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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Eileen Craig, MD
BLA 125522 SD1566
Repatha (evolocumab)

CLINICAL REVIEW

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Applicant Proposed Indication(s)/Population(s)	Patients with Homozygous Familial Hypercholesterolemia (HoFH)
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	HoFH patients, 13 years and older

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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
EAS	evaluative analysis set
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GFR	glomerular filtration rate
GRMP	good review management practice
HAS	HoFH analysis set
HDL-C	high density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia

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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
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)
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
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan

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SAS	severe FH analysis set
SC	subcutaneous
SD	standard deviation
SGE	special government employee
SOC	standard of care
TAS	evolocumab titration analysis set
TEAE	treatment emergent adverse event

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 to PCSK9 and inhibits circulating PCSK9 from binding 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, 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 (CVD), who require additional lowering of LDL-C at two subcutaneous (SC) dose levels: 140 mg every 2 weeks or 420 mg once monthly. These two dosing regimens yield similar LDL-C reduction but provide patients a choice between an injection every 2 weeks or every month.

Evolocumab was also approved as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. FDA approved the 420 mg once monthly (QM) SC dose for HoFH on 27 August 2015. A Complete Response Letter (CRL) was issued for the 420 mg every 2 weeks (Q2W) dose for HoFH patients, because the safety and efficacy data were insufficient to support approval. In the original biologics license application (BLA) application, the mean LDL-C reduction achieved with uptitration of evolocumab from 420 mg every 4 weeks to 420 mg every 2 weeks in 25 patients (28 patients in the 120-day safety update) with HoFH was small (~6%) and there was limited data to evaluate the safety of this dose.

In 2017, evolocumab 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.

The Applicant submits in this application additional data to support the 420 mg Q2W dose in patients with HoFH.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided sufficient clinical data to demonstrate that the 420 mg Q2W dose of

evolocumab reduces LDL-C in individuals with HoFH, aged 13 years and older, when added to other LDL-C-lowering therapies (LLT). In some patients, the 420 mg Q2W dosing regimen provided additional, clinically meaningful, LDL-C reduction as compared to the 420 mg QM dosing regimen.

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 trial with titration from evolocumab 420 mg QM to 420 mg Q2W in the subset of patients who did not have suppression of PCSK9 (<100 ng/mL). The observed treatment effect in patients with HoFH cannot be attributed to other influences, such as spontaneous change, placebo effect, or biased observation. The approval decision for the new dose may also rely on the previous finding of effectiveness for the 420 mg QM dose in the same population, including a randomized, controlled trial plus confirmatory evidence from open-label trials.

An open-label 5-year extension study (Study 20110271/Taussig) in patients with HoFH assessed the effectiveness of up-titration of evolocumab to the 420 mg every 2 weeks dosing (Q2W) on additional LDL-C reduction. Non-apheresis subjects could up-titrate to 420 mg Q2W dosing based on LDL-C response and insufficient suppression of PCSK9 (≥ 100 ng/mL) at the end of a dosing interval. Subjects on lipid apheresis at the time of enrollment initiated treatment with evolocumab 420 mg Q2W dosing to correspond with their apheresis schedule, which is typically performed weekly or biweekly. Subjects on apheresis with $\geq 5\%$ LDL-C reduction from baseline with Q2W treatment and suppressed PCSK9 (<100 ng/mL) could down-titrate to QM dosing. Dose frequency changes (420 mg QM vs 420 mg Q2W) for both apheresis and non-apheresis subjects were permitted at open-label extension (OLE) week 12, 24, or other visits with Applicant approval. Subjects with $< 5\%$ LDL-C reduction from baseline despite suppressed serum unbound PCSK9 (< 100 ng/mL) could discontinue evolocumab (for lack of efficacy). Investigators were not required to report the reason for up-titration or down-titration as long as protocol criteria were met.

To evaluate the effect of dose titration from 420 mg QM to 420 mg Q2W, the applicant defined an analysis population consisting of 48 patients (including 7 adolescent patients) exposed to 420 mg QM for at least 12 weeks and 420 mg Q2W for at least 12 weeks. In this subset of patients, the mean LDL-C was 374 mg/dL at baseline. The mean absolute change and percent change in LDL-C from baseline to Week 12 of 420 QM treatment were approximately -69 mg/dL and -20%, respectively. Subsequent up-titration to the 420 mg every 2 weeks dosing in this population resulted in an approximate mean 10% *additional* reduction in LDL-C (i.e., approximately -105 mg/dL and -30% mean change in LDL-C from baseline).

