analysis to assess for new-onset diabetes was performed using the 4-component definition employed in the adult population in BLA 125522. The 4-component definition consisted of the following:

- 2 fasting blood glucose measurements ≥126 mg/dL,
- HbA1c ≥6.5%,
- diabetes adverse events, or
- initiation of anti-diabetic medication in non-diabetic subjects who had normoglycemia, impaired fasting glucose, or both at baseline.

For Trial 20120123, clinical endpoints (death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack (TIA), and hospitalization for heart failure) were adjudicated by an independent, blinded Clinical Events Committee (CEC) comprised of cardiologists not participating in the trial, who reviewed and adjudicated all major adverse cardiac events.

Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1 in Trial 20120123. For Trial 20120124, adverse events were coded using MedDRA Version 23.0.

Adverse Event Grading Scale
The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 scale was used for adverse event grading (http://ctep.cancer.gov/protocolDevelopment/electronic_applications\ctc.htm).

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-

appropriate instrumental ADL.[33]

- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.[34]
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE

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.

8.3.3. Routine Clinical Tests

Measurement of Vital Signs

According to the protocol, BP and HR was measured at each visit, preferably using an automated oscillometric device. BP was recorded in both arms, and the arm with the higher systolic reading at screening was used for BP determinations throughout the trial. BP and HR measurements were performed after the subject was seated for at least 5 minutes. The subject's pulse was measured for 30 seconds and the number multiplied by 2 to obtain heart rate. Detailed instructions on the preferred method to assess height, weight, and waist circumference were included in the protocols (Sections 7.7.2 and 7.7.3).

Tanner Staging

Tanner staging was used to assess the pediatric subjects' physical development during puberty (stage 1 of preadolescent through stage 5 of adult) in trial 20120123 (Day 1 and Week 24/EOS) and in trial 20120124 (Day 1, Weeks 24, 48 and 80/EOS). The developmental stages of the subject's sexual characteristics were rated separately (for example, one stage for pubic hair and one stage for breasts in females or genitals in males) because these characteristics may differ in their degree of maturity.

[33] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[34] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 22 Tanner Stages (Sexual Maturity Ratings) for Trial 20120123 and Trial 20120124

FEMALES:

Stage	BREAST	PUBIC HAIR STAGING	CONCOMITANT CHANGES
1	Prepubertal, papilla elevation	No pigmented hair	
2	Budding; larger areole; palpable and visible elevated contour	Pigmented hair, mainly labial	Accelerating growth rate
3	Enlargement of the breast and areola	Coarser, spread of pigmented hair over mons	Peak growth rate, thicker vaginal mucosa, axillary hair
4	Secondary mound of areola and papilla	Adult type but smaller area	Menarche (stage 3 or 4) decelerating growth rate
5	Mature	Adult distribution	

MALES:

Stage	GENITAL SIZE	PUBIC HAIR STAGING	CONCOMITANT CHANGES	PRADER ORCHIDOMETER
1	Prepubertal	No pigmented hair	Long testis axis < 1.5 cm	1 – 3 mL
2	Early testicular, penile and scrotal growth	Minimal pigmented hair at base of penis	Early voice changes; testes length 2.5 – 3.3 cm	3 – 6 mL
3	Increased penile length and width; scrotal and testes growth	Dark, coarse, curly hair extends midline above penis	Light hair on upper lip, acne, maximal growth, testes length 3.3 – 4.0 cm	8 – 12 mL
4	Increased penis size including breadth; pigmented scrotum	Considerable, but less than adult distribution	Early sideburns; testes 4.0 – 4.5 cm	> 12 mL
5	Adult size and shape	Adult distribution, spread to medial thighs or beyond	Beard growth; testes > 4.5 cm	> 15 mL

Source: Appendix D in Trial 20120124 Protocol

Electrocardiograms

In trial 20120123, ECGs were performed at Day 1, Week 12, and Week 24/EOS and in trial 20120124 at Day 1 and Week 80/EOS). ECGs were performed in a standardized method, in triplicate, and run consecutively, prior to blood draws or other invasive procedures. Using equipment supplied to each site, all protocol-specified ECGs were transmitted to the centralized ECG services provider. The centralized ECG services' cardiologists performed standard interpretations of all tracings. The average of the 3 (or all available) ECG readings were used for analysis. In each treatment group, subjects were categorized and summarized per their maximum post-baseline absolute QTc interval using limits of 450 ms, 480 ms, and 500 ms and by their maximum change from baseline QTc interval using limits of 30 ms and 60 ms.

Neurocognitive Assessments

The Cogstate cognitive battery is a set of largely language-independent neuropsychological tests administered to subjects via computer in approximately 15 to 20 minutes. The Cogstate battery has been used in multiple clinical trials to detect both enhancement and deterioration of cognition associated with drug effects. The timing of the cognitive battery assessment tool in these trials varies from several hours post-dose to 12 or more weeks of continued drug use. Maruff et al. report study results that demonstrate construct validity of the Cogstate brief battery in measuring attention/vigilance, processing speed, memory, and working memory functions in adults which was sensitive to detecting subtle cognitive

impairment in mild traumatic brain injury, schizophrenia, and AIDS dementia complex[35]. The Cogstate tests have been used to examine the cognitive effects of treatment with stimulant medication in children 6 to 16 years old[36] and 8 to 12 years old[37] with attention deficit hyperactivity disorder (ADHD). Cogstate tests have also been used for monitoring and evaluating the safety of central nervous system (CNS) drugs in pediatric indications, such as epilepsy.[38] According to the literature, performance on the Cogstate battery is independent of education level, estimated intelligence quotient,[39] and language or culture of origin[40,41] which allows for accurate classifications of cognitive change using a child's age and gender.

In Trial 20120123, the battery was administered during screening, on study day 1 (baseline), and at Week 24 (EOS) and in trial 20120124 was given at Day 1 (HoFH only), Weeks 24, 48 (HoFH only) and 80/EOS. It consisted of the following 4 tests:

- Groton Maze Learning Task (GMLT; Executive Function): The GMLT measures problem solving and reasoning and uses a maze learning paradigm. In this task, the subject is shown a 10 x 10 grid of boxes on a computer screen. A 28-step pathway is hidden among these 100 possible locations. Each box represents move locations, and the grid refers to the box array (i.e., 10 × 10). Subjects are required to find the hidden pathway guided by 4 search rules. These rules are: do not move diagonally, do not move more than 1 box, do not move back on the pathway, and return to the last correct location after an error. At each step, only the most recently selected box is shown. Feedback is given with visual and auditory cues (green check marks and red crosses) to indicate whether the selected box is correct or incorrect. The head of path, or the last correct location, flashes with a green check when two errors are made in succession (failing

[35] Maruff P, Thomas E, Cysique L, et al. Validity of the CogState Brief Battery: Relationship to Standardized Tests and Sensitivity to Cognitive Impairment in Mild Traumatic Brain Injury, Schizophrenia, and AIDS Dementia Complex. Archives of Clinical Neuropsychology, Volume 24, Issue 2, March 2009, Pages 165–178, https://doi.org/10.1093/arclin/acp010

[36] Snyder AM, Maruff P, Pietrzak RH, Cromer JR, Snyder P. Effect of treatment with stimulant medication on nonverbal executive function and visuomotor speed in children with attention deficit/hyperactivity disorder (ADHD). Child Neuropsychol. 2008;14(3):211-226.

[37] Mollica CM, Maruff P, Vance A. Development of a statistical approach to classifying treatment response in individual children with ADHD. Hum Psychopharmacol. 2004;19(7):445-456.

[38] NCT01389596: A Study of the Efficacy and Safety of Pregabalin as Add-On Therapy for Partial Onset Seizures in Children Ages 4-16 Years (PERIWINKLE) used changes from baseline in the CogState Battery scores at week 12.

[39] Crutcher E, Ali M, Harrison J, Sovago J, Gomez-Mancilla B, Schaaf CP. Assessment of Cognitive Outcome Measures in Teenagers with 15q13.3 Microdeletion Syndrome. J Autism Dev Disord. 2016;46(4):1455-1463. doi:10.1007/s10803-015-2694-0

[40] Bangirana, P., Sikorskii, A., Giordani, B. et al. Validation of the CogState battery for rapid neurocognitive assessment in Ugandan school age children. Child Adolesc Psychiatry Ment Health 9, 38 (2015). https://doi.org/10.1186/s13034-015-0063-6

[41] Yamashita Y, Mukasa A, Anai C, Honda Y, Kunisaki C, Koutaki J et al (2011) Summer treatment program for children with attention deficit hyperactivity disorder: Japanese experience in 5 years. Brain Develop 33(3):260–267.

to return errors). There are 20 well-matched alternate pathways available. The software records each move as an error or as a correct move.

- One Card Learning Test (OCL; Visual Memory): The OCL measures visual recognition memory and uses a pattern separation paradigm using card stimuli. The cards are similar to those found in a deck of playing cards. The subject is asked whether the card currently being presented in the center of the screen was seen previously in this test. The subject responds by pressing the Yes or No key.
- Identification Test (IDN; Attention/Vigilance): The identification test measures visual attention and uses a choice reaction time paradigm using card stimuli. In this test, the playing cards are all either red or black. The subject is asked whether the card currently being presented in the center of the screen is red. The subject responds by pressing the Yes key when the card is red and No when it is black.
- Detection Test (DET; Psychomotor Speed): The Detection test measures information processing speed and uses a simple reaction time paradigm using card stimuli. In this test, the playing cards are all red and black. The subject is asked to press the Yes key as soon as the card in the center of the screen flips over.

The change from baseline to EOS in the standardized score were summarized by treatment group for each test.

Neurologic Examination

Physical examination (at screening and EOS) included a neurologic examination with assessments of motor, sensory, reflexes, coordination, and gait.

Anti-evolocumab Antibody Testing

Blood samples for detection of anti-evolocumab antibodies were assessed at Day 1, Week 12, and Week 24/EOS in trial 20120123 and at Day 1 and Week 80/EOS for trial 20120124 for all subjects who received at least 1 administration of evolocumab. Samples testing positive for binding antibodies to evolocumab were tested for neutralizing antibodies. Additional blood samples could be obtained to rule out anti-evolocumab antibodies during the trial because of a clinical event, such as hypersensitivity.

Laboratory Testing

Table 23. Analyte Listing[1] for Trial 20120123

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix A)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	Total cholesterol
Chloride		Blood	RBC	HDL-C
Bicarbonate		Protein	RDW	LDL-C
Total protein		Glucose	MCV	Triglycerides
Albumin		Bilirubin	MCH	VLDL-C
Calcium		WBC	MCHC	non-HDL-C
Magnesium		RBC	WBC	ApoA1
Phosphorus		Epithelial cells	Platelets	ApoB
Fasting glucose		Bacteria		Estradiol (females)
BUN or Urea		Casts		Testosterone (males)
Creatinine		Crystals		Cortisol
Uric acid				Luteinizing hormone (LH)
Total bilirubin				Adrenocorticotropic hormone (ACTH)
Direct bilirubin				Dehydroepiandrosterone sulfate (DHEA-S)
CK				**Fasting vitamins A, D, E, and K**
ALP				hsCRP
LDH				Lp(a)
AST (SGOT)				Anti-evolocumab antibodies
ALT (SGPT)				PCSK9
				Evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH
				TSH
				HCV antibody[2]
				HCV viral load[3]

1 Day 1 and week 24 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.
2 HCV antibodies are measured before initiating treatment with IP in subjects at high risk for, or with history of HCV infection and in subjects with ALT or AST > 2x ULN at any time during screening. Please note that subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting.
3 Viral load will be tested at the time points indicated in Table 1 in subjects who are positive for HCV.
Source: Applicant's Table 2; CSR 20120123 protocol

Table 24 Laboratory Testing for Trial 20120124

Chemistry	Coagulation	Urinalysis	Hematology	Other Labs
Sodium	PT/INR (per Appendix A)	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	Total cholesterol
Chloride		Blood	RBC	HDL-C
Bicarbonate		Protein	RDW	LDL-C
Total protein		Glucose	MCV	Triglycerides
Albumin		Bilirubin	MCH	VLDL-C
Calcium		WBC	MCHC	non-HDL-C
Magnesium		RBC	WBC	ApoA1
Phosphorus		Epithelial cells	Platelets	ApoB
Fasting glucose		Bacteria	Differential	Estradiol (females)
BUN or Urea		Casts	• Neutrophils	Testosterone (males)
Creatinine		Crystals	• Bands	Cortisol
Uric acid		Urine Creatinine	• Eosinophils	Luteinizing hormone (LH)
Total bilirubin		Urine microalbumin	• Basophils	Adrenocorticotropic hormone (ACTH)
Direct bilirubin		Urine Albumin/ Creatinine ratio	• Lymphocytes	Dehydroepiandrosterone sulfate (DHEA-S)
CK			• Monocytes	hsCRP
ALP				Fasting vitamins A, D, E, and K
LDH				Lp(a)
AST (SGOT)				Anti-evolocumab antibodies
ALT (SGPT)				PCSK9
				Evolocumab (PK)
				HbA1c
				Pregnancy test (females of childbearing potential)
				FSH
				HCV antibody[2]
				HCV viral load[3]

1 Day 1 and week 80 visits must be scheduled at approximately the same time of day, and should be performed as close as possible to 8 am as the hormones measured have diurnal variation.
2 HCV antibodies are measured before initiating treatment with IP in HoFH subjects only at high risk for or with history of HCV infection and in HoFH subjects with ALT or AST > 2x ULN at any time during screening. Please note that HoFH subjects with ALT or AST > 2x ULN must be screen failed unless the elevation is transient as confirmed by retesting.
3 Viral load will be tested at the time points indicated in Table 15 in subjects who are positive for HCV.
Source: Applicant's Table 3; CSR 20120124 protocol

Central laboratories were used in the studies 20120123 and 20120124. Where local laboratories were used (on-site urine pregnancy test only), their participation in internal and external quality control, quality assurance, and accreditation schemes was reportedly evaluated by the study monitors.

Laboratory parameters were summarized for specific analytes using descriptive statistics at each scheduled visit. Lab shift tables, using the CTCAE Version 4.03 grading, were generated for analytes of interest. The results were based on the maximum (worst) shift from baseline to the EOS. CK and liver enzyme abnormalities were assessed by the incidence overall and by visits for

the following categories:

- CK >5x ULN
- CK >10x ULN
- ALT or AST ≥3x ULN
- ALT or AST ≥5x ULN
- Total bilirubin ≥2x ULN
- ALT or AST ≥3x ULN) and Total bilirubin ≥2x ULN and Alkaline Phosphatase <2x ULN

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

8.4. Safety Results

An overall summary of TEAEs in trials 20120123 and 20120124 are presented in the following two tables.

Table 25 Summary of Treatment-emergent Adverse Events in Trial 20120123 (FAS-Actual Treatment)

	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
Number of subjects reporting TEAEs	34 (64.2)	64 (61.5)
Deaths	0	0
Serious Adverse Events	0	1 (1.0)
TEAEs leading to discontinuation of IP	0	1 (1.0)
Severity Grade of TEAEs		
Grade ≥ 2	22 (41.5)	46 (44.2)
Grade ≥ 3	0	4 (3.8)
Grade ≥ 4	0	0

EvoMab =Evolocumab; HeFH-heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; IP=investigational product; N=number of subjects randomized and dosed in the full analysis set; QM=once monthly (subcutaneous); TEAEs= treatment-emergent adverse events
Coded using MedDRA version 22.1.
Source: Reviewer created from 2.7.4 Summary of Clinical Safety, Table 3

Table 26 Summary of Treatment-emergent Adverse Events in Trial 20120124 (FAS-Actual Treatment)

	HeFH:	HoFH:	Total:

	EvoMab 420 mg QM (N = 150) n (%)	EvoMab 420 mg QM (N = 12) n (%)	EvoMab 420 mg QM (N = 162) n (%)
Number of subjects reporting TEAEs	100 (66.7)	7 (58.3)	107 (66.0)
Deaths	0	0	0
Serious Adverse Events	4 (2.7)	2 (16.7)	6 (3.7)
TEAEs leading to discontinuation of IP	0	0	0
Severity Grade of TEAEs			
Grade ≥ 2	79 (52.7)	5 (41.7)	84 (51.9)
Grade ≥ 3	6 (4.0)	2 (16.7)	8 (4.9)
Grade ≥ 4	1 (0.7)	0	1 (0.6)

EvoMab =Evolocumab; HeFH-heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; IP=investigational product; N=number of subjects randomized and dosed in the full analysis set; QM=once monthly (subcutaneous); TEAEs= treatment-emergent adverse events
Coded using MedDRA version 23.0.
Source: Reviewer created from 2.7.4 Summary of Clinical Safety, Tables 4 and 5 and Table 14-6.1.1 of Trial 20120124 Interim CSR

8.4.1. Deaths

No pediatric patients had a fatal adverse event during Trial 20120123 or Trial 20120124.

8.4.2. Serious Adverse Events

Trial 20120123 (HeFH): One (1%) patient in the evolocumab group reported a serious adverse event (SAE) of cholelithiasis[42]; the event was not considered related to investigational product by the investigator and investigational product was continued. I concur with that assessment. No subject in the placebo group had an SAE.

Trial 20120124 (HeFH): Four (3%) patients reported an SAE. One patient had 2 SAEs of perforated appendicitis and peritonitis; all other events occurred in only 1 subject each and

[42] Subject (b) (6): 15-year-old white female; medical history included HeFH, painful axillary lumps, intermittent abdominal pain since (b) (6), heart murmur (benign) and fractured right wrist. Concomitant medications included rosuvastatin, fish oil, vitamin D, cefalexin, and multivitamin. Within a week of starting IP, she reported abdominal pain. On Day 35, an abdominal ultrasound showed a single mobile gallstone within the gallbladder, and the subject was diagnosed with cholelithiasis (grade 3). Approximately 2 ½ months later, she was hospitalized and underwent elective cholecystectomy without complications. Histopathology showed gallbladder consistent with cholelithiasis. The next day she was discharged from the hospital and the event was considered resolved. Action taken with IP was dose not changed. The investigator considered the cholelithiasis unrelated to IP. I agree that the event of cholelithiasis is not related to evolocumab.

included anorexia nervosa[43], headache[44], and wrist fracture (occurred after slipping on ice and falling). No serious treatment-emergent adverse event was considered by the investigator to be related to evolocumab. I concur with that assessment.

Trial 20120124 (HoFH): Two (17%) patients reported an SAE; 1 had appendicitis and 1 had an arteriovenous fistula aneurysm. No SAE was considered by the investigator to be related to evolocumab. I concur with that assessment.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Trial 20120123: One (1%) patient with HeFH in the evolocumab group in Trial 20120123 reported a nonserious adverse event of arthropathy (of toes) leading to discontinuation of investigational product[45]. This event was considered related to investigational product by the investigator, but the narrative does not provide compelling evidence that it was drug-related as the arthropathy did not resolve with discontinuation of evolocumab. No patient in the placebo group reported an adverse event leading to discontinuation of investigational product.

Trial 20120124: No patient with HeFH or HoFH reported an adverse event that led to withdrawal of evolocumab.

[43] Subject (b) (6): 16-year-old white female, current medical conditions included HeFH. Concomitant medications included pravastatin, valproic acid, paroxetine, and olanzapine. She received the first dose of blinded IP (evolocumab) in (b) (6) and the first dose of open label evolocumab in (b) (6). In (b) (6) (Day 315), she was hospitalized with decreased appetite and weight loss and was diagnosed with anorexia nervosa (grade 4). At the time of hospital admission, the patient weighed 45 kg (50.5 kg at time of study enrollment). There were no recent illnesses, infections, or predisposing factors for the event. Treatment medication included sertraline. In early (b) (6), she was discharged from the hospital, weighing 49.3 kg. The outcome of the event was reported as resolved in (b) (6) (Day 508). Action taken with open label evolocumab was dose not changed. The investigator considered the anorexia nervosa unrelated to open label evolocumab and device. I agree that it is unlikely to be related to evolocumab.