The treatment response to the increased dose of evolocumab 420mg Q2W was modest and variable in this subset of the HoFH population. However, some individuals, after 12 weeks of 420 mg Q2W dosing, did experience a likely clinically meaningful improvement in LDL reduction with an increase in the dose of evolocumab. A health care provider can easily assess LDL-C

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levels and decide whether an individual patient is or is not responding to an increase in the dose of evolocumab and adjust treatment accordingly.

In addition, Study 20110271 provides support, although limited, as this is 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.

1.3. **Benefit-Risk Assessment**

Benefit-Risk Integrated Assessment

HoFH is a rare genetic disorder caused by, in the majority of cases, mutations in which both LDL receptor (LDLR) alleles are defective. The US prevalence of HoFH has been estimated in the literature, using a definition based on clinical phenotype, as ~1 in 1,000,000 persons; thus approximately 330 individuals in the US may be affected. Using more sophisticated genetic cascade testing analyses, the worldwide prevalence may be higher, ranging from 1 in 160,000 to 1 in 320,000^{1,2}. Using these more recent worldwide estimates of prevalence, as many as 2,000 individuals in the US may be affected.

Untreated individuals have very high concentrations of LDL-C, often in the range of 650 to 1000 mg/dL, cutaneous and tendinous xanthomata, corneal arcus, premature coronary artery disease and aortic stenosis. Individuals with HoFH are at increased risk for premature cardiovascular disease and death due to the early onset and prolonged duration of elevated lipid values.

High-dose statin therapy, lomitapide, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapies and lipid apheresis are the main treatment options for 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, mipomersen) and cost, availability and patient burden (lipid apheresis). Patients with HoFH typically have severe hyperlipidemia (LDL-C $\geq$ 190 mg/dL) even after treatment with multiple lipid-lowering agents.

As described in Section 1.2, an open-label 5-year extension study (Study 20110271/Taussig) in patients with HoFH assessed the effectiveness of up-titration of evolocumab to the 420 mg every 2 weeks dosing (Q2W) in additional LDL-C reduction. In the 48 patients with HoFH who initiated evolocumab on 420 mg once monthly dosing (achieving mean change from baseline in LDL-C of approximately -20%), up-titration to the 420 mg every 2 weeks dosing resulted in an approximate mean 10% additional reduction in LDL-C (mean percent change from baseline -30%).

¹ Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J. 2014;35: 2146-2157.

² Nordestgaard BG, Chapman MJ, Humphries SE, et al. A European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013;34:3478-3490

Although this application relies primarily on a single, open-label trial, the results constitute substantial evidence of effectiveness in this serious, rare condition with a well-characterized natural history. The approval decision for the new dose may also rely on the previous finding of effectiveness for the 420 mg QM dose in the same population, including a randomized, controlled trial plus confirmatory evidence from open-label trials.

The safety assessment of this 420 mg Q2W dosing regimen is based on the data from the final analysis of Study 20110271, the totality of data from over 28,000 individuals who received evolocumab (420 mg QM or 140mg Q2W) in the clinical development program, and approximately 5 years of worldwide post-marketing experience since evolocumab's initial approval which includes the use of the 420mg Q2W dose in HoFH populations in 65 other countries.

Risks associated with evolocumab include injection site reactions and allergic reactions, such as angioedema, rash and urticaria. Other adverse reactions include nasopharyngitis, upper respiratory tract infection and influenza/influenza-like illness. In clinical trials, these reactions generally occurred at low incidence and were mild in severity. The safety profile of the 420 mg Q2W dosing regimen in Study 20110271 was consistent with the safety data from clinical trials using the 420 mg QM or 140 mg Q2W dosing regimens. The safety data for the 420 mg Q2W dose, while limited, does not suggest an increased risk or new safety findings.

All review disciplines support approval.