[44] Subject (b) (6): 16-year-old white female, current medical conditions included HeFH, migraine, and frequent headaches. Concomitant medications included simvastatin, caffeine/phenacetin/propyphenazone and paracetamol. The subject received the first dose of blinded IP (evolocumab) in (b) (6) and the first dose of open label evolocumab in (b) (6). In (b) (6) (Day 415), she was hospitalized with more frequent headaches (grade 3) and ambulatory blood pressure monitoring was initiated. The outcome of the event was reported as resolved and she was discharged from the hospital on Day 418. Action taken with open label evolocumab was dose not changed. The investigator considered the headache unrelated to open label evolocumab and device. I concur with that assessment.

[45] Subject (b) (6): 12-year-old white female with HeFH; concomitant medications included rosuvastatin. On Day 30, she reported nonserious metatarsal toes arthropathy (grade 2). The investigator considered the arthropathy related to IP, and IP was discontinued. The metatarsal toes arthropathy (grade 2) was reported as resolved on Day 166. On Day 167, an event of metatarsal toes arthropathy (grade 1) was reported which was considered unrelated to IP by the investigator.

8.4.4. Significant Adverse Events

Trial 20120123

Table 27 Summary of TEAEs, Grade ≥3, by Maximum Severity-Toxicity in Trial 20120123

Preferred Term	EvoMab: 420 mg QM (N=104)						Placebo (N=53)					
	Grade 1 to 5		Grade 3 to 5		Grade 5		Grade 1 to 5		Grade 3 to 5		Grade 5	
	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Blood creatine phosphokinase increased	1	(1.0)	1	(1.0)	0	(0.0)	2	(3.8)	0	(0.0)	0	(0.0)
Cholelithiasis	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Headache	11	(10.6)	1	(1.0)	0	(0.0)	1	(1.9)	0	(0.0)	0	(0.0)
Neurogenic shock	1	(1.0)	1	(1.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Source: OCS Analysis Studio, AutoSafety Tool.
Filters: None (Subjects); TRTEMFL = "Y" (Adverse Events).
Percent Threshold: Group 1 - Grade 3 to 5 ≥ 1%.
TEAEs Grade ≥3 are included in the table.

Four (3.8%) patients in the evolocumab group and 0 in the placebo group reported an adverse event that was CTCAE grade 3. The grade 3 events included nonserious events of neurogenic shock (verbatim term: vasovagal shock), headache[44], and blood creatine phosphokinase increased (reportedly due to intense physical activity[46]) and a serious event of cholelithiasis; none were considered related to investigational product by the investigator or this reviewer, and none led to discontinuation of investigational product. No patient experienced a grade 4 or 5 adverse event.

Reviewer Comment: Headache is a listed adverse reaction in Repatha labeling for the 52-week trial (Table 1 in the Repatha PI). In that trial, headache was reported in 4.0% of Repatha subjects and 3.6% of placebo subjects. In this trial, it is reported in 11% of the Repatha group and 2% in the placebo; the majority of cases (10 out of 11) were severity grade 1 or 2. Thus, headache is likely a drug-related adverse reaction in both populations.

- Trial 20120124 (HeFH): Five (3.3%) HeFH subjects experienced 6 CTCAE grade 3 treatment-emergent adverse events: 1 nonserious event of panic attack, 1 nonserious event of increased weight, 1 serious event of wrist fracture, 1 serious event of headache, and 1 subject experienced serious events of perforated appendicitis and peritonitis. One subject experienced a CTCAE grade 4 serious event of anorexia nervosa[43]. No grade 3 or 4 treatment-emergent adverse events were considered related to evolocumab by the investigator or this reviewer.

- Trial 20120124 (HoFH): Two (16.7%) HoFH subjects experienced a grade 3 event; 1 subject had a serious event of arteriovenous fistula aneurysm and 1 subject had both a nonserious event of myositis and a serious event of appendicitis (described in more detail below). None of the grade 3 treatment-emergent adverse events were considered related to evolocumab by the investigator. No HoFH subjects experienced a grade 4 treatment-emergent adverse event.
    - Subject (b) (6) was an 11-year-old white male with HoFH participating in Trial 20120124 and receiving open-label evolocumab 420 mg SC QM. Concomitant medications included atorvastatin, ezetimibe, and acetylsalicylic acid. On Trial Day 333, he experienced an upper respiratory tract infection (grade 2) and was treated with amoxicillin/clavulanate and chlorpheniramine/ pseudoephedrine/acetaminophen. On Trial Day 337, at the Week 48 visit, the subject's creatine kinase (CK) was 1433 U/L (5.7xULN). At the same visit, ALT was 33 U/L (normal range 5-30 U/L) and AST was 59 U/L (normal range 4-37 U/L); alkaline phosphatase and total bilirubin were within normal limits at 194 U/L and 0.2 mg/dL, respectively. The investigator reported an event of increased creatine

[46] In this 16-year-old white female (b) (6)), on ezetimibe 10 mg and rosuvastatin 20 mg at baseline, CK increase started on Day 1 and resolved on Study Day 6. No action was taken with evolocumab. Reportedly due to intense physical activity.

phosphokinase and was subsequently queried by the sponsor to provide a diagnosis. The investigator revised the event term to myositis (grade 3) and attributed the event to the upper respiratory tract infection. No information regarding concurrent symptoms was reported. Other than the elevated CK, no other evidence or test to support the diagnosis of myositis was provided by the investigator. There were no reported interventions for the myositis, and no concomitant medication or dose changes. On Trial Day 340, the event of myositis was considered resolved. On Trial Day 362, the event of upper respiratory tract infection was considered resolved. The investigator considered the upper respiratory tract infection and myositis unrelated to evolocumab and attributed the myositis event to the upper respiratory tract infection. No action was taken with respect to evolocumab dosing in response to the event. Following the Week 48 visit, the subject's CK was next tested at the Week 80 visit and was normal at 83 U/L; ALT and AST were also normal at 29 U/L and 25 U/L, respectively. Creatine kinase values for the duration of trial participation are provided below. Other AEs include appendicitis, headache, and upper respiratory infections at later time points in the trial.

Table 28 Subject (b) (6) Creatine Kinase Values

Study Visit	Relative Day	CK U/L (normal range 2-251 U/L)
Screening	-28	90
Day 1	1	90
Week 12	85	102
Week 48	337	1433
Week 80	568	83

Reviewer Comment: The adverse event of myositis was associated with an increase in CK >5x ULN. Although follow-up labs were not obtained until Week 80, the investigator indicated that the event resolved without intervention within 3 days. It does not appear likely that evolocumab played a significant role in this case of myositis and CK elevation, given the apparent rapid improvement without drug dechallenge, but it cannot be ruled out definitively as a contributing factor.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Trial 20120123

Trial 20120123 (HeFH): The most commonly reported (evolocumab, placebo) adverse events, where the incidence with evolocumab was greater than placebo, were:

- nasopharyngitis: (12 [11.5%], 6 [11.3%]);
- headache: (11 [10.6%], 1 [1.9%]);
- oropharyngeal pain (7 [6.7%], 0 [0%]);
- upper respiratory tract infection: (6 [5.8%], 1 [1.9%]);
- influenza (6 [5.8%], 2 [3.8%])

These adverse events were nonserious and mostly grade 1 or 2 (1 event of headache was grade 3[44]), and none led to discontinuation of investigational product.

Three (2.9%) patients in the evolocumab group and 2 (3.8%) patients in the placebo group reported a device-related adverse event; all of the events were consistent with injection site reactions (preferred terms of injection site pain, application site pain, erythema, and injection site haematoma), and all were CTCAE grade 1 in severity.

Table 29 Treatment-Emergent Adverse Events Reported by >1% of Patients in the Evolocumab Group by Preferred Term (where EvoMab>PBO) in Trial 20120123 (Full Analysis Set - Actual Treatment)

Preferred Term	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)
Nasopharyngitis	6 (11.3)	12 (11.5)	0.2 (-10.3,10.7)	1.0 (0.4,2.6)
Headache	1 (1.9)	11 (10.6)	8.7 (1.7,15.6)	5.6 (0.7,42.3)
Oropharyngeal pain	0	7 (6.7)	6.7 (1.9,11.5)	7.7 (0.4,132.5)
Upper respiratory tract infection	1 (1.9)	6 (5.8)	3.9 (-1.9,9.7)	3.1 (0.4,24.7)
Influenza	2 (3.8)	6 (5.8)	2.0 (-4.8,8.8)	1.5 (0.3,7.3)
Influenza like illness	0	3 (2.9)	2.9 (-0.3,6.1)	3.6 (0.2,68.4)
Constipation	0	3 (2.9)	2.9 (-0.3,6.1)	3.6 (0.2,68.4)
Arthralgia	0	2 (1.9)	1.9 (-0.7,4.6)	2.6 (0.1,52.6)
Dermatitis allergic	0	2 (1.9)	1.9 (-0.7,4.6)	2.6 (0.1,52.6)
Pain	0	2 (1.9)	1.9 (-0.7,4.6)	2.6 (0.1,52.6)
Pharyngitis	0	2 (1.9)	1.9 (-0.7,4.6)	2.6 (0.1,52.6)
Viral upper respiratory tract infection	0	2 (1.9)	1.9 (-0.7,4.6)	2.6 (0.1,52.6)

EvoMab =Evolocumab; QM=once monthly; N=number of subjects randomized and dosed in the full analysis set
Coded using MedDRA version 22.1.
Source: 20120123 ADAE and ADSL dataset; Software: JMP Clinical 7.1 and OCS Analysis Studio, AutoSafety Tool. Filters: None (Subjects); TRTEMFL = "Y" (Adverse Events). Percent Threshold: Group 1 ≥ 1% and MAED (MedDRA 22.1)

Reviewer Comments: These adverse reactions are consistent with the known adverse drug reactions for evolocumab seen in other clinical trials and described in product labeling, such as

headache, nasopharyngitis, upper respiratory tract infection, influenza/influenza-like illness, and injection site reactions. Constipation is not described in labeling, but this adverse event only occurred in 3 (3%) subjects in the evolocumab group in trial 20120123. There were no cases of new onset of diabetes mellitus observed during the trial.

The table below focuses on the HLGTs of administration site reactions, general system disorders, and epidermal and dermal conditions. Injection site reaction (ISR)-related AEs could be coded across multiple preferred terms (PTs), and the signal can be more challenging to detect. As shown in the table below, ISRs/administration site reactions are balanced between the evolocumab group and the placebo group. Of note, the placebo product does not contain evolocumab but does contain the same excipients (inactive ingredients) that are present in evolocumab; thus, any observed imbalances between drug arms would presumably be evolocumab-related. The imbalance in the HLGT of general system disorders is primarily driven by the PTs of influenza-like illness and pain, which are represented in Table 25. Likewise, the imbalance in the HLGT of epidermal and dermal conditions is primarily driven by the PT of dermatitis allergic although the terms of erythema and papule also contribute to the finding.

Table 30 Subject Incidence of Select Treatment-Emergent Adverse Events by System Organ Class, High Level Group Term and Preferred Term in Trial 20120123 (Full Analysis Set - Actual Treatment)

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
# of subjects reporting TEAEs	34 (64.2)	64 (61.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	7 (13.2)	12 (11.5)
Administration site reactions	3 (5.7)	6 (5.8)
Injection site pain	1 (1.9)	2 (1.9)
Injection site erythema	1 (1.9)	1 (1.0)
Injection site haematoma	1 (1.9)	1 (1.0)
Application site pain	0	1 (1.0)
Injection site reaction	0	1 (1.0)
Injection site urticaria	0	1 (1.0)
Injection site vesicles	1 (1.9)	0
General system disorders NEC	1 (1.9)	6 (5.8)
Influenza like illness	0	3 (2.9)
Pain	0	2 (1.9)
Malaise	0	1 (1.0)

Peripheral swelling	0	1 (1.0)
Fatigue	1 (1.9)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	6 (5.8)
Epidermal and dermal conditions	0	5 (4.8)
Dermatitis allergic	0	2 (1.9)
Erythema	0	1 (1.0)
Papule	0	1 (1.0)
Psoriasis	0	1 (1.0)

EvoMab =Evolocumab; TEAEs= treatment-emergent adverse events; N=number of subjects randomized and dosed in the full analysis set; QM= once monthly (subcutaneous)
Coded using MedDRA version 22.1.
Source: Reviewer created from 20120123 ADAE dataset; Software: JMP Clinical 7.1 and Table 14-6.2.1. of Trial 20120123 CSR

Reviewer Comment: Looking at treatment-emergent adverse events by system organ class (SOC), high level group term (HLGT), and preferred term yields a similar collection of AEs with no new safety findings.

Trial 20120124

Trial 20120124 (HeFH): As shown in the following table, the most commonly reported adverse events (>5% of subjects) were nasopharyngitis (22 [15%] subjects), followed by headache (13 [9%]), influenza-like illness (13 [9%]), gastroenteritis (9 [6%]), upper respiratory tract infection (8 [5%]), and oropharyngeal pain (8 [5%]). These events were nonserious and grade 1 or 2 in severity, with the exception of one grade 3 serious adverse event of headache. None of these events led to discontinuation of evolocumab.

Trial 20120124 (HoFH): Out of 12 subjects, 7 (58%) subjects experienced at least 1 treatment-emergent adverse event. All adverse events occurred in only 1 subject each except for epistaxis, which occurred in 2 (17%) subjects. Both epistaxis events were nonserious grade 1. No events led to discontinuation of evolocumab.

Table 31 Treatment-Emergent Adverse Events Reported by ≥ 4 Subjects Overall by Preferred Term in Descending Order of Frequency Trial 20120124 (Full Analysis Set - Actual Treatment)

Preferred Term	HeFH: EvoMab 420 mg QM (N = 150) n (%)	HoFH: EvoMab 420 mg QM (N = 12) n (%)	Total: EvoMab 420 mg QM (N = 162) n (%)
Nasopharyngitis	22 (14.7)	0	22 (13.6)
Headache	13 (8.7)	1 (8.3)	14 (8.6)

Influenza like illness	13 (8.7)	0	13 (8.0)
Gastroenteritis	9 (6.0)	0	9 (5.6)
Upper respiratory tract infection	8 (5.3)	1 (8.3)	9 (5.6)
Oropharyngeal pain	8 (5.3)	0	8 (4.9)
Abdominal pain upper	6 (4.0)	1 (8.3)	7 (4.3)
Fatigue	6 (4.0)	0	6 (3.7)
Pharyngitis	6 (4.0)	0	6 (3.7)
Pyrexia	6 (4.0)	0	6 (3.7)
Attention deficit hyperactivity disorder	4 (2.7)	1 (8.3)	5 (3.1)
Back pain	5 (3.3)	0	5 (3.1)
Diarrhoea	5 (3.3)	0	5 (3.1)
Gastroenteritis viral	5 (3.3)	0	5 (3.1)
Injection site erythema	5 (3.3)	0	5 (3.1)
Myalgia	5 (3.3)	0	5 (3.1)
Tonsillitis	4 (2.7)	1 (8.3)	5 (3.1)
Influenza	3 (2.0)	1 (8.3)	4 (2.5)
Injection site reaction	4 (2.7)	0	4 (2.5)
Viral infection	4 (2.7)	0	4 (2.5)
Vitamin D deficiency	3 (2.0)	1 (8.3)	4 (2.5)

EvoMab=Evolocumab; HeFH-heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; N = number of subjects enrolled and dosed in this trial; QM=once monthly (subcutaneous)
Interim analysis data cutoff date: June 8, 2020
Coded using MedDRA version 23.0.
Source: 20120123 ADAE dataset; Software: JMP Clinical 7.1 and reviewer modified from Table 14-6.7.1 of Trial 20120124 Interim CSR

The table below focuses on the HLGTs of gastrointestinal motility and defaecation conditions, gastrointestinal signs and symptoms, administration site reactions, and general system disorders. These adverse events occurred more frequently and represented a potential drug-related reaction.

Table 32 Subject Incidence of Select Treatment-Emergent Adverse Events by System Organ Class, High Level Group Term and Preferred Term in Trial 20120124 (Full Analysis Set - Actual Treatment)

SYSTEM ORGAN CLASS High Level Group Term *Preferred Term*	HeFH EvoMab 420 mg QM (N = 150) n (%)	HoFH EvoMab 420 mg QM (N = 12) n (%)	TOTAL HeFH + HoFH EvoMab 420 mg QM (N = 162) n (%)

GASTROINTESTINAL DISORDERS	19 (12.7)	2 (16.7)	21 (13.0)
Gastrointestinal motility and defaecation conditions	6 (4.0)	0	6 (3.7)
Constipation	1 (0.7)	0	1 (0.6)
Diarrhoea	5 (3.3)	0	5 (3.1)
Gastrointestinal signs and symptoms	10 (6.7)	2 (16.7)	12 (7.4)
Abdominal pain	1 (0.7)	0	1 (0.6)
Abdominal pain upper	6 (4.0)	1 (8.3)	7 (4.3)
Dyspepsia	2 (1.3)	0	2 (1.2)
Nausea	1 (0.7)	1 (8.3)	2 (1.2)
Vomiting	1 (0.7)	0	1 (0.6)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	35 (23.3)	1 (8.3)	36 (22.2)
Administration site reactions	13 (8.7)	1 (8.3)	14 (8.6)
Injection site pain	3 (2.0)	0	3 (1.9)
Injection site erythema	5 (3.3)	0	5 (3.1)
Application site haematoma	1 (0.7)	0	1 (0.6)
Injection site reaction	4 (2.7)	0	4 (2.5)
Injection site bruising	2 (1.3)	0	2 (1.2)
Injection site haemorrhage	1 (0.7)	1 (8.3)	2 (1.2)
Injection site induration	1 (0.7)	0	1 (0.6)
Injection site oedema	1 (0.7)	0	1 (0.6)
Injection site pruritus	1 (0.7)	0	1 (0.6)
Injection site rash	1 (0.7)	0	1 (0.6)
Injection site swelling	2 (1.3)	0	2 (1.2)
Injection site warmth	1 (0.7)	0	1 (0.6)
General system disorders NEC	19 (12.7)	0	19 (11.7)
Influenza like illness	13 (8.7)	0	13 (8.0)
Fatigue	6 (4.0)	0	6 (3.7)
Swelling	1 (0.7)	0	1 (0.6)

Interim analysis data cutoff date: June 8, 2020
N = number of subjects with HeFH enrolled and dosed from parent trial 20120123 and number of subjects with HoFH enrolled and dosed in this trial; EvoMab =Evolocumab; QM = monthly (subcutaneous); HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia
Coded using MedDRA version 23.0.
Source: 20120123 ADAE dataset; Software: JMP Clinical 7.1 and CSR 20120124 Table 14-6.2.1

Reviewer Comment: Looking at the most commonly reported adverse events and the treatment-emergent adverse events by system organ class (SOC), high level group term (HLGT), and preferred term in Trial 20120124 yields a similar collection of AEs as was seen in Trial 20120123

with no new safety findings.

Device-Related AEs

A total of 11 HeFH (7%) subjects reported at least 1 device-related adverse event. Most device-related adverse events were CTCAE grade 1 and were consistent with injection site reactions.[47] Three subjects experienced grade 2 events of injection site pain, injection site reaction, and pyrexia. One case of grade 2 injection site pain lasted for 27 days and resolved with medication.

Of the 13 subjects who used the AMD for at least 1 dose of evolocumab, 4 subjects had a device-related adverse event; all were grade 1 or 2 in severity.

One (8%) HoFH subject reported 2 device-related treatment-emergent adverse events (CTCAE grade 1 in severity) of nausea and injection site hemorrhage.

8.4.6. Laboratory Findings

Trial 20120123

Chemistry laboratory samples were scheduled to be collected at screening, Week 12, and Week 24 (EOS). Change from baseline to Week 12 data were generally missing in 0 placebo and 3 evolocumab (3%) patients, depending on the analyte. Change from baseline to Week 24 data were missing in approximately 10 placebo (19%) and 29 (28%) evolocumab patients, depending on the analyte.

The Applicant was asked by this reviewer to provide an explanation for the missing lab data at Week 24. The Applicant responded that the parent trial (20120123) EOS visit coincided with the extension trial (20120124) Day 1 visit for subjects rolling over directly into open-label Trial 20120124. Protocol 20120124 Schedule of Assessments for Day 1, and the associated Day 1 lab kits, did not include tubes for the collection of chemistry and hematology samples because these samples should have been collected as part of the Trial 20120123 Week 24 EOS visit for rollover subjects. For the Trial 20120123 Week 24 EOS visit, the Applicant determined that some trial sites inadvertently used the Trial 20120124 Day 1 lab kit, which did not contain chemistry or hematology tubes, instead of the Trial 20120123 EOS lab kit. This resulted in numerous subjects missing chemistry, fasting glucose, and hematology assessments for the Trial 20120123 Week 24 time point. The most common reasons that data were missing for the analysis of change from baseline to Week 24 for chemistry, HbA1c, and hematology assessments were “no sample available for testing” at Week 24 and “late assessment” (i.e., sample was obtained outside the SAP-specified analysis window for Week 24).

Chemistry laboratory values resulting in changes in grades:

[47] Preferred terms include injection site (IS) pain, IS bruising, IS erythema, IS reaction, IS induration, application site haematoma, post procedural haemorrhage and pyrexia.

- Uric acid: 7 (7%) patients in the evolocumab group and 2 (4%) in the placebo group reported shifts from baseline grade 0 to postbaseline grade 3. One patient in the placebo group had an AE of increased uric acid reported; no other adverse events associated with increases uric acid were reported.
- Other lab values that shifted from baseline grades 0, 1, or 2 to postbaseline grade 3 were single occurrences: one placebo subject went from baseline grade 2 to maximum post-baseline grade 3 in total bilirubin; one evolocumab subject went from baseline grade 1 to maximum post-baseline grade 3 in total cholesterol; one placebo subject went from baseline grade 2 to maximum post-baseline grade 3 in total cholesterol.
- No patient reported a grade 4 laboratory toxicity.

Hematology laboratory samples were scheduled to be collected at screening, Week 12, and Week 24 (EOS). Change from baseline to Week 12 data were missing in 3 (6%) placebo and 5 (5%) evolocumab patients. Change from baseline to Week 24 data were missing in approximately 19 (36%) placebo and 35 (34%) evolocumab patients, depending on the analyte. Refer to the previous discussion for details on the cause of most missing data. My review of the hematology data found no clinically meaningful changes between groups.

Hemoglobin A1c (HbA1c) and Fasting Blood Glucose

- Fasting glucose was scheduled to be collected at screening, Week 12, and Week 24 (EOS). Change from baseline to Week 12 data were missing in 0 placebo and 3 evolocumab (3%) patients. Change from baseline to Week 24 data were missing in 10 placebo (19%) and 29 (28%) evolocumab patients. Fasting glucose values were similar between treatment groups at baseline, Week 12, and Week 24.
- HbA1c was scheduled to be collected at screening and Week 24 (EOS). Change from baseline to Week 24 data were missing in 16 (30%) placebo and 22 (21%) evolocumab patients. HbA1c values, in the patients with reported data, were similar between treatment groups at baseline and Week 24. The change from baseline to Week 24 in glucose and HbA1c, shown in the table below, is similar between placebo and evolocumab groups.

Table 33 Changes in Glucose Parameters at Week 24 in Trial 20120123

Change from baseline to Week 24	**Placebo (N=53)**	**Evolocumab (N=104)**
Fasting blood glucose: # of patients	42	75
mean (SD), mg/dL	–1.2 (5.9)	–2.0 (8.2)
median	-1.0	-2.0
Glycated hemoglobin (HbA1c): # of patients	37	82
mean (SD), %	–0.06 (0.04)	–0.01 (0.3)

median	0	0

SD = standard deviation
Source: datasets adam.adsl, adam.adlb and reviewer modified from CSR 20120123 Tables 14-7.10.2 and 14-7.27.1

Creatine Kinase Elevations
CK testing was done at Day 1 and Week 24. Almost all patients (except one evolocumab patient at Week 24) had CK data at baseline and Week 24. No patient had a postbaseline CK value >5x ULN at Week 24.

Liver Enzyme Elevations
Chemistries were collected at screening, Week 12, and Week 24 (EOS). At Week 12, no placebo patients and 2 (2%) evolocumab patients had missing chemistry tests. At Week 24, 10 (19%) placebo patients and 28 (27%) evolocumab patients had missing chemistry tests. One (1.9%) patient in the placebo group had total bilirubin >2x ULN at baseline, Week 12, and Week 24. One (1.0%) patient in the evolocumab group with normal total bilirubin at baseline had total bilirubin >2x ULN at the Week 24 visit (subject had normal ALT/AST values at that assessment with no concurrent adverse events reported). No patient had ALT or AST >3x ULN at any time during the trial.

Steroid Hormones
Steroid hormones were collected at Day 1 and Week 24 (EOS). For cortisol, adrenocorticotropic hormone (ACTH), and dehydroepiandrosterone sulfate (DHEA-S), change from baseline to Week 24 data were missing in 9 (17%) placebo and 16 (15%) evolocumab patients. For follicle-stimulating hormone (FSH) and luteinizing hormone (LH), change from baseline to Week 24 data were missing in 8 (15%) placebo and 9 (9%) evolocumab patients. For estradiol (females), change from baseline to Week 24 data were missing in 6 (22%) placebo and 10 (16%) evolocumab patients. For testosterone (males), change from baseline to Week 24 data were missing in 5 (19%) placebo and 2 (5%) evolocumab patients. With the limitation of missing data, median changes from baseline to Week 24 in steroid hormones were variable but, in general, minimal for both treatment groups.

Table 34 Changes in Steroid Hormones at Week 24 in Trial 20120123

Change from Baseline to Week 24	**Placebo (N=53)**	**Evolocumab (N=104)**
Baseline Estradiol: # of patients	27	60
Baseline Mean (SD), pmol/L	184.3 (200.3)	271.5 (409.9)
Week 24 Mean (SD), pmol/L	164.5 (28.3)	249.5 (315.5)
Change in Estradiol: # of patients	21	51
Mean (SE), pmol/L	9.2 (31.9)	–21.0 (68.3)
Median (Q1, Q3)	0 (-29, 40)	0 (-72, 83)

Baseline Total Testosterone: # of patients	22	43
Baseline Mean (SD), nmol/L	7.1 (7.2)	8.8 (7.4)
Week 24 Mean (SD), nmol/L	8.9 (7.1)	9.6 (7.4)
Change in Total testosterone: # of patients	21	41
Mean (SE), nmol/L	0.20 (0.60)	0.62 (0.49)
Median (Q1, Q3)	0.16 (-0.2, 1.7)	0.32 (-0.7, 2.7)
Baseline Cortisol: # of patients	52	101
Baseline Mean (SD), nmol/L	356.5 (170.1)	376.3 (198.5)
Week 24 Mean (SD), nmol/L	368.2 (182.2)	355.5 (173.3)
Change in Cortisol: # of patients	43	88
Mean (SE), nmol/L	10.7 (22.6)	–26.4 (17.0)
Median (Q1, Q3)	-8.3 (-91, 82)	-29.9 (-116, 73)
Baseline Luteinizing hormone: # of patients	52	104
Baseline Mean (SD), IU/L	3.3 (4.5)	4.5 (7.2)
Week 24 Mean (SD), IU/L	3.4 (3.9)	4.3 (5.8)
Change in Luteinizing hormone: # of patients	45	95
Mean (SE), IU/L	0.4 (0.6)	0.4 (0.7)
Median (Q1, Q3)	0 (-0.6, 0.9)	0.2 (-0.4, 1.4)
Baseline Adrenocorticotropic hormone: # of patients	52	98
Baseline Mean (SD), pmol/L	4.6 (2.5)	5.1 (3.1)
Week 24 Mean (SD), pmol/L	4.4 (2.2)	5.0 (3.2)
Change in Adrenocorticotropic hormone: # of patients	43	83
Mean (SE), pmol/L	–0.12 (0.3)	–0.41 (0.5)
Median (Q1, Q3)	-0.3 (-1.2, 1.0)	-0.5 (-1.5, 1.0)
Baseline Dehydroepiandrosterone: # of patients	51	100
Baseline Mean (SD), µmol/L	3.5 (2.6)	3.7 (3.0)
Week 24 Mean (SD), µmol/L	3.9 (3.1)	3.6 (3.0)
Change in Dehydroepiandrosterone: # of patients	44	87
Mean (SE), µmol/L	0.38 (0.2)	0.13 (0.12)
Median (Q1, Q3)	0.26 (-0.3, 0.8)	0.03 (-0.3, 0.6)
Baseline Follicle-stimulating hormone: # of patients	52	104
Baseline Mean (SD), IU/L	4.5 (2.9)	4.6 (2.9)
Week 24 Mean (SD), IU/L	4.6 (2.8)	4.5 (2.4)
Change in Follicle-stimulating hormone: # of patients	45	95
Mean (SE), IU/L	0.5 (0.3)	0.1 (0.2)
Median (Q1, Q3)	0.2 (-0.3, 0.9)	0 (-0.8, 1.0)

SD= standard deviation; SE = standard error
Source: datasets adam.adsl, adam.adlb and reviewer modified from CSR 20120123 Tables 14-7.24.1 to 14-7.24.7

Vitamins A, D, and K
Vitamins A/D/K were collected at Day 1 and Week 24 (EOS). For vitamin A, change from baseline to Week 24 data were missing in 36 (68%) placebo and 54 (52%) evolocumab patients. Unlike chemistry and hematology laboratory assessments where nearly all subjects had a baseline assessment, a significant proportion of vitamin A assessments were also missing at baseline. The Applicant was asked by this reviewer to provide an explanation for the missing lab data. Amgen stated that in April 2019 they were notified by (b) (4) the laboratory contracted for this trial, about an issue they had identified with vitamin A sample processing at several sites where samples were not being frozen on the day of collection and shipped to the lab. Instead, some sites were batching vitamin A samples for bulk shipping at a later date (e.g., monthly). The vitamin A samples only have a 28-day stability, so this delay resulted in samples arriving at the lab out of the stability window and unable to be tested. Vitamin A tests were also canceled because the sample volume received at the lab was insufficient for testing.

Table 35 Missing Vitamin A Values in Trial 20120123

	Placebo (N = 53)	Evolocumab (N = 104)
Results available - (n)		
Baseline	33	72
Week 24	26	61
Change from baseline to Week 24	17	50
Reasons for missing assessments, where available		
Vitamin A (baseline)	18 insufficient sample volume 2 specimens beyond stability	27 insufficient sample volume 5 specimens beyond stability
Vitamin A (Week 24)	22 insufficient sample volume 4 late assessments 1 specimen beyond stability	25 insufficient sample volume 11 specimens beyond stability 5 late assessments 2 no specimen received

Source: Applicant's Table 5 from Response to FDA IR from March 1, 2021

For vitamin D, change from baseline to Week 24 data were missing in 11 (21%) placebo and 10 (10%) evolocumab patients. For vitamin K, change from baseline to Week 24 data were missing in 45 (85%) placebo and 79 (76%) evolocumab patients. As was seen with Vitamin A, a significant proportion of vitamin K assessments were missing at both the baseline and Week 24 timepoints. Amgen, in response to FDA's query regarding this missing data, stated that two memos were issued to investigators and trial sites regarding vitamin K sample processing issues that resulted from samples arriving at the lab beyond stability. The first memo, dated November 5, 2018, notified sites of a high cancellation rate for vitamin K tests due to failure of site staff to protect samples from light by wrapping them in aluminum foil; the memo also restated the proper sample handling and processing instructions. The second memo, dated

May 31, 2019, notified sites that, because of a high cancellation rate of vitamin K tests due to samples arriving at (b) (4) unprotected from light, the tube required for the vitamin K test was changed to an amber transfer tube instead of a clear transfer tube wrapped in foil. The memo also provided instructions for proper use of the new tubes and disposal of the previous tubes. Similar to vitamin A, vitamin K tests were also canceled because the sample volume received at the lab was insufficient for testing.

Table 36 Missing Vitamin K Values in Trial 20120123

	Placebo (N = 53)	Evolocumab (N = 104)
Results available - (n)		
Baseline	21	43
Week 24	20	42
Change from baseline to Week 24	8	25
Reasons for missing assessments, where available		
Vitamin K (baseline)	11 insufficient sample volume for testing 9 improper sample submitted (eg, whole blood, sample hemolyzed) 6 no light protection 4 beyond stability 1 no sample received 1 technical problem	15 no light protection 18 insufficient sample volume for testing 20 improper sample submitted (eg, whole blood, sample hemolyzed, frozen) 4 no sample received 4 beyond stability
Vitamin K (Week 24)	15 insufficient sample volume for testing 6 no light protection 5 no sample received 3 late assessments 3 improper sample submitted 1 beyond stability	22 insufficient sample volume for testing 20 no light protection 6 no sample received 6 beyond stability 5 improper sample submitted 3 late assessments

Source: Applicant's Table 6 from Response to FDA IR from March 1, 2021

With the limitation of missing data, median and mean change from baseline to Week 24 in Vitamins A and D was minimal for both treatment groups.

Table 37 Changes in Vitamins at Week 24 in Trial 20120123

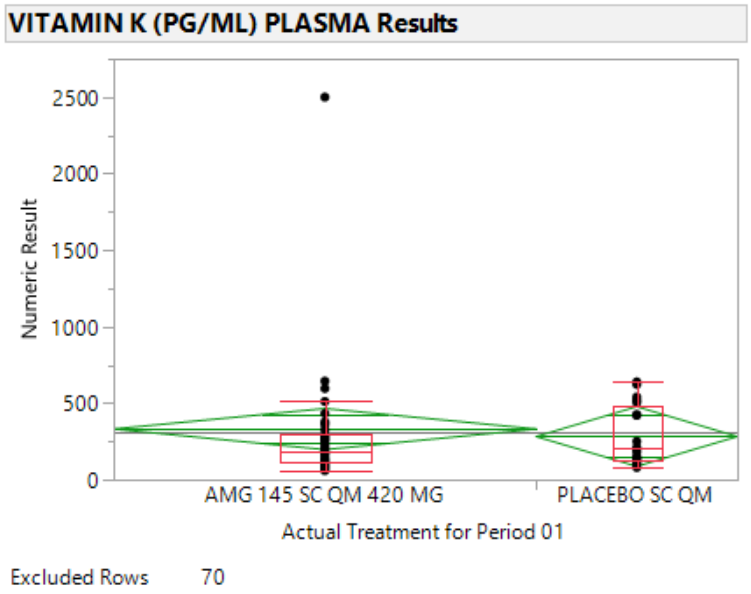
Change from baseline to Week 24	**Placebo (N=53)**	**Evolocumab (N=104)**
Vitamin A: # of patients	17	50
mean (SE), mg/L	–0.03 (0.02)	–0.05 (0.01)

median	-0.03	-0.03
Vitamin D: # of patients	42	94
mean (SE), ng/mL	–1.5 (1.3)	1.4 (1.2)
median	-3.5	2.0
Vitamin K: # of patients	8	25
mean (SE), pg/ml	–62.9 (116.5)	154.3 (136.6)
median	29.0	-8.0

SE = standard error
Source: datasets adam.adsl, adam.adlb and reviewer modified from CSR 20120123 Tables 14-7.25.1, 14-7.25.2 and 14-7.25.4

As shown in the figure below, with the exception of one outlier subject in the evolocumab group, vitamin K levels were generally similar between the evolocumab and placebo groups at Week 24.

Figure 7 Vitamin K Levels at Week 24 in Trial 20120123 (Full Analysis Set)



AMG 145=evolocumab
Source: 20120123 ADLB dataset; Software: JMP Clinical 7.1

Vitamin E Assessment
Lipoproteins are the major carriers of plasma lipid-soluble antioxidants, including vitamin E. Plasma α-tocopherol (vitamin E) levels are well correlated with plasma lipid levels.[48] In humans,

[48] Rigotti A. Absorption, transport, and tissue delivery of vitamin E. Molecular Aspects of Medicine 28 (2007) 423–436.

relative lipoprotein distribution analysis indicates that tocopherols are mostly transported in LDL and HDL at similar proportions with less than 20% carried in VLDL and other lipoproteins[49]. Thus, plasma vitamin E homeostasis is connected to mechanisms underlying normal lipoprotein metabolism.

Alpha-tocopherol levels of less than 0.5 mg/dL (5 mcg/mL or 11.5 micromol/L) are considered deficient. However, measurement of serum alpha-tocopherol concentrations may not be an accurate measure of vitamin E status in patients with significant hyperlipidemia. For these patients, effective vitamin E levels can be calculated as the ratio of serum alpha-tocopherol per gram total lipids (alpha-tocopherol [mg] / total lipids [g], where total lipids = cholesterol + triglycerides). A normal result is >0.8 mg.[50]

Patients given PCSK9 inhibitors may develop low LDL-C levels, but HDL-C levels do not decrease with PCSK9 inhibitor therapy. This is important because HDL is also a major carrier of plasma α-tocopherol as well as a source of vitamin E for cellular uptake. Because of this theoretical concern that vitamin E levels may decrease with PCSK9 inhibitor use, in the original submission for evolocumab, a vitamin E substudy was performed in the 52-week trial 20110109 (DESCARTES). Approximately 100 adult patients were enrolled in a vitamin E substudy where additional blood samples were collected at Day 1, Week 12 and Week 52 visits for a vitamin E analysis, which included serum vitamin E, LDL-vitamin E, HDL-vitamin E, red blood cell (RBC)-vitamin E, and non-HDL-vitamin E. The mean and median concentration of total serum vitamin E at all postbaseline timepoints was decreased in the evolocumab group as compared to placebo and baseline values. This was expected as vitamin E plasma concentrations may decrease when lipoproteins (such as chylomicrons, VLDL-C and LDL-C) transporting vitamin E decrease. However, the mean and median concentration of normalized serum vitamin E (Serum Vitamin E [µmol/L] / Total Cholesterol [mmol/L]) at Week 52 was similar to baseline concentrations for both the evolocumab and placebo groups.

In Trial 20120123, change from baseline to Week 24 data for vitamin E were missing in 8 (15%) placebo and 11 (11%) evolocumab patients. As expected, a reduction in *total* vitamin E over time was seen in the evolocumab group compared with the placebo group but remained within the normal range (data not shown). In contrast, *normalized* mean (SD) vitamin E concentrations at Week 24 were numerically higher in both groups compared with baseline. The mean (SD) change from baseline to Week 24 in normalized vitamin E concentration was numerically higher in the evolocumab group compared with the placebo group (0.79 [0.95] and 0.21 [0.81] µmol/L, respectively); however, the standard deviations surrounding both point estimates overlap and contain both values.

[49] Perugini, C., Bagnati, M., Cau, C., Bordone, R., Paffoni, P., Re, R., Zoppis, E., Albano, E., Bellomo, G., 2000. Distribution of lipid-soluble antioxidants in lipoproteins from healthy subjects. Effects of in vivo supplementation with a-tocopherol. Pharmacol. Res.2000. 41, 65–72.
[50] Pazirandeh S, Burns DL. Overview of vitamin E. In: UpToDate, Post, TW (Ed), UpToDate, Waltham, MA, 2021.