Approval of the 420 mg every 2 weeks dosing regimen for evolocumab in individuals with HoFH would provide an additional therapeutic option for LDL-C reduction in a patient population with an unmet medical need. The safety profile of evolocumab in this study was generally consistent with the safety profile described in controlled trials involving patients with primary hyperlipidemia (including HeFH) and HoFH. There is cardiovascular outcomes data to confirm that LDL-C reduction with evolocumab in a non-HoFH population translates to CV risk reduction.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HoFH ○ Rare genetic disorder (1 in 160,000 to 1 in 1,000,000); estimated 330-2000 affected individuals in the U.S. ○ Most common mutations: LDL-C receptor (90%), Apo B, PCSK9, LDLRAP1; mutations result in ineffective plasma clearance of LDL-C ○ Persistent hyperlipidemia >400-500 mg/dL beginning in childhood ○ Progressive and early heart disease • Premature atherosclerosis, valvular stenosis, supraaortic stenosis • Premature CVD and increased risk for CV events (MI beginning 2nd decade) ○ Decreased life expectancy (mid-40s) without aggressive treatment • Patients with HoFH are treated with aggressive lipid-lowering therapies to reduce CV risk, primarily based on extrapolation of evidence from LDL-C reduction in primary hyperlipidemia • LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes in Heterozygous familial hypercholesterolemia (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	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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mmol/L) absolute reduction in LDL-C³. Unknown if this can be extrapolated to the extreme levels of LDL-C that characterize individuals with HoFH. - o CV outcomes trials of the two approved PCSK9 inhibitors, alirocumab and evolocumab, demonstrated that reduction in LDL-C led to reduced risk of CV events.^{4,5} - o A CV outcomes trial with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering⁶. • Patients with HoFH are typically unable to achieve LDL-C goals and respond poorly to approved lipid-lowering therapies, since most therapies target the LDL-C receptor	
Current Treatment Options	Treatment options for HoFH • Statins (-14% to -30% LDL-C reduction in HoFH) • Ezetimibe (-21% LDL-C reduction in HoFH) • Evolocumab (-31% LDL-C reduction in HoFH) • Lomitapide (-40% LDL-C reduction in HoFH): risk of hepatosteatorosis, tolerability issues, not approved in pediatrics • Mipomersen is no longer marketed • Apheresis: limited availability, high patient burden and cost	Currently approved lipid-lowering therapies, whether approved for HoFH or used off-label, do not adequately meet the need for LDL-C reduction in HoFH.

³ 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.

⁴ Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med 2018; 379: 2097-107.

⁵ 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

⁶ 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
Benefit	• In an open-label extension study, 48 patients with HoFH who took evolocumab as add-on to background lipid-lowering therapy (typically high-intensity statin, ezetimibe, and apheresis), up-titration from 420 mg QM to 420 mg Q2W resulted in approximate mean 10% (median 13%) additional reduction in LDL-C from baseline. • As expected, patients with null/null mutations (<2% LDLR activity demonstrated on in vitro assays) have little to no response to evolocumab treatment. • Evolocumab also lowered Apo B, non-HDL-C, and TC. • The CV risk-reducing effect of evolocumab on cardiovascular morbidity and mortality has been determined in a non-HoFH population	The treatment response to the increased dose of evolocumab 420mg Q2W was modest and variable in this subset of the HoFH population. However, some individuals, after 12 weeks of 420 mg Q2W dosing, did experience a likely clinically meaningful improvement in LDL reduction with an increase in the dose of evolocumab. Health care providers can assess LDL-C levels and decide whether an individual patient is or is not responding to an increase in the dose of evolocumab and adjust treatment accordingly.
Risk and Risk Management	An open-label extension study evaluated the 420 mg Q2W dosing regimen of evolocumab as compared to the 420 mg QM dosing regimen in 106 patients with HoFH. • 29 (27%) subjects on lipid apheresis: only 420 mg Q2W dosing; median treatment exposure of 36 months, • 58 (55%) subjects: both 420 mg QM and Q2W dosing; median treatment exposure of 53 months, and • 19 (18%) subjects: only 420 mg QM dosing; median treatment exposure of 49 months. Although the data is limited, there does not appear to be any adverse event(s) that is more likely to occur or is related to the 420 mg Q2W dosing regimen as compared to QM dosing regimen.	Risks associated with evolocumab include injection site reactions and allergic reactions, such as angioedema, rash and urticaria. Other adverse reactions include nasopharyngitis, upper respiratory tract infection and influenza/influenza-like illness. Risks associated with evolocumab are clinically manageable and can be adequately addressed through labeling.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons

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)	
☒	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

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 persons⁷, 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 individuals⁸.