Table 38 Normalized Vitamin E in µmol/L by Scheduled Visit in Trial 20120123 (Full Analysis Set - Actual Treatment)

Normalized Vitamin E (µmol/L)	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)
Baseline		
N	52	103
Mean (SD)	4.91 (0.96)	5.10 (0.84)
Median	4.88	4.99
Week 24		
N	43	92
Mean (SD)	5.15 (0.89)	5.88 (0.89)
Median	5.09	5.87
Change from baseline to Week 24		
N	42	92
Mean (SD)	0.21 (0.81)	0.79 (0.95)
Median	-0.03	0.81

N = number of subjects randomized and dosed in the full analysis set; n = number of subjects with observed data;
EvoMab=Evolocumab; QM=monthly (subcutaneous);
Normalized Serum Vitamin E =Serum Vitamin E (µmol/L) / Total Cholesterol (mmol/L)
Subjects receiving Vitamin E supplements during the trial are excluded; however, no subject met this criterion.
Summary is based on observed data and no imputation is used for missing values.
Source: Table 3 from Applicant's response to FDA IR (March 1, 2021)

Trial 20120124

All patients had at least 28 weeks of exposure in Trial 20120124 at the time of the interim data cut. Some HeFH patients had not reached the Week 48 or Week 80 timepoints at the time of data cut.

Chemistry laboratory samples were collected at screening, Week 12, Week 48, and Week 80 (EOS). Change from baseline to Week 12 data were available in approximately 98% of evolocumab patients, depending on the analyte; baseline to Week 48 in ~81% of evolocumab patients; and baseline to Week 80 in ~67% of evolocumab patients. No clinically meaningful changes were noted in the chemistry labs. Changes in CK and liver enzyme test are discussed separately below.

Hematology laboratory samples were scheduled to be collected at screening, Week 48, and Week 80 (EOS). Change from baseline to Week 48 data were available in approximately 129

(80%) evolocumab patients, depending on the analyte, and from baseline to Week 80 in ~107 (66%) evolocumab patients. No clinically meaningful changes were noted.

Hemoglobin A1c (HbA1c) and Fasting Blood Glucose

- Fasting glucose was collected at screening, Week 12, Week 48, and Week 80 (EOS). Change from baseline to Week 12 data were available in 99% of evolocumab patients, baseline to Week 48 in 81% of evolocumab patients, and baseline to Week 80 in 66% of evolocumab patients. Fasting glucose values were similar at all timepoints tested, and there were no clinically meaningful changes noted.
- HbA1c was scheduled to be collected at screening and Week 80 (EOS). Change from baseline to Week 80 data were available in 106 (65%) evolocumab patients. HbA1c values, in the patients with reported data, were similar at baseline and at Week 80, with no clinically meaningful changes.

Creatine Kinase Elevations

CK testing was performed at screening, Week 12, Week 48, and Week 80 (EOS). Change from baseline to Week 12 data were available in 98% of evolocumab patients, from baseline to Week 48 in 81% of evolocumab patients, and from baseline to Week 80 data in 67% of evolocumab patients.

- HeFH Subjects

Two (1.4%) subjects, both with normal CK at baseline, had a postbaseline CK value that was >5x ULN at Week 12. One subject (Subject 20120123-(b) (6)) had a CK of 1128 U/L, and one subject had a postbaseline CK value that was >10x ULN (see details below). In both subjects, CK values returned to normal at Weeks 48 and 80.

- Subject: (b) (6)
  Treatment Assignment 20120123: Blinded Placebo
  Treatment Assignment 20120124: Open-label Evolocumab 420 mg SC QM
  Subject (b) (6) was a 16-year-old white female participating in both Studies 20120123 and 20120124. The subject's medical history included HeFH, osteogenesis imperfecta, and attention deficit disorder. Concomitant medications included methylphenidate and pravastatin. The subject received the first dose of blinded investigational product (placebo) in parent Trial 20120123 in (b) (6). The subject continued into open-label extension Trial 20120124 and received the first dose of open-label evolocumab in (b) (6). In (b) (6), at the Trial 20120124 Week 12 visit, the subject's CK was 1128 U/L (5.9x ULN). At the same visit, ALT was 14 U/L (normal range 5-30 U/L) and AST was 29 U/L (normal range 4-31 U/L); alkaline phosphatase and total bilirubin were within normal limits at 85 U/L and 0.2 mg/dL, respectively. When queried by the sponsor, the investigator reported the CK increase was not clinically significant and did not meet the definition of an adverse event. No information regarding

concurrent symptoms was reported, and no alternate etiology or explanation of elevated CK was provided by the investigator. There were no reported interventions, no concomitant medication or dose changes, nor any other adverse events reported in the same relative timeframe. No action was taken with respect to evolocumab dosing in response to the CK elevation. Following the Week 12 visit, the subject's CK was tested at the Week 48 and Week 80 visits and was normal at 67 U/L and 71 U/L, respectively. ALT and AST were also normal at Week 48 (15 U/L and 21 U/L, respectively) and Week 80 (12 U/L and 13 U/L, respectively). Creatine kinase values for the duration of trial participation are provided below.

Table 39 Subject (b) (6) Creatine Kinase Values

Date	Treatment Assignment	Trial Visit	Relative Day	CK U/L
(b) (6)	Trial 20120123 (CK normal range 2-147 U/L)			
	Placebo	Screening	-12	80
	Placebo	Day 1	1	146
	Placebo	Week 12	86	63
	Evolocumab[a]	Week 24	186	96
	Trial 20120124 (CK normal range 26-192 U/L)			
	Evolocumab	Week 12	84	1128
	Evolocumab	Week 48	336	67
	Evolocumab	Week 80	561	71

[a] Subject received first dose of open-label evolocumab in Trial 20120124
Source: Applicant's Response to FDA Information Request dated April 13, 2021

- Subject: (b) (6)
  Treatment Assignment 20120123: Blinded Placebo
  Treatment Assignment 20120124: Open-label Evolocumab 420 mg SC QM
  Subject (b) (6) was a 15-year-old white male participating in both Studies of 20120123 and 20120124. The subject's medical history included heterozygous familial hypercholesterolemia, Osgood-Schlatter's disease of the right knee, and oral herpes. Concomitant medications included zovirax/acyclovir BID; paracetamol prn; and rosuvastatin 5 mg QD. The subject received the first dose of blinded investigational product (placebo) in (b) (6) The subject continued into open-label extension Trial 20120124 and received the first dose of open-label evolocumab in (b) (6). In (b) (6), at the Trial 20120124 Week 12 visit (Study Day 85), the subject's CK was 6372 U/L (20.7x ULN). At the same visit, ALT was 40 U/L (normal range 5-30 U/L) and AST was 99 U/L (2.6x ULN) (normal range 4-38 U/L); alkaline phosphatase and total bilirubin were within normal limits at 129 U/L and 0.5 mg/dL, respectively. Creatinine was also in the normal range. When queried, the investigator reported the CK increase was sports-related and did not meet the definition of an adverse event. There were no reported interventions, no

concomitant medication or dose changes, nor any other adverse events reported in the same relative timeframe. No information regarding concurrent symptoms was reported. No action was taken with respect to evolocumab dosing in response to the CK elevation. Following the Week 12 visit, the subject's CK was tested at the Week 48 and Week 80 visits and was normal at 86 U/L and 138 U/L, respectively; ALT and AST were also normal at both Week 48 (13 U/L and 14 U/L, respectively) and Week 80 (12 U/L and 16 U/L, respectively). Creatine kinase values for the duration of trial participation are provided below.

Table 40 Subject (b) (6) Creatine Kinase Values

Date	Treatment Assignment	Visit	Relative Day	CK U/L
(b) (6)	Trial 20120123 (CK normal range 2-251 U/L)			
	Placebo	Screening	-23	204
	Placebo	Day 1	1	81
	Placebo	Week 12	83	79
	Evolocumab[a]	Week 24	167	106
	Trial 20120124 (CK normal range 39-308 U/L)			
	Evolocumab	Week 12	85	6372
	Evolocumab	Week 48	337	86
	Evolocumab	Week 80	568	138

[a] Subject received first dose of open-label evolocumab in Trial 20120124
Source: Applicant's Response to FDA Information Request dated April 13, 2021

Reviewer Comment: It does not appear likely that evolocumab played a significant role in these cases of CK elevation, as the CK elevations in both subjects resolved without intervention and one case is likely exercise-related. However, we are lacking data on how quickly the CK elevations resolved. Section 6.4 of the protocol states that if CK is > 5x ULN, CK must be retested before evolocumab is administered. Both of these patients did not have a CK re-test until the next scheduled timepoint; thus, a CK retest was not done prior to the next administration of evolocumab.

- HoFH Subjects

Two (16.7%) subjects with normal baseline CK had at least 1 postbaseline CK value that was >5x ULN. One subject had CK elevations at Week 12 (Subject 20120124-(b) (6), CK: 1454 U/L) and Week 80 (CK: 1909 U/L) with no relevant co-reported adverse events. The other subject had CK elevations at Week 48 (CK: 1433 U/L) along with an upper respiratory tract infection and a grade 3 nonserious event of myositis (discussed in more detail in Section 8.4.4 Significant Adverse Events, see Table 24). No HoFH subjects had a postbaseline CK value >10x ULN.

Liver Enzyme Elevations

- HeFH Subjects

  - Total bilirubin: A total of 3 (2.0%) subjects had a postbaseline total bilirubin >2x ULN; one of the 3 subjects had an elevated total bilirubin at baseline. In the subject with an elevated bilirubin at baseline, the total bilirubin was also elevated at Week 12 but not at Week 48 or 80. Amongst subjects with normal total bilirubin at baseline, 2 (1.5%) subjects had total bilirubin >2x ULN at Week 12. These 2 subjects also had a total bilirubin >2x ULN at the Week 48 visit, but only one subject had a total bilirubin >2x ULN at Week 80.
  - ALT or AST: No subjects had ALT or AST >3x ULN at baseline. One (0.7%) subject had ALT or AST >3x ULN at Week 12 (Subject 20120123-(b) (6), 11-year-old white male, ALT: 116 U/L), which returned to normal at Week 48 (during the 120-day safety update period). No subject had ALT or AST >5x ULN at any time during the trial.
- HoFH Subjects
  - One (8%) subject (Subject 20120124-(b) (6)) had total bilirubin >2x ULN at baseline and at each postbaseline timepoint (Weeks 12, 48, and 80). No subjects with normal total bilirubin at baseline had total bilirubin >2x ULN at any time during the trial.
  - ALT or AST: No subject had ALT or AST >3x ULN at any time during the trial.

No HeFH or HoFH subject experienced Hy's Law (ALT or AST >3x ULN and total bilirubin >2x ULN and alkaline phosphatase <2x ULN) at any time during the trial.

hsCRP

- HeFH: Shifts in hsCRP from baseline <3 mg/L to maximum postbaseline >3 mg/L were reported in 11 (7%) subjects.
- HoFH: Shifts in hsCRP from baseline <3 mg/L to maximum postbaseline >3 mg/L were reported in 2 (16.7%) subjects.

Steroid Hormones

Steroid hormones were scheduled to be collected at Day 1 and Week 80 (EOS). For cortisol, ACTH, and DHEA-S, change from baseline to Week 80 data were available in approximately 109 (67%) evolocumab patients, depending on the analyte. For FSH and LH, change from baseline to Week 80 data were available in 108 (67%) evolocumab patients. For estradiol (females), change from baseline to Week 80 data were available in 57 (68%) evolocumab female patients. For testosterone (males), change from baseline to Week 80 data were available in 45 (58%) evolocumab male patients. There were median increases in estradiol in the 57 female subjects at Week 80 and in testosterone in the 45 male subjects. There were small increases in cortisol, LH, ACTH, DHEA-S and no meaningful change in FSH.

Vitamins A, D, and K

Vitamins A/D/K were collected at Day 1 and Week 80 (EOS). For vitamin A, change from

baseline to Week 80 data were available in 53 (33%) evolocumab patients. For vitamin D, change from baseline to Week 80 data were available in 107 (66%) evolocumab patients. For vitamin K, change from baseline to Week 80 data were available in 13 (8%) evolocumab patients. Median changes in Vitamins A and D from baseline to Week 80 were minimal. Median concentrations of Vitamin K were similar at baseline (n=66) and at Week 80 (n=38) with values of 211 and 259 pg/mL respectively. However, because only 13 out of 162 subjects had data on 'change from baseline to week 80' reported, there was more variability in this data point with a Week 80 (median [Q1, Q3] change from baseline to Week 80 of -60.0 [-330.0, 12.0]). This is largely a reflection of the incomplete sample size at this timepoint.

Vitamin E Assessment
Change from baseline to Week 80 data for vitamin E were available in 65% of evolocumab patients. As expected, and discussed previously for Trial 20120123, a reduction in total vitamin E over time was seen in the evolocumab group but remained in the normal range. For normalized vitamin E, small numerical increases in vitamin E levels were observed at Week 80 in the HeFH and HoFH populations on evolocumab.

Table 41 Normalized Vitamin E in µmol/L by Scheduled Visit in Trial 20120124 (Full Analysis Set - Actual Treatment)

Normalized Vitamin E (µmol/L)	HeFH (N = 150)	HoFH (N = 12)	TOTAL HeFH + HoFH (N=162)
Baseline			
n	148	12	160
Mean (SD)	5.02 (0.88)	4.26 (0.91)	4.97 (0.90)
Median	4.96	3.95	4.94
Week 80			
n	92	11	103
Mean (SD)	5.80 (0.94)	4.77 (0.83)	5.69 (0.98)
Median	5.74	4.81	5.66
Change from baseline to Week 80			
n	91	11	102
Mean (SD)	0.83 (0.91)	0.57 (0.55)	0.81 (0.88)
Median	0.78	0.34	0.77

Interim analysis data cutoff date: June 8, 2020
N = number of subjects randomized and dosed in the full analysis set; n = number of subjects with observed data; EvoMab=Evolocumab; QM=monthly (subcutaneous); HeFH = heterozygous familial hypercholesterolemia; HoFH =homozygous familial hypercholesterolemia
Normalized Serum Vitamin E =Serum Vitamin E (µmol/L) / Total Cholesterol (mmol/L)

Subjects receiving Vitamin E supplements during the trial are excluded; however, no subject met this criterion.
Summary is based on observed data and no imputation is used for missing values.
Source: Table 5 from Applicant's response to FDA IR (March 1, 2021)

Reviewer Comment: Administration of evolocumab in pediatric patients with HeFH and HoFH in studies 20120123 and 20120124 did not negatively affect vitamin E levels.

In conclusion, there were no clinically significant treatment-related laboratory abnormalities or significant changes in steroid hormones or vitamin levels reported in Trial 20120123 or Trial 20120124. Steroid and vitamin assessments were limited because of small sample sizes at multiple timepoints. The incidence of liver enzyme and CK elevations was low throughout the trials. HbA1c and fasting blood glucose values remained largely unchanged throughout the studies.

8.4.7. Electrocardiograms (ECGs)

Trial 20120123 (HeFH):
My review of systolic and diastolic blood pressure and heart rate (beats per minute) changes at Weeks 4, 12, 20, 22, and 24 did not reveal any clinically meaningful changes in these vital signs for either group throughout the 24-week trial.

A review of ECG parameters, such as PR interval, QRS interval, QT interval, QTcB interval (Bazett's correction), QTcF interval (Friedricia's correction), and RR interval, assessed at baseline and Weeks 12 and 24, showed no clinically meaningful changes in these parameters in either treatment group.

- Using Bazett's correction method for QTc (QTcB):
  -
  - Seven (7%) and 0 (0%) patients in the evolocumab and placebo treatment groups, respectively, had a maximum postbaseline QTcB interval of >450 to 480 msec. No patient had a postbaseline QTcB interval >480 msec.
  - A maximum increase of >30 to 60 msec from baseline was reported for 6 (6%) evolocumab patients and 0 (0%) placebo patients; no evolocumab patients and 1 (2%) placebo patient had a maximum increase >60 msec from baseline.
- Using Fridericia's correction method for QTc (QTcF):
  - No postbaseline QTcF intervals >450 msec were reported in either treatment group.
  - A maximum increase of >30 to 60 msec from baseline was reported for 4 (4%) evolocumab patients and 2 (4%) placebo patients; no increases >60 msec from baseline were reported.

Trial 20120124 (HeFH):
My review of systolic and diastolic blood pressure and heart rate (beats per minute) changes at

Weeks 4, 12, 24, 48, and 80 (EOS) did not reveal any clinically meaningful changes throughout the trial.

ECGs were performed at Day 1 and Week 80. Change from baseline to Week 80 data was available in ~55% of HeFH subjects and ~83% of HoFH subjects. A review of ECG parameters, such as PR interval, QRS interval, QT interval, QTcB interval (Bazett's correction), QTcF interval (Friedricia's correction), and RR interval showed no clinically meaningful changes in these parameters.

- Using Bazett's correction method for QTc (QTcB):
  - No subjects had a maximum QTcB interval of >450 msec at any time postbaseline.
  - A maximum increase of >30 to 60 msec from baseline was reported for 6 (4%) evolocumab patients.
  - No subjects had a maximum increase >60 msec from baseline.
- Using Fridericia's correction method for QTc (QTcF):
  - No subject reported a postbaseline QTcF interval >450 msec or maximum increase of >30 msec from baseline.

Trial 20120124 (HoFH):
No HoFH subjects had QTc >450 msec or a maximum increase from baseline >30 msec at any time point using either the Bazett's or Fridericia's correction method.

8.4.8. Immunogenicity

Anti-evolocumab Antibodies
Trial 20120123: Anti-evolocumab antibodies were collected at Day 1, Week 12, and Week 24 (EOS). A total of 104 subjects in the evolocumab group had at least 1 on-study binding antibody assay result available, and 102 subjects had a baseline result available. No subject in the evolocumab group had baseline or post-baseline anti-evolocumab binding antibodies detected at any time point during the trial.

Trial 20120124: Anti-evolocumab antibodies were tested at Day 1 and Week 80. A total of 109 (67%) subjects had a result at baseline, and 143 (88%) had a postbaseline test at some point during the trial. No HeFH or HoFH subjects had baseline or postbaseline anti-evolocumab binding antibodies detected at any time point during the trial.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Adjudicated Clinical Endpoint Events

Events of all-cause death, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure were adjudicated by an independent CEC in Trial 20120123 but not in open-label Trial 20120124. No patient had a cardiovascular endpoint adverse event.

8.5.2. Hypersensitivity Events and Injection Site Reactions

Adverse events associated with injectable protein therapies (i.e., potential hypersensitivity events and potential injection site reactions) were evaluated in Trial 20120123 and Trial 20120124 using narrow and broad SMQs or AMQs. This reviewer agreed with the terms listed in the Applicant's query for injection site reactions; it was relevant and specific for this application. Refer to Appendices 13.3 and 13.4 for a listing of terms included in the SMQ and AMQ.

Trial 20120123 (HeFH):

- ISRs/hypersensitivity: As shown in the following table, the subject incidence of potential injection site reactions was similar between the evolocumab (5 subjects [5%] using both narrow and broad AMQ) and placebo (3 subjects [6%] using both narrow and broad AMQ) treatment groups. Potential hypersensitivity events occurred in a higher percentage of evolocumab subjects (4 [4%] narrow SMQ; 7 [7%] broad SMQ) than placebo subjects (0% for both narrow and broad SMQ). The reported events were all nonserious and grade 1 or 2.

Table 42 Adverse Events of Special Interest Using Narrow SMQ and AMQ Search Strategy for Potential Hypersensitivity Events and Potential Injection Site Reaction Events in Trial 20120123 (Full Analysis Set - Actual Treatment)

TEAE of SPECIAL INTEREST High Level Term *Preferred Term*	Placebo QM (N = 53) n (%)	EvoMab 420 mg QM (N = 104) n (%)
POTENTIAL INJECTION SITE REACTION EVENTS	3 (5.7)	5 (4.8)
Injection site reactions	3 (5.7)	5 (4.8)
Injection site pain	1 (1.9)	2 (1.9)
Injection site erythema	1 (1.9)	1 (1.0)
Injection site haematoma	1 (1.9)	1 (1.0)
Injection site reaction	0	1 (1.0)
Injection site urticaria	0	1 (1.0)
Injection site vesicles	1 (1.9)	0

POTENTIAL HYPERSENSITIVITY EVENTS	0	4 (3.8)
Allergic conditions NEC	0	1 (1.0)
Hypersensitivity	0	1 (1.0)
Dermatitis and eczema	0	2 (1.9)
Dermatitis allergic	0	2 (1.9)
Injection site reactions	0	1 (1.0)
Injection site urticaria	0	1 (1.0)

EvoMab =Evolocumab; TEAEs= treatment-emergent adverse events; N=number of subjects randomized and dosed in the full analysis set; QM= once monthly (subcutaneous)
Coded using MedDRA version 22.1.
Each TEAE has a unique set of PTs while one PT can be categorized into more than one event category.
Source: 20120123 ADAE dataset; Software: JMP Clinical 7.1 and CSR 20120123: Table 14-6.8.3

Trial 20120124 (HeFH):

- ISRs/hypersensitivity:
  - Potential injection site reaction events occurred in 13 (9%) subjects using both the narrow and broad AMQ. Using the narrow search strategy, the preferred terms were injection site erythema (5), injection site reaction (4), injection site pain (3), injection site bruising (2), injection site swelling (2), injection site hemorrhage (1), injection site induration (1), injection site edema (1), injection site pruritus (1), injection site rash (1), and injection site warmth (1); see Table 28 in Section 8.4.5.
  - Potential hypersensitivity events occurred in 6 (4%) subjects using the narrow SMQ and 11 (7%) subjects using the broad SMQ. Using the narrow search strategy, the preferred terms were allergic dermatitis (1), allergy to vaccine (1), dermatitis (1), eczema (1), injection site reaction (1), and skin reaction (1). The events of injection site reaction and skin reaction were considered related to evolocumab by the investigator; both events were grade 1.
  - All potential hypersensitivity and injection site reaction events were nonserious and CTCAE grade 1 or 2 in severity.

Trial 20120124 (HoFH):

- ISRs/hypersensitivity: For the 12 subjects treated with evolocumab, no potential hypersensitivity events were noted and 1 subject (8%) had a potential injection site reaction (nonserious, grade 1 injection site hemorrhage).

Reviewer Comment: The incidence of hypersensitivity and injection site reaction events observed in trials 20120123 and 20120124 were consistent with the known safety profile of evolocumab.

8.5.3. Neurologic Development and Cognition

An assessment of potential neurocognitive adverse events using high level group terms was

performed in Trial 20120123 and Trial 20120124.

Trial 20120123 (HeFH):

- Neurocognitive: The subject incidence of potential neurocognitive events was low and similar between the evolocumab (1 subject [1%]) and placebo (0 subjects [0%]) groups. The neurocognitive preferred term of 'disturbance in attention' occurred in one subject in the evolocumab group.

Trial 20120124 (HeFH):

- Neurocognitive: Five (3%) patients with HeFH had potential neurocognitive events of attention deficit hyperactivity disorder (4), amnesia (1), and disturbance in attention (1). All events were nonserious, grade 1 or 2, and considered unrelated to evolocumab by the investigator. Of the subjects with events of attention deficit hyperactivity disorder (ADHD), 2 subjects had pre-existing ADHD and another subject had pre-existing anxiety. The event of amnesia was attributed to gamma-hydroxybutyrate (GHB) or Xyrem, a central nervous system depressant.

Trial 20120124 (HoFH):

- Neurocognitive: One (8%) patient had a potential neurocognitive event (nonserious, grade 2 attention deficit hyperactivity disorder); this individual had pre-existing ADHD.

Reviewer Comment: The incidence of neurocognitive events was low and predominantly associated with pre-existing conditions or attributable to alternate etiologies.

Neurocognitive assessments using the Cogstate cognitive battery are described in Section 8.3.3: Routine Clinical Tests. These tests have been used in clinical trials to assess cognitive changes in trials of 12 weeks duration or longer; thus, the interval of testing in trials 20120123 (week 24) and 20120124 (weeks 24, 48 and 80) is reasonable to assess for any potential changes.

Trial 20120123 (HeFH):

- Cogstate Cognitive Battery of neurological tests: When interpreting the results in the table below, for speed of performance: detection, total errors, and speed of performance: identification parameters, a lower score indicates better performance; for the accuracy of performance parameter, a higher score indicates better performance. As shown in Table 39, for each test, the mean and median change from baseline at Week 24 was small and similar between the evolocumab and placebo treatment groups. This was also true when the results were analyzed by age (<14 years and ≥14 years). No significant effect on cognition from use on evolocumab in this 24-week trial was seen using the Cogstate Cognition Battery of testing.

Table 43 Summary of Change from Baseline to Week 24 in Cogstate Testing in Trial 20120123 (Full Analysis Set - Actual Treatment)

Cogstate Testing Battery	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)
Speed of Performance (Detection Test) in Log10 msecs[a]		
Baseline		
N	53	104
Mean (SD)	2.52 (0.13)	2.55 (0.12)
Median	2.49	2.53
Change from Baseline to Week 24		
N	45	95
Mean (SD)	0.017 (0.11)	-0.016 (0.10)
Median	-0.008	-0.017
Total Errors (Groton Maze Learning Test)[a]		
Baseline		
N	53	103
Mean (SD)	50.59 (15.3)	53.30 (17.8)
Median	48.00	51.00
Change from Baseline to Week 24		
N	45	96
Mean (SD)	-4.62 (14.6)	-6.84 (12.8)
Median	1.33	1.35
Speed of Performance (Identification Test) in Log10 msecs[a]		
Baseline		
N	53	104
Mean (SD)	2.71 (0.11)	2.74 (0.11)
Median	2.71	2.73
Change from Baseline to Week 24		
N	45	95
Mean	0.010 (0.07)	-0.021 (0.07)
Median	-0.002	-0.021
Accuracy of Performance in Arcsine square root proportion correct (One-card learning test)[b]		
Baseline		

N	53	104
Mean (SD)	1.01 (0.15)	1.02 (0.17)
Median	1.01	1.02
Change from Baseline to Week 24		
N	45	96
Mean (SD)	0.022 (0.14)	0.012 (0.12)
Median	0.010	0.008

EvoMab = Evolocumab; QM = monthly (subcutaneous)
N = number of subjects randomized and dosed in the full analysis set; n = number of subjects with reported data.
a Lower score = better performance
b Higher score = better performance
Source: adam.adsl, adam.adft and reviewer modified from Applicant's Table 14-8.6.1, Table 14-8.6.4, Table 14-8.6.7, and Table 14-8.6.10 from CSR 20120123

- Neurologic examinations: Ninety-six (92%) evolocumab patients and 46 (87%) placebo patients had neurological assessments at baseline and Week 24; 2 (2%) evolocumab patients did not have reflexes reported. In both treatment groups, all patients had normal exams as assessed by motor system, sensory system, reflexes, coordination, and gait. One patient in the evolocumab group tested abnormal for reflexes at baseline and during the trial; however, the assessment at Week 24 was not considered worse than that at baseline by the investigator.

Trial 20120124:

- Cogstate Cognitive Battery of neurological tests:
  - HeFH: tested at Weeks 24 and 80/EOS
  - HoFH: tested at screening, Day 1, Weeks 24, 48, and 80/EOS
  - Interpretation of results in Table 40: for speed of performance: detection, total errors, and speed of performance: identification parameters, a lower score indicates better performance; for the accuracy of performance parameter, a higher score indicates better performance.
- Neurological exam was performed at screening (HoFH only) and Week 80/EOS; refer to Table 41 for findings.

Table 44 Summary of Change from Baseline to Week 80 in Cogstate Testing in Trial 20120124 (Full Analysis Set - Actual Treatment)

Cogstate Testing Battery	**HeFH** EvoMab 420 mg QM (N = 150)	**HoFH** EvoMab 420 mg QM (N = 12)	**TOTAL HeFH+HoFH** EvoMab 420 mg QM (N = 162)
Speed of Performance (Detection Test) in Log10 msecs[a]			
Baseline			

N	150	12	162
Mean (SD)	2.55 (0.13)	2.54 (0.12)	2.55 (0.13)
Median	2.52	2.52	2.52
Change from Baseline to Week 80			
N	90	11	101
Mean (SD)	-0.02 (0.11)	-0.01 (0.04)	-0.02 (0.10)
Median	-0.02	-0.02	-0.02
Total Errors (Groton Maze Learning Test)[a]			
Baseline			
N	149	12	161
Mean (SD)	52.7 (17.3)	43.7 (14.5)	52.1 (17.2)
Median	50.00	43.00	50.00
Change from Baseline to Week 80			
N	90	11	101
Mean (SD)	-9.33 (13.1)	-3.09 (12.2)	-8.65 (13.1)
Median	-8.00	-1.00	-8.00
Speed of Performance (Identification Test) in Log10 msecs[a]			
Baseline			
N	150	12	162
Mean (SD)	2.74 (0.11)	2.74 (0.09)	2.74 (0.11)
Median	2.73	2.74	2.73
Change from Baseline to Week 80			
N	90	11	101
Mean	-0.03 (0.09)	0.004 (0.06)	-0.03 (0.09)
Median	-0.04	-0.007	-0.02
Accuracy of Performance in Arcsine square root proportion correct (One-card learning test)[b]			
Baseline			
N	150	12	162
Mean (SD)	1.01 (0.17)	0.99 (0.17)	1.01 (0.17)
Median	1.02	1.00	1.02
Change from Baseline to Week 80			
N	91	11	102
Mean (SD)	0.01 (0.13)	0.08 (0.14)	0.02 (0.13)
Median	0.04	0.05	0.05

EvoMab = Evolocumab; QM = monthly (subcutaneous)
N = number of subjects randomized and dosed in the full analysis set; n = number of subjects with reported data.
a Lower score = better performance
b Higher score = better performance
Source: Modified from Applicant's Table 14-8.6.1, Table 14-8.6.4, Table 14-8.6.7, and Table 14-8.6.10 from CSR 20120124

Reviewer Comment: The mean and median change from baseline to Week 80 was small; there does not appear to be a negative treatment effect on cognition, based on these tests, with use of evolocumab over 80 weeks in these subjects. When test results were compared by age (<14 years and ≥14 years), the younger subjects had a greater improvement in scores than the older subjects.

Table 45 Subject Incidence of Neurological Examination Findings at Week 80 in Trial 20120124 (Full Analysis Set - Actual Treatment)

Neurological Examination Findings	HeFH EvoMab 420 mg QM (N = 150) n (%)	HoFH EvoMab 420 mg QM (N = 12) n (%)	TOTAL HeFH+HoFH EvoMab 420 mg QM (N = 162) n (%)
Motor System	98 (65)	11 (92)	109 (67)
Normal	98 (65)	11 (92)	109 (67)
Abnormal	0	0	0
Sensory System	98 (65)	11 (92)	109 (67)
Normal	98 (65)	11 (92)	109 (67)
Abnormal	0	0	0
Reflexes	98 (65)	11 (92)	109 (67)
Normal	96 (64)	11 (92)	107 (66)
Abnormal	2 (1)	0	2 (1)
Coordination	98 (65)	11 (92)	109 (67)
Normal	98 (65)	11 (92)	109 (67)
Abnormal	0	0	0
Gait	98 (65)	11 (92)	109 (67)
Normal	98 (65)	11 (92)	109 (67)
Abnormal	0	0	0

Interim analysis data cutoff date: June 8, 2020
EvoMab = Evolocumab; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; QM = monthly (subcutaneous)
N = number of subjects randomized and dosed in the full analysis set; n = number of subjects with reported data.
Source: datasets adam.adsl, adam.adpe and modified from Applicant's Table 14-8.7.1 from CSR 20120124

Reviewer Comment: All HeFH and HoFH subjects tested normal when assessing their motor system, sensory system, coordination, and gait at Week 80, except for two (1%) HeFH subjects who tested abnormal for reflexes at Week 80. Both subjects had abnormal reflexes at baseline,

and there was no evidence that they had worsened at Week 80. No clinically meaningful neurologic findings were reported during this trial.

8.6. Safety Analyses by Demographic Subgroups

This section provides analyses of safety information by demographic subgroups (e.g., age, sex, and racial subgroups) in Studies 20120123 and 20120124 to explore the effect of possible interactions on safety signals/events.

Trial 20120123
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.

In Trial 20120123, there were 73 subjects that were <14 years old and 84 subjects that were 14 years of age or older. The adverse event data were analyzed by these age groups for both the evolocumab and placebo groups. As shown in the tables below, for subjects <14 years of age, subjects in the evolocumab group had a greater incidence of AEs compared to older subjects on evolocumab and a greater incidence of AEs (gastroenteritis, headache, influenza, nasopharyngitis, oropharyngeal pain and upper respiratory tract infection) compared to subjects <14 years of age in the placebo group. Although occurring at higher incidence, the types of adverse events observed in the <14 years of age subgroup receiving evolocumab are consistent with the adverse event profile seen with evolocumab use in pediatric and adult populations. For subjects ≥14 years of age, the findings were mixed; subjects in the evolocumab group had a greater incidence of constipation and headache, but the placebo group had a greater incidence of CPK increase, gastroenteritis, and nasopharyngitis.

Table 46 Treatment-Emergent Adverse Events Reported by Subjects <14 Years of Age by Preferred Term (where the total count is ≥3) in Trial 20120123 (Full Analysis Set - Actual Treatment)

	Actual Treatment for Period 01				
	AMG 145 SC QM 420 MG (N = 48)		PLACEBO SC QM (N = 25)		
Dictionary-Derived Term	Count	%	Count	%	Total
Cough	2	4.2%	1	4.0%	3
Gastroenteritis	5	10.4%	1	4.0%	6
Headache	6	12.5%	.	.	6
Influenza	4	8.3%	1	4.0%	5
Injection site pain	2	4.2%	1	4.0%	3
Nasopharyngitis	7	14.6%	1	4.0%	8
Oropharyngeal pain	5	10.4%	.	.	5
Pyrexia	3	6.3%	1	4.0%	4
Upper respiratory tract infection	5	10.4%	.	.	5

AMG 145= Evolocumab
Source: adsl.xpt, adae.xpt; Software: JMP Clinical 7.1

Table 47 Treatment-emergent Adverse Events Reported by Subjects ≥14 Years of Age by Preferred Term (where the total count is ≥ 3) in Trial 20120123 (Full Analysis Set - Actual Treatment)

	Actual Treatment for Period 01				
	AMG 145 SC QM 420 MG (N = 56)		PLACEBO SC QM (N = 28)		
Dictionary-Derived Term	Count	%	Count	%	Total
Blood creatine phosphokinase increased	1	1.8%	2	7.1%	3
Constipation	3	5.4%	.	.	3
Gastroenteritis	.	.	3	10.7%	3
Headache	5	8.9%	1	3.6%	6
Influenza	2	3.6%	1	3.6%	3
Nasopharyngitis	5	8.9%	5	17.9%	10

AMG 145= Evolocumab;
Source: adsl.xpt, adae.xpt; Software: JMP Clinical 7.1

In Trial 20120123, there were 69 male and 88 female subjects. The adverse event data was analyzed by these two groups for both the evolocumab and placebo groups. As shown in the table below, in general, female subjects receiving evolocumab had both a greater incidence of

AEs than females receiving placebo and a greater incidence of AEs than males receiving evolocumab, particularly for the AEs of constipation, headache, influenza/influenza-like illness, and nasopharyngitis. However, small sample size and small numbers of AEs limit interpretation of these subgroup data.

Table 48 Treatment-Emergent Adverse Events Reported by Male and Female Subjects in the Evolocumab Treatment Group (where the total count is ≥ 3) in Trial 20120123 (Full Analysis Set - Actual Treatment)

	Female Subjects N=88				Male Subjects N=69			
	Evolocumab 420 MG SC QM		Placebo SC QM		Evolocumab 420 MG SC QM		Placebo SC QM	
	(n = 61)		(N = 27)		(n = 43)		(N = 26)	
Dictionary-Derived Term	**Count**	**%**	**Count**	**%**	**Count**	**%**	**Count**	**%**
Abdominal pain	2	3.3%	.	.	.	.	1	3.8%
Abdominal pain upper	1	1.6%	.	.	1	2.3%	1	3.8%
Blood creatine phosphokinase increased	1	1.6%	1	3.7%	.	.	1	3.8%
Constipation	3	4.9%	.	.	.	.	.	.
Contusion	1	1.6%	.	.	1	2.3%	1	3.8%
Cough	1	1.6%	2	7.4%	1	2.3%	1	3.8%
Gastroenteritis	3	4.9%	2	7.4%	2	4.7%	2	7.7%
Headache	8	13.1%	.	.	3	7.0%	1	3.8%
Influenza	5	8.2%	.	.	1	2.3%	2	7.7%
Influenza like illness	2	3.3%	.	.	1	2.3%	.	.
Injection site pain	2	3.3%	1	3.7%	.	.	.	.
Nasopharyngitis	10	16.4%	1	3.7%	2	4.7%	5	19.2%
Oropharyngeal pain	4	6.6%	.	.	3	7.0%	.	.
Pyrexia	1	1.6%	.	.	2	4.7%	3	11.5%
Upper respiratory tract infection	2	3.3%	1	3.7%	4	9.3%	.	.
Vomiting	2	3.3%	1	3.7%	.	.	.	.

Source: Reviewer modified from ADAE; Software: JMP Clinical 7.1

Trial 20120124

Due to its ongoing status and small sample size for some of the demographic subgroups, interpretations about the subgroup data should be made with caution. As shown in the table below, adverse event data by race is limited because of the small sample size of non-white subjects; no meaningful conclusions can be made.

Table 49 Subject Incidence of Treatment-Emergent Events by Race in Trial 20120124 where Total ≥6 Events

Preferred Term	Asian EvoMab 420 mg QM (N = 4) n (%)	Black EvoMab 420 mg QM (N = 2) n (%)	Other EvoMab 420 mg QM (N = 21) n (%)	White EvoMab 420 mg QM (N = 135) n (%)	Total: EvoMab 420 mg QM (N = 162) n (%)
Nasopharyngitis	-	-	1 (5)	21 (16)	22 (14)
Headache	-	-	2 (10)	12 (9)	14 (9)
Influenza like illness	-	-	1 (5)	12 (9)	13 (8)
Gastroenteritis	1 (25)	-		8 (6)	9 (6)
Upper respiratory tract infection	-	-	2 (10)	7 (5)	9 (6)
Oropharyngeal pain	-	-	1 (5)	7 (5)	8 (5)
Abdominal pain upper	-	-		7 (5)	7 (4)
Fatigue	1 (25)	-		5 (4)	6 (4)
Pharyngitis	-	-	2 (10)	4 (3)	6 (4)
Pyrexia	-	-	1 (5)	5 (4)	6 (4)

Source: 20120124 ADAE dataset; Software: JMP Clinical 7.1

In Trial 20120124, there were 77 male and 85 female subjects. The adverse event data was analyzed by these two groups for the evolocumab-receiving population. As shown in the table below, in general, female subjects receiving evolocumab had a slightly greater incidence of AEs than males receiving evolocumab, particularly for the AEs of influenza-like illness and nasopharyngitis. However, the small sample size and small numbers of AEs limit interpretation of these subgroup data.