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.⁹ Many individuals with HoFH may be compound heterozygotes with different mutations on each of the LDL receptor alleles¹⁰.

When patients with HoFH come to medical attention because of a classic clinical phenotype, untreated individuals typically have very high concentrations of LDL-C, often in the range of 650 to 1000 mg/dL, cutaneous and tendinous xanthomata, corneal arcus, and premature coronary artery disease and aortic stenosis¹¹. 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 treatment¹².

⁷ 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

⁸ 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.

⁹ Raal FJ, Santos RD. Homozygous familial hypercholesterolemia: current perspectives on diagnosis and treatment. Atherosclerosis 223(2), 262–268 (2012).

¹⁰ 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.

¹¹ Goldstein AL, Brown MS. Molecular Medicine. The cholesterol quartet. Science. 2001;292(5520):1310-2.

¹² Raal FJ, Santos RD, Homozygous familial hypercholesterolemia: Current perspectives on diagnosis and treatment, Atherosclerosis 2012; 223: 262-68.

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

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. LDL apheresis is FDA approved and indicated if the LDL-C is: >500 mg/dl in patients with homozygous FH, >300 mg/dl in HeFH patients without CAD, or >200 mg/dl in HeFH 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 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.¹³

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, and evolocumab.

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 with the following symbol: †

¹³ Thompson GR. Lipoprotein apheresis. *Curr Opin Lipidol*. 2010;21: 487–491.

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Table 1. 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, Apo B, 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, LDL-C, and Apo B 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

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						Adjunct therapy to diet to reduce elevated total-C, LDL-C, apo B, 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 apo B 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, non-HDL-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, LDLC 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, <u>as add-on to statin</u>						
Ezetimibe (Zetia) Intestinal	Combination of ZETIA and atorvastatin or	2002	10 mg tablet PO once daily	LDL-C reduction: -21% at Week 12 (N=50)	Elevations in liver enzymes, myopathy/	Reduce elevated total-C, LDLC, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate

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cholesterol/ phytosterol absorption inhibitor NDA 21445	simvastatin is 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.				rhabdomyolysis	Adjunct to diet to reduce elevated total-C, LDL-C, Apo B, 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, Apo B, 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, apo B, 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	2013	200 mg once weekly as a	LDL-C reduction: At Wk 28 (N=51): Mean: -21%;	Hepatotoxicity with elevations in	

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	diet to reduce LDL-C, apo B, TC, and non-HDL-C in patients with HoFH		subcutaneous injection	Median: -19%	transaminases and 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, Apo B, 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 diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with HoFH who require additional lowering of LDL-C	2015	420 mg SC injection once monthly	LDL-C reduction: At Wk 12 (N=49) Mean -31%	Allergic reactions (angioedema, rash, urticaria)	To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease Adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C
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:		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,	

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	Group A – functional hypercholesterole mic homozygotes with LDL-C >500 mg/dL				hemolysis	
Source: Individual drug prescribing information HoFH= homozygous familial hypercholesterolemia; PO=by mouth *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 2015, evolocumab, 420 mg QM administered by subcutaneous injection, was approved in the USA 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.

The indication for individuals with HoFH was supported by two trials, trial 20110233 (placebo-controlled, N=49) and the ongoing open-label extension trial 20110271 (TAUSSIG, N=96). Trial 20110233 used an evolocumab dose of 420 mg every 4 weeks (QM) and ongoing trial 20110271 used doses of 420 mg QM and 420 mg every 2 weeks (Q2W). The duration of exposure was 12 weeks in trial 20110233 and 84 weeks (planned) in trial 20110271.