Table 50 Subject Incidence of Treatment-Emergent Events by Sex where Total ≥ 5 Events in Trial 20120124

	Sex				
	F (N=85)		M (N=77)		
Reported Term for AE	N	(%)	n	(%)	Fishers Exact P-value
Total	60	(71)	47	(61)	.245
Abdominal pain upper	2	(2)	5	(6)	.259
Attention deficit hyperactivity disorder	2	(2)	3	(4)	.669

	Sex				
	F (N=85)		M (N=77)		
Reported Term for AE	N	(%)	n	(%)	Fishers Exact P-value
Back pain	4	(5)	1	(1)	.370
Diarrhoea	2	(2)	3	(4)	.669
Fatigue	5	(6)	1	(1)	.214
Gastroenteritis	4	(5)	5	(6)	.737
Gastroenteritis viral	4	(5)	1	(1)	.370
Headache	7	(8)	7	(9)	1.00
Influenza like illness	10	(12)	3	(4)	.084
Injection site erythema	4	(5)	1	(1)	.370
Myalgia	4	(5)	1	(1)	.370
Nasopharyngitis	16	(19)	6	(8)	.064
Oropharyngeal pain	5	(6)	3	(4)	.722
Pharyngitis	1	(1)	5	(6)	.103
Pyrexia	2	(2)	4	(5)	.425
Tonsillitis	2	(2)	3	(4)	.669
Upper respiratory tract infection	4	(5)	5	(6)	.737

Source: 20120124 ADAE dataset; Software: JMP Clinical 7.1

In Trial 20120124, there were 72 subjects that were <14 years old and 90 subjects that were 14 years of age or older. The adverse event data was analyzed by these age groups for the evolocumab group. As shown in the tables below, subjects <14 years of age in the evolocumab group had a greater incidence of attention deficit hyperactivity disorder and headache compared to older subjects on evolocumab but had a smaller incidence of influenza-like illness, back pain, gastroenteritis, injection site erythema, injection site reaction, and vitamin D deficiency as compared to subjects ≥14 years of age in the evolocumab group.

Table 51 Subject Incidence of Treatment-Emergent Events by Age where Total ≥ 4 Events

Preferred Term	Age < 14 Years EvoMab 420 mg QM (N = 72) n (%)	Age ≥ 14 Years EvoMab 420 mg QM (N = 90) n (%)	Total: EvoMab 420 mg QM (N = 162) n (%)
Nasopharyngitis	10 (14)	12 (13)	22 (14)

Headache	8 (11)	6 (7)	14 (9)
Influenza like illness	2 (3)	11 (12)	13 (8)
Gastroenteritis	2 (3)	7 (8)	9 (6)
Upper respiratory tract infection	2 (3)	7 (8)	9 (6)
Oropharyngeal pain	2 (3)	6 (7)	8 (5)
Abdominal pain upper	3 (4)	4 (4)	7 (4)
Fatigue	3 (4)	3 (3)	6 (4)
Pharyngitis	2 (3)	4 (4)	6 (4)
Pyrexia	2 (3)	4 (4)	6 (4)
Attention deficit hyperactivity disorder	4 (6)	1 (1)	5 (3)
Back Pain	1 (1)	4 (4)	5 (3)
Diarrhoea	2 (3)	3 (3)	5 (3)
Gastroenteritis viral	0	5 (6)	5 (3)
Injection site erythema	1 (1)	4 (4)	5 (3)
Myalgia	3 (4)	2 (2)	5 (3)
Tonsillitis	2 (3)	3 (3)	5 (3)
Influenza	1 (1)	3 (3)	4 (2)
Injection site reaction	0	4 (4)	4 (2)
Viral infection	2 (3)	2 (2)	4 (2)
Vitamin D deficiency	0	4 (4)	4 (2)

EvoMab=Evolocumab; HeFH-heterozygous familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; N = number of subjects enrolled and dosed in this trial; QM=once monthly (subcutaneous)
Interim analysis data cutoff date: June 8, 2020
Coded using MedDRA version 23.0.
Source: 20120124 ADAE dataset; Software: JMP Clinical 7.1

8.7. Specific Safety Studies/Clinical Trials

Carotid intima-media thickness

Carotid intima-media thickness (cIMT) is the thickness of the inner 2 layers of the carotid artery, the intima and media, as measured by ultrasound. Lateral, anterior, and posterior measurements of the right common carotid artery (RCCA) and left common carotid artery (LCCA) were assessed in Trial 20120123 and Trial 20120124.

Reviewer Comment: The cIMT test does not measure actual atherosclerosis but is used to approximate the extent of carotid atherosclerotic vascular disease. Risk factors contributing to increased carotid intima-media thickness include advancing age and hypertension as well as elevated lipoprotein levels, smoking, diabetes, obesity and a sedentary lifestyle. Despite the association between increased carotid IMT and cardiovascular disease, it remains unclear whether routine carotid IMT measurement is useful for the detection of subclinical atherosclerosis in clinical practice.[51]

[51] Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid intima-media thickness for atherosclerosis.J Atheroscler Thromb. 2016; 23:18–31.

Randomized, controlled trials have shown that interventions may slow progression of cIMT, but it is unclear whether effects on cIMT progression translate into reduced risk of CVD events and whether cIMT progression is a valid surrogate marker for CVD. Meta-analyses have yielded conflicting results[52,53,54] and have been criticized for methodological flaws.[55]

Mean values of cIMT in adults range around 650 to 900 µm (0.65 to 0.9 mm) and increase—on average—at a rate of 0 to 40 µm/y (0 to 0.04 mm/y).[56,57] For children, some data report that cIMT is constant in healthy children younger than 10 years, regardless of sex or BMI but increases after the age of 10 years; normal values reported of ~ 0.43±0.06 mm.[58] Other studies have shown some effect from sex, age and height and provided normative data on mean cIMT in a healthy pediatric population.[59] These age- and height-specific charts are consistent that the majority of the pediatric population has a cIMT < 0.6 mm.

A recent meta-analysis of 119 clinical trials, involving over 100,000 patients and using a Bayesian meta-regression approach to evaluate progression of cIMT as a surrogate marker for cardiovascular events, concluded that across all interventions tested (antidiabetic agents, antihypertensive medications, lipid-lowering agents, and diet/vitamins), each 10 µm/y reduction in cIMT progression was associated with ~9% relative CVD risk reduction; however, part of the

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[52] Espeland MA, O'leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. Curr Control Trials Cardiovasc Med. 2005; 6:3.

[53] Goldberger ZD, Valle JA, Dandekar VK, Chan PS, Ko DT, Nallamothu BK. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. Am Heart J. 2010; 160:701–714.

[54] Costanzo P, Perrone-Filardi P, Vassallo E, Paolillo S, Cesarano P, Brevetti G, Chiariello M. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol. 2010; 56:2006–2020.

[55] Bots ML, Taylor AJ, Kastelein JJ, Peters SA, den Ruijter HM, Tegeler CH, Baldassarre D, Stein JH, O'Leary DH, Revkin JH, et al. Rate of change in carotid intima-media thickness and vascular events: meta-analyses can not solve all the issues. A point of view. J Hypertens. 2012; 30:1690–1696.

[56] Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, Sander D, Plichart M, Catapano AL, Robertson CM, et al.; PROG-IMT Study Group. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. Lancet. 2012; 379:2053–2062.

[57] Willeit P, Thompson SG, Agewall S, Bergström G, Bickel H, Catapano AL, Chien KL, de Groot E, Empana JP, Etgen T, et al.; PROG-IMT study group. Inflammatory markers and extent and progression of early atherosclerosis: Meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration. Eur J Prev Cardiol. 2016; 23:194–205.

[58] Baroncini LA, Sylvestre Lde C, Pecoits Filho R. Assessment of Intima-Media Thickness in Healthy Children Aged 1 to 15 Years. Arq Bras Cardiol. 2016 Apr;106(4):327-32.

[59] Drole Torkar A, Plesnik E, Groselj U, Battelino T and Kotnik P (2020) Carotid Intima-Media Thickness in Healthy Children and Adolescents: Normative Data and Systematic Literature Review. Front. Cardiovasc. Med. 7:597768. doi: 10.3389/fcvm.2020.597768

CVD risk reduction was unrelated to reduction in cIMT .[60] An editorial commenting on this study suggested that changes in carotid plaque burden and high-risk phenotype may be a more robust technique to assess the effect of therapeutic interventions than cIMT alone.[61]

Other authors have concluded that the results of cIMT trials should be used as a decision tool to help in the choice to launch or not launch a large-scale morbidity and mortality trial.[62] Furthermore, cIMT measurement may be useful in evaluating cardiovascular disease risk in select patient populations but may not always be an appropriate surrogate for clinical endpoints.[63]

Since the approval of the 'slow the progression of atherosclerosis' indication for Crestor, which utilized cIMT, in November 2007, the Division has held the position that we view imaging-based studies, including those that assess cIMT and intravascular ultrasound (IVUS) endpoints, primarily as proof-of-concept studies or drug development tools rather than definitive trials demonstrating a therapeutic agent's effectiveness. The relationship between cIMT, the rate of progression or regression in cIMT, and cardiovascular outcomes is not established.

Trial 20120123 (HeFH):

cIMT was measured by ultrasonography at Day 1 and Week 24/EOS. Mean and median baseline values in each treatment group (46 of 53 [87%] patients in the placebo group; 82 of 104 [79%] patients in the evolocumab group) at each site were <0.6 mm. An analysis of the average measurements of the RCCA and LCCA by treatment group (37 placebo and 76 evolocumab patients) showed small mean and median reductions (-0.003 and -0.010 mm, respectively) from baseline to Week 24 in the evolocumab group and small mean and median increases (0.006 and 0.010 mm, respectively) from baseline to Week 24 in the placebo group.

Table 52 Change in Carotid Intima-Media Thickness from Baseline to Week 24 in Trial 20120123

	Placebo QM (N = 53)	EvoMab 420 mg QM (N = 104)
Lateral right common carotid artery		

[60] Willeit P, Tschiderer L, Allara E, Reuber K, Seekircher L, Gao L, Liao X, Lonn E, Gerstein HC, Yusuf S, et al.. Carotid intima-media thickness progression as surrogate marker for cardiovascular risk: meta-analysis of 119 clinical trials involving 100 667 patients. Circulation. 2020; 142:621–642.
[61] Shah PK. Does Reduced Carotid Intima Media Thickness Progression Predict Cardiovascular Risk Reduction? Circulation. 2020; 142:643–644.
[62] Peters SA, den Ruijter HM, Grobbee DE, Bots ML. Results From a Carotid Intima-Media Thickness Trial as a Decision Tool for Launching a Large-Scale Morbidity and Mortality Trial. Circ Cardiovasc Imaging. 2013;6:20-25.
[63] Sharma K, Blaha MJ, Blumenthal RS, Musunuru K. Clinical and research applications of carotid intima-media thickness. Am J Cardiol. 2009;103(9):1316-1320.

N	37	74
Mean (SD), mm	0.002 (0.05)	–0.01 (0.08)
Anterior right common carotid artery		
N	34	60
Mean (SD), mm	0.02 (0.08)	–0.001 (0.06)
Posterior right common carotid artery		
N	34	73
Mean (SD), mm	0.004 (0.07)	–0.003 (0.07)
Lateral left common carotid artery		
N	34	71
Mean (SD), mm	0.003 (0.08)	–0.007 (0.07)
Anterior left common carotid artery		
N	33	67
Mean (SD), mm	0.02 (0.07)	–0.01 (0.07)
Posterior left common carotid artery		
N	37	74
Mean (SD), mm	0.005 (0.06)	0.006 (0.08)
Average of largest left and right common carotid artery		
N	37	76
Mean (SD), mm	0.006 (0.05)	–0.003 (0.05)

EvoMab=Evolocumab; mm = millimeter; QM = monthly; SD = standard deviation.
Source: Modified from Applicant's Tables 14-8.5.1 to 14-8.5.7 from CSR 20120123

Trial 20120124 (HeFH): cIMT was measured by ultrasonography at Day 1 and Week 24, Week 48, and Week 80/EOS. In HeFH subjects, mean baseline values at each site were <0.6 mm. The mean and median change from baseline to Weeks 24, 48, and 80 at most artery locations assessed were negative (reduction in thickness), although there were some locations where the change was slightly positive. The assessment is limited by the small number of subjects with data at Week 48 (34%) and Week 80 (30%).

Trial 20120124 (HoFH): Eight of 12 HoFH subjects had cIMT data at baseline. In HoFH subjects, median baseline value in the lateral and posterior LCCA was <0.6 mm. The median changes from baseline to Weeks 24, 48, and 80 were negative in the HoFH group except for the following time points and locations: Week 24 (lateral LCCA), Week 48 (lateral RCCA, lateral LCCA, posterior LCCA), and Week 80 (anterior RCCA, posterior RCCA, posterior CCA). By Week

80, some anatomic sites had data on only 4 of the 12 HoFH subjects.

Reviewer Comment: In Trial 20120123, the average measurements of the RCCA and LCCA in the evolocumab group showed a small decrease in thickness from baseline to Week 24 as compared to the placebo group. Additional decreases were observed in Trial 20120124, although the data was less consistent and more subjects had missing measurements, particularly at later timepoints. Overall, this finding is consistent with the observed LDL-C reduction in the evolocumab group and suggests a possible beneficial effect on atherosclerosis in these patients treated with evolocumab.

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

No pregnancies were reported during these studies. There is no new information on pregnancy or lactation from this submission.

8.8.3. Pediatrics and Assessment of Effects on Growth

Height, weight, and Tanner stage assessments were performed at Day 1 and Week 24 (EOS) in Trial 20120123 and Day 1, Weeks 24, 48, and 80 (EOS) in Trial 20120124.

Trial 20120123 (HeFH): Tanner staging for growth and pubertal development assessments – using the criteria of genital size for males, breast development for females, or pubic hair – were done at Day 1 and Week 24 (EOS). The developmental stages of the patient's sexual characteristics were rated separately (one stage for pubic hair and one stage for breasts in females or genitals in males), as these characteristics may reflect different degrees of maturity.

Reviewer Comment: This assessment is limited as the trial period is only 24 weeks in duration; it is unlikely that any meaningful changes in growth or development would be detected in adolescents over such a short period of time.

Sixty-six males (42 [98%] evolocumab, 24 [92%] placebo) and 76 females (54 [89%] evolocumab, 22 [82%] placebo) had assessments of growth and pubertal development at baseline and Week 24. In this group of patients with Tanner staging data, the mean age at baseline for female patients was slightly older than male patients but was similar for each gender between the placebo and evolocumab groups. The mean (SD) age at baseline for females was 14.0 (2.5)

years for the placebo group and 13.9 (2.3) years for the evolocumab group. The mean (SD) age at baseline for males was 13.3 (2.4) years for the placebo group and 13.6 (2.4) years for the evolocumab group.

Most patients did not have a change in Tanner staging by any criterion during the trial. No patients had a Tanner staging assessed at a lower stage than at the baseline visit. As shown in the following table, the percentage of patients with Tanner stage changes was fairly similar between the placebo and evolocumab groups for each development assessment.

Table 53 Tanner Staging at Baseline and Week 24 –Trial 20120123 (Full Analysis Set)

Tanner Staging Assessment	Placebo	Evolocumab
by genital size – Males – n at baseline	26	44
# of patients with increased stage from baseline* – n (%)	5/24 (20.8)	11/42 (26.2)
# of patients with decreased stage from baseline* – n (%)	0	0
by breast development - Females – n at baseline	27	61
# of patients with increased stage from baseline* – n (%)	3/22 (13.6)	8/54 (14.8)
# of patients with decreased stage from baseline* – n (%)	0	0
by pubic hair - Males – n at baseline	26	43
# of patients with increased stage from baseline* – n (%)	4/24 (16.7)	9/42 (21.4)
# of patients with decreased stage from baseline* – n (%)	0	0
by pubic hair - Females – n at baseline	27	61
# of patients with increased stage from baseline* – n (%)	4/22 (14.8)	9/54 (16.7)
# of patients with decreased stage from baseline* – n (%)	0	0

n = number of subjects with Tanner stage data at baseline
* Number and percentage with change in Tanner Staging excluded subjects with missing values at Week 24.
Source: datasets adam.adsl, adam.adpe and reviewer modified from CSR 20120123 Table 14-8.10.1 and Table 14-8.10.2

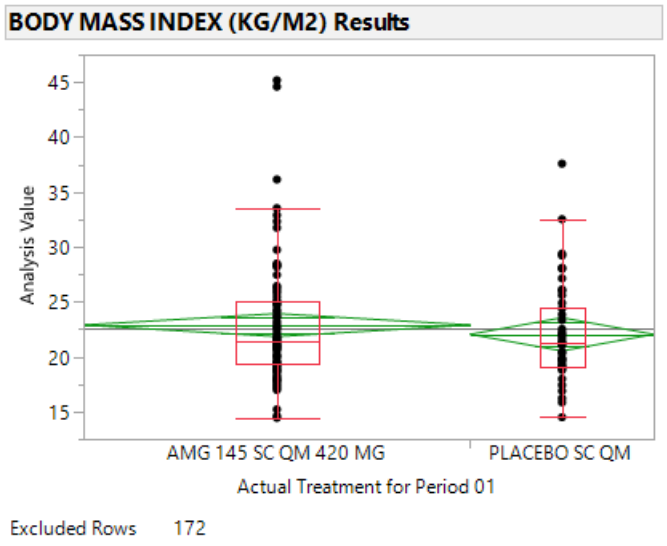
The change in growth parameters between the placebo and evolocumab groups was also similar in Trial 20120123, as shown in the following tables and figures.

Table 54 Change in Growth Parameters at Week 24 –Trial 20120123 (Full Analysis Set)

Change from baseline to Week 24	Placebo (N=53)	Evolocumab (N=104)
# of patients	46	96
Height, mean (SD), cm	1.6 (1.6)	1.6 (2.1)
# of patients	46	96
Weight, mean (SD), Kg	2.1 (2.9)	1.9 (2.8)
# of patients	46	96
Body mass index, mean (SD), kg/m^2	0.5 (1.2)	0.3 (1.0)

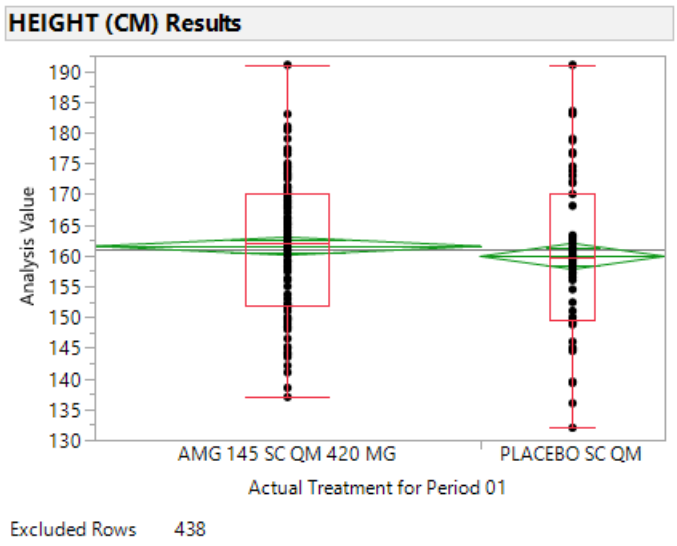
cm = centimeter; Kg = kilogram; SD = standard deviation

Figure 8 BMI (kg/m^2) at Week 24 in Trial 20120123 (Full Analysis Set)



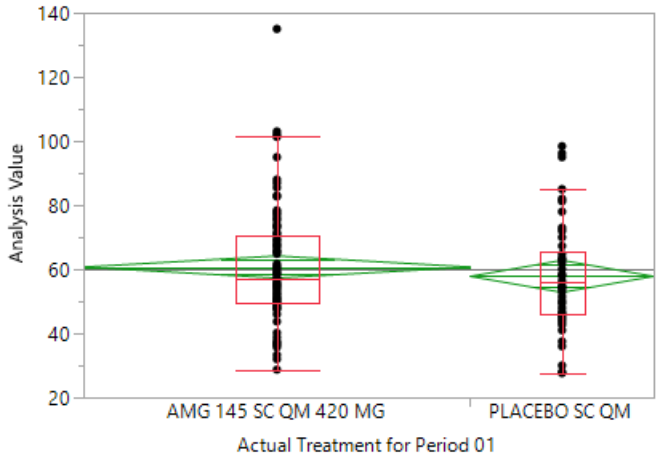
Source: dataset: ADVS, JMP Clinical 7.1

Figure 9 Height (cm) at Week 24 in Trial 20120123 (Full Analysis Set)



Source: dataset: ADVS, JMP Clinical 7.1

Figure 10 Weight (kg) at Week 24 in Trial 20120123 (Full Analysis Set)



Source: dataset: ADVS, JMP Clinical 7.1

Trial 20120124: At the interim analysis data cutoff date, not all HeFH subjects had reached Week 80 in Trial 20120124.

Males

- At Week 24: 62 out of 67 (93%) male HeFH subjects had a genital size and pubic hair assessment. All subjects either stayed at the same stage or shifted to a higher stage at

Week 24, except for one 17-year-old male, who received placebo in Trial 20120123, who was Tanner stage 4 by pubic hair assessment at baseline and Tanner stage 3 by pubic hair assessment at Week 24. This may represent an assessment discrepancy rather than a true decrease in Tanner stage development.

- At Week 48: 53 out of 67 (79%) male HeFH subjects had a genital size and pubic hair assessment. Most subjects shifted to a higher stage, but a few subjects stayed at the same stage at Week 48. One subject, a 17-year-old male subject who received placebo in Trial 20120123, was Tanner stage 4 by pubic hair assessment at baseline and Tanner stage 3 by pubic hair assessment at Week 48.
- At Week 80: 42 out of 67 (63%) male HeFH subjects had a genital size and pubic hair assessment. Most subjects (not at stage 5 already) shifted to a higher stage, but a few subjects stayed at the same stage at Week 80. One subject, a 17-year-old male subject who received placebo in Trial 20120123, was Tanner stage 4 by pubic hair assessment at baseline and Tanner stage 3 by pubic hair assessment at Week 80.

Females

- At Week 24: 75 out of 83 (90%) female HeFH subjects had breast development and pubic hair assessment. Subjects either stayed at the same stage or shifted to a higher stage at Week 24 except for one female, who received evolocumab in Trial 20120123, who was Tanner stage 2 by breast development at baseline and Tanner stage 1 by breast development at Week 24. This subject was 10 years old, so this may have been an assessment discrepancy rather than a true decrease in Tanner stage development.
- At Week 48: 66 out of 83 (80%) female HeFH subjects had a breast development and pubic hair assessment. Most subjects shifted to a higher stage, but a few subjects stayed at the same stage at Week 48.
- At Week 80: 57 out of 83 (69%) female HeFH subjects had a breast development and pubic hair assessment. Most subjects (not at stage 5 already) shifted to a higher stage, but a few subjects stayed at the same stage at Week 80.

HoFH

At the interim analysis data cutoff date, all HoFH subjects had reached Week 80 in Trial 20120124. Nine out of 10 (90%) male HoFH subjects and 2 out of 2 (100%) female HoFH subjects had assessments of Tanner stage reported at Week 80. All subjects either stayed at the same pubic hair or gender criteria stage (particularly those already at Stage 5) or shifted to a higher stage over the course of the trial.

In conclusion, for both the HeFH and HoFH populations, subjects had normal Tanner staging appropriate for their age at baseline and throughout the trial. No clinically concerning changes in the mean and median group height and weight values were seen throughout the trial for the HeFH or HoFH populations.

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

No overdoses in HeFH or HoFH subjects were reported during the included studies. No new evaluation of overdose, drug abuse potential, or withdrawal and rebound were performed in this submission.

8.8.5. 120-Day Safety Update

In the ongoing, open-label extension Trial 20120124, all 13 (100%) pediatric patients with HoFH had completed or discontinued the trial at the interim analysis (data cutoff date: June 8, 2020). For pediatric patients with HeFH, 104 (69%) had completed evolocumab, 40 (27%) were still on evolocumab, and 6 (4%) had discontinued evolocumab at the interim analysis in the sBLA.

This 120-day safety update only includes updated information from patients with HeFH in the open-label extension Trial 20120124 collected through the 120-day data cutoff date of December 9, 2020.

During the 120-day update period, 15 additional patients completed evolocumab for a total of 119 (79%) subjects, and 25 (17%) are still on evolocumab. No additional patients discontinued evolocumab during this 6-month interval from June to December 2020. One patient received all required doses of evolocumab but discontinued the trial (withdrawal of consent).

Table 55 Summary of Subject Disposition Between the Original Pediatric Application and 120-Day Safety Update Trial 20120124 (All Enrolled Subjects)

	Original Application (data cutoff date: June 8, 2020)	**120-Day Update** (data cutoff date: Dec 9, 2020)
	HeFH	**HeFH**
	EvoMab 420 mg QM in 20120124 (N = 150) n (%)	EvoMab 420 mg QM in 20120124 (N = 150) n (%)
Investigational Product Assessment		
Subjects who completed IP	104 (69)	119 (79)
Subjects still on IP	40 (27)	25 (17)
Subjects who discontinued IP	6 (4)	6 (4)
Adverse event	0	0
Pregnancy	0	0
Death	0	0
Subject request	6 (4)	6 (4)
Decision by sponsor	0	0

Lost to follow-up	0	0
Other	0	0
Study Completion Assessment		
Subjects who completed study	105 (70)	121 (81)
Subjects still on study	42 (28)	25 (17)
Subjects who discontinued study	3 (2)	4 (3)
Withdrawal of consent from study	3 (2)	4 (3)
Death	0	0
Decision by sponsor	0	0
Lost to follow-up	0	0

EvoMab = Evolocumab; QM = monthly (subcutaneous); HeFH = heterozygous familial hypercholesterolemia;
Source: reviewer modified from CSR 20120124 120-day-safety-pediatric Table 1-1

For patients with HeFH, overall exposure to evolocumab in Trial 20120124 at the data cutoff (December 9, 2020) for the 120-day safety update was a mean of 17.5 months compared with 16.1 months for these patients in the sBLA (data cutoff date: June 8, 2020).

During the 120-day safety update period (June 8, 2020 to December 9, 2020), no patient had a serious adverse event or a treatment-emergent adverse event leading to discontinuation of investigational product.

During the 120-day safety update period, 11 patients with HeFH had a treatment-emergent adverse event, which were CTCAE grade 1 or 2 in severity and occurred in a single patient (0.7%) each. The preferred terms were abdominal pain upper, autoimmune thyroiditis, back pain, colitis, ear infection, headache, hyperbilirubinaemia, influenza, injection site erythema, injection site pain, injection site swelling, oropharyngeal pain, pharyngitis, sinusitis, toothache, and vulvovaginal candidiasis.

During the 120-day safety update period, 1 patient had a CTCAE grade 1 device-related treatment-emergent adverse event of injection site pain.

No additional patients with HeFH had CK elevations >5 or >10x ULN during the 120-day safety update period.

At the time of the initial sBLA submission, 3 (2%) patients had a postbaseline total bilirubin >2x ULN. During the 120-day safety update period, no additional patients with HeFH had a total bilirubin >2x ULN and no additional subjects had an ALT or AST elevation >3x ULN.

My review of the new data in the 120-day safety update yielded no new safety concerns. The information is consistent with the safety profile, using the data cutoff of June 8, 2020, presented in the pediatric sBLA.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Evolocumab has been approved for marketing in 77 countries. As reported in the 120-day-safety update (January 17, 2021), the exposure to evolocumab includes an estimated (b) (4) patients ((b) (4) patient-years) worldwide in the postmarketing setting.

Postmarketing use of evolocumab has been associated with adverse drug reactions of hypersensitivity, including angioedema and influenza like illness. Evolocumab's label was updated in October 2018 and February 2019, respectively, to include these findings. In February 2019, finger stick adverse events associated with the autoinjector also resulted in revisions to the instructions for use in the US and continued monitoring of device and device use concerns.

Cumulatively through July 17, 2020, post-marketing adverse event case reports have been received for 139 pediatric patients ranging in age from 2 to 17 years. During the reporting interval from the sBLA submission and the 120-day safety update (July 17, 2020 through January 17, 2021), an additional 50 postmarketing adverse event case reports were received for 27 pediatric patients ranging in age from 4 to 15 years. The majority (90%) of reported adverse events were nonserious, and the most commonly reported event (19%) was off-label use (based on age or dosing regimen). The reported events in pediatric patients were consistent with the known safety profile of evolocumab or were not unexpected events in the pediatric population independent of drug exposure.

8.9.2. Expectations on Safety in the Postmarket Setting

Not applicable as evolocumab (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 evolocumab in adults is well characterized and based on a large clinical development program and post-marketing experience. As of July 17, 2020, the total exposure to evolocumab in clinical trials is over 29,000 subjects.

Exposure to evolocumab supporting this current submission includes approximately 150 pediatric patients with HeFH, who completed parent Trial 20120123, and 13 pediatric patients with HoFH who were administered evolocumab, as an adjunct to standard of care, for at least

one year and up to 2 years in some subjects.

No patients died during the trials. In Trial 20120123, one patient with HeFH reported a serious adverse event of cholelithiasis. In Trial 20120124, four patients with HeFH reported SAEs of appendicitis with peritonitis, anorexia nervosa, headache, and wrist fracture. In addition, two patients with HoFH reported SAEs of appendicitis and arteriovenous fistula aneurysm. None of these events were considered related to evolocumab by this reviewer.

One patient with HeFH in Trial 20120123 reported a nonserious adverse event of arthropathy (of toes) leading to discontinuation of evolocumab. This event improved but did not resolve with study drug discontinuation after 136 days. This event was not considered definitively related to evolocumab by this reviewer.

In Trial 20120123, four patients in the evolocumab group and none in the placebo group reported an adverse event that was Common Terminology Criteria for Adverse Events (CTCAE) grade 3. The grade 3 events included nonserious events of neurogenic shock (verbatim term: vasovagal shock), headache, and blood creatine phosphokinase increased (reportedly due to intense physical activity) and a serious event of cholelithiasis. Adverse events of headache were reported in the adult evolocumab trials so evolocumab may have contributed to this case. Lipid lowering therapies, particularly statins, have been associated with CK increases; it is possible that evolocumab contributed to the increase in CK, although CK elevations may also be seen in the setting of intense exercise. In Trial 20120124, five HeFH subjects experienced 6 CTCAE grade 3 treatment-emergent adverse events: nonserious events of panic attack and increased weight and serious events of wrist fracture, headache, and perforated appendicitis associated with peritonitis. One subject experienced a CTCAE grade 4 serious event of anorexia nervosa. Two HoFH subjects experienced a grade 3 event: a serious event of arteriovenous fistula aneurysm, and one subject had both a nonserious event of myositis and a serious event of appendicitis.

Adverse events of special interest, including theoretical concerns of very low LDL-C, safety issues seen with statins, concerns regarding neurocognition and growth and development in children, and safety concerns with PCKS9 inhibitors, were evaluated. There were no instances of LDL-C <25 mg/dL, new onset diabetes mellitus, anti-evolocumab antibodies, Hy's law, or serious allergic events. There was no evidence of adverse effects on growth and development, cognition, or neurologic function with the use of evolocumab in this trial.

Adverse reactions reported in this pediatric population are largely consistent with those identified in adult trials, namely nasopharyngitis, upper respiratory tract infection, headache, influenza and influenza-like illness, and injection site reactions. Although the data were limited by incomplete collection of samples in all subjects, there does not appear to be an adverse effect of evolocumab on steroid hormone levels or on levels of Vitamin A, D, E, and K.

In conclusion, no new adverse drug reaction or change in the safety profile was identified from the evaluation of evolocumab 420 mg QM administered to pediatric patients 10 to 17 years of age with HeFH or HoFH who participated in Trial 20120123 or Trial 20120124. Evolocumab 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 29: Prescribing Information – Review of PI submitted March 12, 2021

1. Section 1 Indications: The Applicant asks for a (b) (4) combination therapy indication in pediatric patients with HeFH: "As an adjunct to diet (b) (4) -lowering therapy, (b) (4) pediatric patients aged 10 years and older with HeFH to reduce LDL-C."
    a. I recommend changing to the following: As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C.
    b. Rationale: (b) (4)

2. Section 1 Indication: Change the HoFH indication to include specific ages for pediatrics: As an adjunct to other LDL C lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C.
    a. Technically, the lower age in the HoFH trial was 11 years. I believe it is acceptable to use 10 years based on safety data in the HeFH group which supports going down to 10 years in the HoFH group. I believe that is a strong enough rationale given the need in the HoFH population and essentially the same pathophysiology. In other parts of the label, such as sections 8.4, 12.3 and 14, we should state that the age range for the HoFH patients is 11-17 and not 10-17.

3. Section 2.1 Recommended Dosage: I concur with the language for the HeFH population. For the HoFH population, add in language clarifying that this includes adults and pediatric patients aged 10 years and older.

4. Section 6 Adverse Reactions: I concur with the Applicant's information in this section. According to FDA labeling guidance, AR rates expressed in percentages should ordinarily be rounded to the nearest integer; I made these edits.

5. Section 8.4 Pediatric Use: I made minor edits to this section.

6. Section 12.3 Pharmacokinetics, Pediatric Patient: Added a comma and changed the age range of the HoFH patients from '10 to 17 years' to '11 to 17 years' as the youngest subject was 11 years of age at enrollment.

7. Section 14 Clinical Studies: Trial 6 (HAUSER-RCT, NCT02392559)

    a. I added additional information to describe the HeFH trial population.
    b. I removed redundant text information that is already conveyed in Table 8.

c. [redacted] We do, however, recommend including figures that show the mean percent change from baseline in LDL-C over time in the longer duration trials, as is demonstrated in Figure 4 in the PI.
d. I removed the columns for [redacted] ApoB [redacted] from Table 8. The applicant can add a column for total cholesterol, if desired. This is consistent with current FDA labeling practice for LDL-C lowering therapies without unexpected changes in other parameters, such as an increase in TG or decrease in HDL (see PI for evinacumab).
e. The statistical team recommended that as [redacted] is not a pre-specified endpoint, the following sentence should be removed from the label in section: [redacted]

8. Section 14 Clinical Studies: Trial 9 (HAUSER-OLE, NCT02624869)
    a. I added additional information to describe the HoFH trial population.
    b. I removed some of the efficacy data. [redacted]

Supplement 29: Prescribing Information – Review of PPI submitted March 12, 2021

1. Section "What is REPATHA": Language changed to be consistent with the language in PI Section 1 Indications for pediatric HeFH and HoFH populations.
2. I defer to the Patient Labeling review team's assessment for the remainder of the PPI edits.

11. Risk Evaluation and Mitigation Strategies (REMS)

Given the favorable safety profile of evolocumab, there are no additional risk management strategies required beyond the recommended labeling changes described above.

12. Postmarketing Requirements and Commitments

In this submission, Amgen submits final results from pediatric trial 20120123 and interim results from pediatric trial 20120124 to support a new indication in pediatric patients with HeFH. This data submission fulfills PMR 2946-1: Part A (randomized, 6-month, double-blind, placebo-controlled, parallel-group, multicenter efficacy and safety trial evaluating evolocumab in patients with HeFH, ages 10 years to less than 18 years). The final CSR for Trial 20120124 will be submitted upon completion in mid-2021 to fulfill PMR 2946-1: Part B (18-month open-label extension in patients 10 years to less than 18 years with HeFH).

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

Covered Clinical Trial: Trials 20120123 and 20120124

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: multiple; listed in Applicant's Appendix 1 of the Financial Disclosure document.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		

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: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
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) multiple; listed in Applicant's Appendix 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

13.3. Standardized MedDRA Query (SMQ)| MedDRA 22.1 for Hypersensitivity

Standardized MedDRA Query| MedDRA 22.1	
Hypersensitivity (SMQ)	
Description: Aim of this SMQ is to support database searches for potentially drug/vaccine related hypersensitivity/allergic reactions in connection with Risk Management Plans, PSUR and other surveillance activities; designed to retrieve all types of cases possibly related to hypersensitivity/ allergic reactions; SMQ is not intended to differentiate between different types of hypersensitivity reactions such as the Coombs classification. A number of SMQs for specific allergic conditions already exist (e.g. SMQ Anaphylactic reaction, SMQ Angioedema). "Hypersensitivity" is often used in a very general way to describe a large number of conditions related to an exaggerated response of the body to a foreign agent; a more restricted use is for allergic reactions of all types. Many terms included in SMQ Hypersensitivity do not permit differentiation between hypersensitivity/allergic reactions and other causes for the given event and therefore further analysis of cases retrieved by the SMQ is required.	
Preferred Term	**Scope**
Acquired C1 inhibitor deficiency	Narrow
Acute generalised exanthematous pustulosis	Narrow
Administration related reaction	Narrow
Administration site dermatitis	Narrow
Administration site eczema	Narrow
Administration site hypersensitivity	Narrow

Administration site rash	Narrow
Administration site recall reaction	Narrow
Administration site urticaria	Narrow
Administration site vasculitis	Narrow
Allergic bronchitis	Narrow
Allergic colitis	Narrow
Allergic cough	Narrow
Allergic cystitis	Narrow
Allergic eosinophilia	Narrow
Allergic gastroenteritis	Narrow
Allergic hepatitis	Narrow
Allergic keratitis	Narrow
Allergic oedema	Narrow
Allergic otitis externa	Narrow
Allergic otitis media	Narrow
Allergic pharyngitis	Narrow
Allergic reaction to excipient	Narrow
Allergic respiratory disease	Narrow
Allergic respiratory symptom	Narrow
Allergic sinusitis	Narrow
Allergic stomatitis	Narrow
Allergic transfusion reaction	Narrow
Allergy alert test positive	Narrow
Allergy test positive	Narrow
Allergy to immunoglobulin therapy	Narrow
Allergy to surgical sutures	Narrow
Allergy to vaccine	Narrow
Anal eczema	Narrow
Anaphylactic reaction	Narrow
Anaphylactic shock	Narrow
Anaphylactic transfusion reaction	Narrow
Anaphylactoid reaction	Narrow
Anaphylactoid shock	Narrow
Anaphylaxis treatment	Narrow
Angioedema	Narrow
Antiallergic therapy	Narrow
Antiendomysial antibody positive	Narrow
Anti-neutrophil cytoplasmic antibody positive vasculitis	Narrow
Application site dermatitis	Narrow
Application site eczema	Narrow

Preferred Term	Scope
Application site hypersensitivity	Narrow
Application site rash	Narrow
Application site recall reaction	Narrow
Application site urticaria	Narrow
Application site vasculitis	Narrow
Arthritis allergic	Narrow
Aspirin-exacerbated respiratory disease	Narrow
Atopic cough	Narrow
Atopy	Narrow
Blepharitis allergic	Narrow
Blood immunoglobulin E abnormal	Narrow
Blood immunoglobulin E increased	Narrow
Bromoderma	Narrow

Bronchospasm	Narrow
Catheter site dermatitis	Narrow
Catheter site eczema	Narrow
Catheter site hypersensitivity	Narrow
Catheter site rash	Narrow
Catheter site urticaria	Narrow
Catheter site vasculitis	Narrow
Chronic eosinophilic rhinosinusitis	Narrow
Chronic hyperplastic eosinophilic sinusitis	Narrow
Circulatory collapse	Narrow
Circumoral oedema	Narrow
Circumoral swelling	Narrow
Conjunctival oedema	Narrow
Conjunctivitis allergic	Narrow
Contact stomatitis	Narrow
Contrast media allergy	Narrow
Contrast media reaction	Narrow
Corneal oedema	Narrow
Cutaneous vasculitis	Narrow
Dennie-Morgan fold	Narrow
Dermatitis	Narrow
Dermatitis acneiform	Narrow
Dermatitis allergic	Narrow
Dermatitis atopic	Narrow
Dermatitis bullous	Narrow
Dermatitis contact	Narrow
Dermatitis exfoliative	Narrow
Dermatitis exfoliative generalised	Narrow
Dermatitis herpetiformis	Narrow
Dermatitis infected	Narrow
Dermatitis psoriasiform	Narrow
Device allergy	Narrow
Dialysis membrane reaction	Narrow
Distributive shock	Narrow
Documented hypersensitivity to administered product	Narrow
Drug eruption	Narrow
Drug hypersensitivity	Narrow
Drug provocation test	Narrow
Drug reaction with eosinophilia and systemic symptoms	Narrow
Eczema	Narrow
Eczema infantile	Narrow
Eczema nummular	Narrow
Eczema vaccinatum	Narrow
Eczema vesicular	Narrow
Eczema weeping	Narrow
Encephalitis allergic	Narrow
Preferred Term	**Scope**
Encephalopathy allergic	Narrow
Eosinophilic granulomatosis with polyangiitis	Narrow
Epidermal necrosis	Narrow
Epidermolysis	Narrow
Epidermolysis bullosa	Narrow
Epiglottic oedema	Narrow
Erythema multiforme	Narrow