In the placebo-controlled HoFH trial 20110233, which did not allow lipid apheresis treatment, evolocumab, compared to placebo, significantly reduced LDL-C from baseline to Week 12 by 31%. The mean change from baseline to Week 12 within the evolocumab arm alone was -23% and within the placebo arm alone was +8%. Efficacy data from 10 adolescent patients, aged 13 to 17 years, enrolled in the trial (7 evolocumab, 3 placebo) were similar. The LDL-C reduction seen in this trial was similar to what had been observed with statin+ezetimibe, somewhat greater than what was observed with statin monotherapy (-22% mean reduction with

rosuvastatin) and mipomersen¹⁴ but less than that observed with lomitapide¹⁵ (mean, -40%; median, -50%) and LDL apheresis (~ -50%, time-averaged).¹⁶

In the open-label extension trial 20110271, evolocumab resulted LDL-C reductions of 19% at Week 12 and 23% at Week 24 in the HoFH analysis set (based on direct measurements of LDL-C by ultracentrifugation [UC]). Participants who were being treated with apheresis had a reduced response to evolocumab (-20%) compared to the non-apheresis participants (-25%) at Week 24. Increasing the frequency of dosing from 420 mg QM to 420 mg Q2W in 25 non-apheresis participants with HoFH resulted in approximately 6% greater reduction of LDL-C.

The evolocumab development program was presented at the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 10 June 2015. Some panelists stated that the mean LDL-C reduction achieved with the uptitration from the 420 mg every 4 weeks to every two weeks dose of evolocumab in patients with HoFH was small and that there were limited data to evaluate the safety of this dose. On the other hand, some members of EMDAC stated that the risk for cardiovascular events is extremely high in the HoFH population and that the potential incremental cardiovascular benefit from the 420 mg Q2W dose could outweigh the additional risk.

FDA approved the 420 mg QM dose for HoFH on 27 August 2015 but a Complete Response Letter (CRL) was issued for the 420 mg Q2W dose for HoFH patients (BLA 125522/Original 2). In the CR letter, the FDA outlined the deficiencies and expectations for resubmitting this portion of the application.¹⁷ In brief, the CRL stated that the limited amount of safety and efficacy data

¹⁴ Mipomersen (once weekly subcutaneous injection), approved by FDA in January 2013, is an oligonucleotide inhibitor of apo B-100 synthesis, which is the principal apolipoprotein of LDL and VLDL. Mipomersen treatment led to mean 25% reduction in LDL-C compared to baseline and mean 21% reduction compared to placebo. Mipomersen, like lomitapide, promotes hepatic steatosis (with or without elevations in transaminases). Injection site reactions are also common (84% of patients, according to PI) and resulted in discontinuation of therapy in 5% of patients in phase 3 trials. Flu-like symptoms were reported in 30% of patients, resulting in discontinuation in 3% of patients in phase 3 trials. Marketing has been discontinued for mipomersen.

¹⁵ Lomitapide (daily oral dosing) is an inhibitor of microsomal transfer protein (MTP), which participates in the formation of VLDL particles (a precursor to LDL), that was approved in December 2012. As a result of its mechanism of action, this drug promotes hepatic steatosis (with or without elevations in transaminases) and fat malabsorption, leading to recommendations for monitoring hepatic transaminases and supplementation with essential fatty acids + Vitamin E, respectively. Gastrointestinal tolerability is an issue given the drug-induced fat malabsorption, although 23 of 29 patients in the 78-week pivotal trial remained on drug throughout.

¹⁶ Cuchel M, Bruckert E, Ginsberg HN et al, Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014 June 13; 35:2146-57.

¹⁷ Insufficient clinical data were provided to describe the effect of the 420 mg every two week dosage in labeling for the treatment of homozygous familial hypercholesterolemia in patients on other lipid-lowering therapies who require additional lowering of LDL-C. Specifically, the submitted data were inadequate to describe for providers

provided in the submission for the 420 mg every 2 weeks dose was insufficient to support approval, especially as the dosing regimen could be used in adolescents.

3.2. Summary of Presubmission/Submission Regulatory Activity

On 26 July 2016, Amgen requested an extension of time to resubmit the application, which was granted by FDA on 29 July 2016. On 25 February 2020, the FDA requested Amgen to indicate plans to resubmit or withdraw BLA 125522/Original 2, and on 08 April 2020 Amgen responded with a notification to FDA of plans to submit the additional information requested in the CRL. Amgen requested clarification on the format and general approach of the submission to which the FDA responded with additional points to be addressed within Amgen's response. Clinical comments sent by email on 22 May 2020 (see document in DARRTS dated 6/9/20; Reference ID: 4621673):

1. You will need to provide a more rigorous assessment of the effect of uptitration from 420 mg QM to 420 mg Q2W than was provided in the original submission.
2. When you provide a summary of worldwide experience on the safety of this drug, including an updated estimate of worldwide use—you should specifically address the exposure and safety experience for the 420 mg Q2W dose, in addition to the safety of all doses.
3. Is the 420 mg Q2W dose being used in children with familial hypercholesterolemia globally? If so, please provide available effectiveness and safety data.
4. One of the issues we had at the time of the initial submission was whether the ~6% additional LDL lowering by increasing the frequency of the 420 mg dose from QM to Q2W in patients with HoFH has a positive benefit to risk ratio given the very limited amount of safety data we had at that dose. Thus, we would like to see all the safety data on the 420 mg Q2W group as well as reasons why patients were either uptitrated or downtitrated from the QM 420 mg to the Q2W 420 mg dose and what the reasons were for down-titration.
5. In the clinical trials, how often was the uptitration driven by the PCSK9 level criterion, which was part of the protocol but would not be available clinically?
6. What criteria do you propose for a physician to determine if a patient with HoFH would benefit from uptitration to 420 mg Q2W in the clinical setting where PCSK9 levels are not followed?
7. What incremental benefit could health care providers expect to see from doubling the dosing frequency?

what incremental benefit, if any, is achieved by doubling the dosing frequency of 420 mg once monthly to 420 mg every two weeks. Additional information from adequate and well-controlled study(ies) will be required to better characterize this dosing regimen.

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Amgen now submits the Final CSR for Study 20110271, a response document providing the information requested by the FDA in the 27 August 2015 CRL and the 08 July 2020 advice letter, and draft labeling which incorporates the proposed dosing regimen updates to the US Prescribing Information (US PI) and to the US Patient Package Insert (US PPI).

3.3. Foreign Regulatory Actions and Marketing History

As of 17 July 2020, Repatha has been approved in 77 countries worldwide; the 420 mg Q2W dosing regimen has been approved in 65 of those countries for use in patients 12 years and older with HoFH.

In 2015, the 420 mg once monthly and 420 mg every 2 weeks dose of Repatha were approved for the treatment of HoFH in the European Union, Canada, Kuwait, Australia, Norway, and Iceland. In 2016 both doses were approved in Japan, Switzerland, Israel, Russia, Hong Kong, Mexico, Lebanon, Jordan, Qatar, United Arab Emirates, Serbia, Bosnia and Herzegovina.

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

4.1. Office of Scientific Investigations (OSI)

The clinical team did not request inspections for the open-label Study 20110271. The original BLA was inspected, in addition to the cardiovascular outcomes (CVOT) study, and no significant issues were found.

4.2. Clinical Pharmacology

The Clinical Pharmacology team reviewed the clinical pharmacology data submitted on 08/27/14 under BLA 125522 for the original submission and recommended approval with the following comment:

- **Homozygous Familial Hypercholesterolemia:** The sponsor has proposed two regimens - 420 mg once monthly or 420 mg every two weeks. The 420 mg every two weeks dose appeared to offer little additional benefit (~6% additional reduction in LDL-C). Based on the exposure-response relationship in the Heterozygous familial Hypercholesterolemia population, the exposures from the once monthly dose are already in the plateau of the response curve and dosing higher amounts will not likely provide additional benefit. Further, from a safety perspective, there may be an insufficient amount of data in patients who received 420 mg every two weeks.

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The clinical-pharmacology review for the current submission (refer to the review by Sang Chung, PhD, in DARRTS 2/1/2021, Reference ID: 4739666), states that the applicant did address the deficiencies in the Complete Response Letter using the final CSR for Study 20110271. Dr. Chung comments that additional exposure data obtained in the final CSR supports the conclusions of exposure-response in the original BLA review. Nevertheless, because dose adjustment was limited to patients with elevated PCSK9 concentration (i.e. not in plateau), additional PCSK9 lowering, and thus additional LDL-C lowering were observed among some patients in this subset. In conclusion, the Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology information of complete response and finds it acceptable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

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Table 2. Listing of Clinical Trials Evaluating Evolocumab in the Treatment of Patients with HoFH