Erythema nodosum	Narrow
Exfoliative rash	Narrow
Eye allergy	Narrow
Eye oedema	Narrow
Eye swelling	Narrow
Eyelid oedema	Narrow
Face oedema	Narrow
Fixed eruption	Narrow
Giant papillary conjunctivitis	Narrow
Gingival oedema	Narrow
Gingival swelling	Narrow
Gleich's syndrome	Narrow
Haemorrhagic urticaria	Narrow
Hand dermatitis	Narrow
Henoch-Schonlein purpura	Narrow
Henoch-Schonlein purpura nephritis	Narrow
Heparin-induced thrombocytopenia	Narrow
Hereditary angioedema	Narrow
Hereditary angioedema with C1 esterase inhibitor deficiency	Narrow
Hypersensitivity	Narrow
Hypersensitivity myocarditis	Narrow
Hypersensitivity pneumonitis	Narrow
Hypersensitivity vasculitis	Narrow
Idiopathic urticaria	Narrow
Immediate post-injection reaction	Narrow
Immune thrombocytopenic purpura	Narrow
Immune tolerance induction	Narrow
Implant site dermatitis	Narrow
Implant site hypersensitivity	Narrow
Implant site rash	Narrow
Implant site urticaria	Narrow
Incision site dermatitis	Narrow
Incision site rash	Narrow
Infusion related hypersensitivity reaction	Narrow
Infusion related reaction	Narrow
Infusion site dermatitis	Narrow
Infusion site eczema	Narrow
Infusion site hypersensitivity	Narrow
Infusion site rash	Narrow
Infusion site recall reaction	Narrow
Infusion site urticaria	Narrow
Infusion site vasculitis	Narrow
Injection related reaction	Narrow
Injection site dermatitis	Narrow
Injection site eczema	Narrow
Injection site hypersensitivity	Narrow
Injection site rash	Narrow
Injection site recall reaction	Narrow
Injection site urticaria	Narrow
Injection site vasculitis	Narrow
Instillation site hypersensitivity	Narrow
Instillation site rash	Narrow

Preferred Term	**Scope**
Instillation site urticaria	Narrow

Interstitial granulomatous dermatitis	Narrow
Intestinal angioedema	Narrow
Iodine allergy	Narrow
Kaposi's varicelliform eruption	Narrow
Kounis syndrome	Narrow
Laryngeal oedema	Narrow
Laryngitis allergic	Narrow
Laryngospasm	Narrow
Laryngotracheal oedema	Narrow
Limbal swelling	Narrow
Lip oedema	Narrow
Lip swelling	Narrow
Mast cell degranulation present	Narrow
Medical device site dermatitis	Narrow
Medical device site eczema	Narrow
Medical device site hypersensitivity	Narrow
Medical device site rash	Narrow
Medical device site recall reaction	Narrow
Medical device site urticaria	Narrow
Mouth swelling	Narrow
Mucocutaneous rash	Narrow
Multiple allergies	Narrow
Nephritis allergic	Narrow
Nikolsky's sign	Narrow
Nodular rash	Narrow
Oculomucocutaneous syndrome	Narrow
Oculorespiratory syndrome	Narrow
Oedema mouth	Narrow
Oral allergy syndrome	Narrow
Oropharyngeal blistering	Narrow
Oropharyngeal oedema	Narrow
Oropharyngeal spasm	Narrow
Oropharyngeal swelling	Narrow
Palatal oedema	Narrow
Palatal swelling	Narrow
Palisaded neutrophilic granulomatous dermatitis	Narrow
Palpable purpura	Narrow
Pathergy reaction	Narrow
Perioral dermatitis	Narrow
Periorbital oedema	Narrow
Periorbital swelling	Narrow
Pharyngeal oedema	Narrow
Pharyngeal swelling	Narrow
Procedural shock	Narrow
Pruritus allergic	Narrow
Radioallergosorbent test positive	Narrow
Rash	Narrow
Rash erythematous	Narrow
Rash follicular	Narrow
Rash macular	Narrow
Rash maculo-papular	Narrow
Rash maculovesicular	Narrow
Rash morbilliform	Narrow
Rash neonatal	Narrow

Rash papulosquamous	Narrow
Rash pruritic	Narrow
Rash pustular	Narrow
Rash rubelliform	Narrow

Preferred Term	Scope
Rash scarlatiniform	Narrow
Rash vesicular	Narrow
Reaction to azo-dyes	Narrow
Reaction to colouring	Narrow
Reaction to excipient	Narrow
Reaction to food additive	Narrow
Reaction to preservatives	Narrow
Red man syndrome	Narrow
Rhinitis allergic	Narrow
Scleral oedema	Narrow
Scleritis allergic	Narrow
Scrotal eczema	Narrow
Scrotal oedema	Narrow
Serum sickness	Narrow
Serum sickness-like reaction	Narrow
Shock	Narrow
Shock symptom	Narrow
SJS-TEN overlap	Narrow
Skin necrosis	Narrow
Skin reaction	Narrow
Skin test positive	Narrow
Solar urticaria	Narrow
Solvent sensitivity	Narrow
Stevens-Johnson syndrome	Narrow
Stoma site hypersensitivity	Narrow
Stoma site rash	Narrow
Swelling face	Narrow
Swelling of eyelid	Narrow
Swollen tongue	Narrow
Symmetrical drug-related intertriginous and flexural exanthema	Narrow
Therapeutic product cross-reactivity	Narrow
Tongue oedema	Narrow
Toxic epidermal necrolysis	Narrow
Toxic skin eruption	Narrow
Tracheal oedema	Narrow
Type I hypersensitivity	Narrow
Type II hypersensitivity	Narrow
Type III immune complex mediated reaction	Narrow
Type IV hypersensitivity reaction	Narrow
Urticaria	Narrow
Urticaria cholinergic	Narrow
Urticaria chronic	Narrow
Urticaria contact	Narrow
Urticaria papular	Narrow
Urticaria physical	Narrow
Urticaria pigmentosa	Narrow
Urticaria vesiculosa	Narrow
Urticarial dermatitis	Narrow
Urticarial vasculitis	Narrow

Vaccination site dermatitis	Narrow
Vaccination site eczema	Narrow
Vaccination site exfoliation	Narrow
Vaccination site hypersensitivity	Narrow
Vaccination site rash	Narrow
Vaccination site recall reaction	Narrow
Vaccination site urticaria	Narrow
Vaccination site vasculitis	Narrow
Vaccination site vesicles	Narrow
Vaginal exfoliation	Narrow

Preferred Term	Scope
Vaginal ulceration	Narrow
Vasculitic rash	Narrow
Vernal keratoconjunctivitis	Narrow
Vessel puncture site rash	Narrow
Vessel puncture site vesicles	Narrow
Vulval eczema	Narrow
Vulval ulceration	Narrow
Vulvovaginal rash	Narrow
Vulvovaginal ulceration	Narrow
Vulvovaginitis allergic	Narrow
Acute respiratory failure	Broad
Administration site photosensitivity reaction	Broad
Airway remodelling	Broad
Allergy to chemicals	Broad
Allergy to fermented products	Broad
Alpha tumour necrosis factor increased	Broad
Alveolitis	Broad
Antibody test abnormal	Broad
Antibody test positive	Broad
Anti-insulin antibody increased	Broad
Anti-insulin antibody positive	Broad
Anti-insulin receptor antibody increased	Broad
Anti-insulin receptor antibody positive	Broad
Application site photosensitivity reaction	Broad
Asthma	Broad
Asthma late onset	Broad
Asthma-chronic obstructive pulmonary disease overlap syndrome	Broad
Asthmatic crisis	Broad
Auricular swelling	Broad
Blister	Broad
Blister rupture	Broad
Blood immunoglobulin A abnormal	Broad
Blood immunoglobulin A increased	Broad
Blood immunoglobulin D increased	Broad
Blood immunoglobulin G abnormal	Broad
Blood immunoglobulin G increased	Broad
Blood immunoglobulin M abnormal	Broad
Blood immunoglobulin M increased	Broad
Bronchial hyperreactivity	Broad
Bronchial oedema	Broad
Bullous impetigo	Broad
Caffeine allergy	Broad
Capillaritis	Broad

Charcot-Leyden crystals	Broad
Cheilitis	Broad
Childhood asthma	Broad
Choking	Broad
Choking sensation	Broad
Complement factor C1 decreased	Broad
Complement factor C2 decreased	Broad
Complement factor C3 decreased	Broad
Complement factor C4 decreased	Broad
Complement factor decreased	Broad
Conjunctivitis	Broad
Corneal exfoliation	Broad
Cytokine release syndrome	Broad
Cytokine storm	Broad
Ear swelling	Broad
Eosinophil count abnormal	Broad

Preferred Term	Scope
Eosinophil count increased	Broad
Eosinophil percentage abnormal	Broad
Eosinophil percentage increased	Broad
Eosinophilia	Broad
Eosinophilia myalgia syndrome	Broad
Eosinophilic bronchitis	Broad
Eosinophilic oesophagitis	Broad
Eosinophilic pneumonia	Broad
Eosinophilic pneumonia acute	Broad
Eosinophilic pneumonia chronic	Broad
Erythema	Broad
Flushing	Broad
Gastrointestinal oedema	Broad
Generalised oedema	Broad
Genital rash	Broad
Genital swelling	Broad
Haemolytic transfusion reaction	Broad
HLA marker study positive	Broad
Human anti-hamster antibody increased	Broad
Human anti-hamster antibody positive	Broad
Immune complex level increased	Broad
Immunoglobulins abnormal	Broad
Immunoglobulins increased	Broad
Immunology test abnormal	Broad
Implant site photosensitivity	Broad
Infusion site photosensitivity reaction	Broad
Injection site panniculitis	Broad
Injection site photosensitivity reaction	Broad
Interstitial lung disease	Broad
Laryngeal dyspnoea	Broad
Laryngeal obstruction	Broad
Leukotriene increased	Broad
Lip exfoliation	Broad
Localised oedema	Broad
Macrophage inflammatory protein 1-alpha increased	Broad
Mechanical urticaria	Broad
Medical device site photosensitivity reaction	Broad

Mesenteric panniculitis	Broad
Monocyte chemotactic protein-2 increased	Broad
Mouth ulceration	Broad
Mucocutaneous ulceration	Broad
Mucosa vesicle	Broad
Mucosal erosion	Broad
Mucosal exfoliation	Broad
Mucosal necrosis	Broad
Mucosal ulceration	Broad
Nasal crease	Broad
Necrotising panniculitis	Broad
Neurodermatitis	Broad
Neutralising antibodies positive	Broad
Noninfective conjunctivitis	Broad
Non-neutralising antibodies positive	Broad
Occupational asthma	Broad
Occupational dermatitis	Broad
Oedema mucosal	Broad
Oral mucosal exfoliation	Broad
Orbital oedema	Broad
Panniculitis	Broad
Penile exfoliation	Broad

Preferred Term	Scope
Penile oedema	Broad
Penile rash	Broad
Penile swelling	Broad
Perineal rash	Broad
Perivascular dermatitis	Broad
Photosensitivity reaction	Broad
Pneumonitis	Broad
Prurigo	Broad
Pruritus	Broad
Pulmonary eosinophilia	Broad
Reactive airways dysfunction syndrome	Broad
Respiratory arrest	Broad
Respiratory distress	Broad
Respiratory failure	Broad
Respiratory tract oedema	Broad
Reversible airways obstruction	Broad
Rhinitis perennial	Broad
Scrotal exfoliation	Broad
Scrotal swelling	Broad
Seasonal allergy	Broad
Septal panniculitis	Broad
Skin erosion	Broad
Skin exfoliation	Broad
Skin oedema	Broad
Skin swelling	Broad
Sneezing	Broad
Status asthmaticus	Broad
Stomatitis	Broad
Streptokinase antibody increased	Broad
Stridor	Broad

Suffocation feeling	Broad
Throat tightness	Broad
Tongue exfoliation	Broad
Tracheal obstruction	Broad
Tracheostomy	Broad
Transplantation associated food allergy	Broad
Upper airway obstruction	Broad
Vaccination site photosensitivity reaction	Broad
Vaginal oedema	Broad
Visceral oedema	Broad
Vulval oedema	Broad
Vulvovaginal swelling	Broad
Wheezing	Broad

13.4. Amgen MedDRA Query (AMQ)| MedDRA 22.1 for Injection Site Reactions

Amgen MedDRA Query| MedDRA 22.1	
Injection site reactions	
Definition: Any adverse event occurring locally at or around the site of an injected therapeutic agent. Methodology: Selected preferred terms. Inclusion: ALL terms from HLT Injection site reactions plus other selected terms from other categories. Exclusion: None	
Preferred Term	**Scope**
Administration site abscess	Narrow
Administration site abscess sterile	Narrow
Administration site anaesthesia	Narrow
Administration site atrophy	Narrow
Administration site bruise	Narrow
Administration site calcification	Narrow
Administration site cellulitis	Narrow
Administration site coldness	Narrow
Administration site cyst	Narrow
Administration site dermatitis	Narrow
Administration site discharge	Narrow
Administration site discolouration	Narrow
Administration site discomfort	Narrow
Administration site dryness	Narrow
Administration site dysaesthesia	Narrow
Administration site eczema	Narrow
Administration site erosion	Narrow
Administration site erythema	Narrow
Administration site exfoliation	Narrow
Administration site extravasation	Narrow
Administration site fibrosis	Narrow
Administration site granuloma	Narrow
Administration site haematoma	Narrow
Administration site haemorrhage	Narrow

Administration site hyperaesthesia	Narrow
Administration site hypersensitivity	Narrow
Administration site hypertrichosis	Narrow
Administration site hypertrophy	Narrow
Administration site hypoaesthesia	Narrow
Administration site indentation	Narrow
Administration site induration	Narrow
Administration site infection	Narrow
Administration site inflammation	Narrow
Administration site injury	Narrow
Administration site irritation	Narrow
Administration site ischaemia	Narrow
Administration site joint discomfort	Narrow
Administration site joint effusion	Narrow
Administration site joint erythema	Narrow
Administration site joint inflammation	Narrow
Administration site joint movement impairment	Narrow
Administration site joint pain	Narrow
Administration site joint warmth	Narrow
Administration site laceration	Narrow
Administration site lymphadenopathy	Narrow
Administration site macule	Narrow
Administration site mass	Narrow
Administration site movement impairment	Narrow
Administration site necrosis	Narrow

Preferred Term	Scope
Administration site nerve damage	Narrow
Administration site nodule	Narrow
Administration site odour	Narrow
Administration site oedema	Narrow
Administration site pain	Narrow
Administration site pallor	Narrow
Administration site papule	Narrow
Administration site paraesthesia	Narrow
Administration site phlebitis	Narrow
Administration site photosensitivity reaction	Narrow
Administration site plaque	Narrow
Administration site pruritus	Narrow
Administration site pustule	Narrow
Administration site rash	Narrow
Administration site reaction	Narrow
Administration site recall reaction	Narrow
Administration site scab	Narrow
Administration site scar	Narrow
Administration site streaking	Narrow
Administration site swelling	Narrow
Administration site thrombosis	Narrow
Administration site ulcer	Narrow
Administration site urticaria	Narrow
Administration site vasculitis	Narrow
Administration site vesicles	Narrow

Embolia cutis medicamentosa	Narrow
Injected limb mobility decreased	Narrow
Injection site abscess	Narrow
Injection site abscess sterile	Narrow
Injection site anaesthesia	Narrow
Injection site atrophy	Narrow
Injection site bruising	Narrow
Injection site calcification	Narrow
Injection site cellulitis	Narrow
Injection site coldness	Narrow
Injection site cyst	Narrow
Injection site deformation	Narrow
Injection site dermatitis	Narrow
Injection site discharge	Narrow
Injection site discolouration	Narrow
Injection site discomfort	Narrow
Injection site dryness	Narrow
Injection site dysaesthesia	Narrow
Injection site eczema	Narrow
Injection site erosion	Narrow
Injection site erythema	Narrow
Injection site exfoliation	Narrow
Injection site extravasation	Narrow
Injection site fibrosis	Narrow
Injection site haematoma	Narrow
Injection site haemorrhage	Narrow
Injection site hyperaesthesia	Narrow
Injection site hypersensitivity	Narrow
Injection site hypertrichosis	Narrow
Injection site hypertrophy	Narrow
Injection site hypoaesthesia	Narrow

Preferred Term	Scope
Injection site indentation	Narrow
Injection site induration	Narrow
Injection site infection	Narrow
Injection site inflammation	Narrow
Injection site injury	Narrow
Injection site irritation	Narrow
Injection site ischaemia	Narrow
Injection site joint discomfort	Narrow
Injection site joint effusion	Narrow
Injection site joint erythema	Narrow
Injection site joint infection	Narrow
Injection site joint inflammation	Narrow
Injection site joint movement impairment	Narrow
Injection site joint pain	Narrow
Injection site joint swelling	Narrow
Injection site joint warmth	Narrow
Injection site laceration	Narrow
Injection site lymphadenopathy	Narrow
Injection site macule	Narrow

Injection site mass	Narrow
Injection site movement impairment	Narrow
Injection site necrosis	Narrow
Injection site nerve damage	Narrow
Injection site nodule	Narrow
Injection site oedema	Narrow
Injection site pain	Narrow
Injection site pallor	Narrow
Injection site papule	Narrow
Injection site paraesthesia	Narrow
Injection site phlebitis	Narrow
Injection site photosensitivity reaction	Narrow
Injection site plaque	Narrow
Injection site pruritus	Narrow
Injection site pustule	Narrow
Injection site rash	Narrow
Injection site reaction	Narrow
Injection site recall reaction	Narrow
Injection site scab	Narrow
Injection site scar	Narrow
Injection site streaking	Narrow
Injection site swelling	Narrow
Injection site telangiectasia	Narrow
Injection site thrombosis	Narrow
Injection site ulcer	Narrow
Injection site urticaria	Narrow
Injection site vasculitis	Narrow
Injection site vesicles	Narrow
Injection site warmth	Narrow
Malabsorption from injection site	Narrow
Injection related reaction	Broad
Injection site alopecia	Broad
Injection site granuloma	Broad
Puncture site abscess	Broad
Puncture site bruise	Broad
Puncture site discharge	Broad
Puncture site erythema	Broad

Preferred Term	Scope
Puncture site haematoma	Broad
Puncture site haemorrhage	Broad
Puncture site hernia	Broad
Puncture site hypoaesthesia	Broad
Puncture site induration	Broad
Puncture site infection	Broad
Puncture site oedema	Broad
Puncture site pain	Broad
Puncture site reaction	Broad
Puncture site swelling	Broad
Systemic leakage	Broad
Vessel puncture site anaesthesia	Broad
Vessel puncture site bruise	Broad

Vessel puncture site cellulitis	Broad
Vessel puncture site discharge	Broad
Vessel puncture site erythema	Broad
Vessel puncture site haematoma	Broad
Vessel puncture site haemorrhage	Broad
Vessel puncture site hypoaesthesia	Broad
Vessel puncture site induration	Broad
Vessel puncture site infection	Broad
Vessel puncture site inflammation	Broad
Vessel puncture site pain	Broad
Vessel puncture site paraesthesia	Broad
Vessel puncture site pruritus	Broad
Vessel puncture site reaction	Broad
Vessel puncture site swelling	Broad
Vessel puncture site thrombosis	Broad
Vessel puncture site vesicles	Broad

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