Trial Name	Study Population	Trial Design	Test Product(s): Dosage Regimen, Allocation	Duration of Therapy	Primary Endpoint	# Enrolled
PHASE 2: HoFH						
20110233	HoFH: On a stable low-fat diet and pre-existing, lipid-lowering therapies at least 4 weeks prior with LDL-C $\geq$ 130 mg/dL Age 12 to 80 years	Part A: phase 2, open-label, single- arm, pilot Part B: phase 3, double-blind, randomized, PBO- controlled	Part A: EvoMab 420 mg SC QM Part B: PBO or EvoMab 420 mg SC QM Via vial and syringe or AI/pen Allocation 2:1 EvoMab:PBO	Part A: 12 weeks Part B: 12 weeks	percent change from baseline in LDL-C at week 12.	Part A: 8 Part B: 50
PHASE 2/3: HoFH and “Severe” HeFH^a						
20110271	Completion of a qualifying EvoMab protocol without treatment related SAE that led to IP discontinuation and have a diagnosis of “severe” FH ^a If de-novo subject, then must have “severe” FH and be on background lipid-lowering therapy for $\geq$ 4 weeks prior LDL-C $\geq$ 100 mg/dL (with CHD or CHD risk equivalent) or $\geq$ 130 mg/dL (no CHD or CHD risk equivalent) Age 13 to 80 years	Phase 2/3, open-label, long-term	EvoMab 420 mg SC QM or SC Q2W (if eligible) Via vial and syringe, AI/pen, or AMD; All on EvoMab	mean (SD) duration of exposure in HoFH subject was 41.4 (19.6) months (median =50 months). Study Initiation Date: 01 June 2012 Study Completion Date: 11 May 2018 Database lock date of 13 July 2018	subject incidence of treatment emergent adverse events	106 subjects with HoFH; 194 with severe FH Adolescent HoFH subgroup (N = 14): 10 non-apheresis and 4 apheresis subjects

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^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, and ≥ 130 mg/dL for subjects without diagnosed coronary heart disease or risk equivalent). There was No LDL-C entry requirement for apheresis subjects. (b) (4)

AI/pen = autoinjector/pen; AMD = auto mini-doser; EvoMab=evolocumab; PFS = prefilled syringe

Publications based on these 2 studies:

- Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation*. 2013;128:2113-2120.
- Raal FJ, Hovingh GK, Blom D, Santos RD, Harada-Shiba M, Bruckert E, Couture P, Soran H, Watts GF, Kurtz C, Honarpour N, Tang L, Kasichayanula S, Wasserman SM, Stein EA. Long-term treatment with evolocumab added to maximal drug therapy with or without apheresis in patients with homozygous familial hypercholesterolemia: an interim subset analysis of the open-label TAUSSIG study. *Lancet Diabetes and Endocrinol* 2017;5:280-290

5.2. Review Strategy

The primary focus of this review is the HoFH subjects in Study 20110271 (TAUSSIG), particularly the subjects who were titrated to the 420 mg Q2W dose of evolocumab. The applicant's analyses were verified and supplemented with the clinical and statistical reviewers' analyses, where applicable. Refer to the statistical review by Kiya Hamilton, PhD, in DARRTS dated 1/25/2021, for additional analyses. The statistical reviewer concludes that findings from this study suggest that up titration to Q2W from QM for some subjects could lead to further reduction of LDL-C. The statistical review team recommends approval of the 420 mg Q2W dose of evolocumab in patients with HoFH.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 (evolocumab) on LDL-C in Subjects with Severe Familial Hypercholesterolemia (Protocol Number: 20110271; TAUSSIG)

6.1.1. Study Design

Overview and Objective

Primary Objective: To characterize the safety and tolerability of long-term administration of evolocumab among subjects with severe familial hypercholesterolemia

Secondary Objectives: To characterize the efficacy of long-term administration of evolocumab as assessed by low density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), lipoprotein(a) [Lp(a)], apolipoprotein B (ApoB), total cholesterol/HDL-C ratio, ApoB/Apolipoprotein A-1 (ApoA1) ratio, and response of LDL-C reduction (15% or greater) in subjects with severe familial hypercholesterolemia

Trial Design

A multicenter, open-label study designed to assess the long-term safety, tolerability, and efficacy of evolocumab. The study was to continue until the date when the last subject had completed the assessments for Week 260 (approximately 5 years), the investigator's recommendation of discontinuation, Amgen's recommendation of discontinuation, the

subject's decision to discontinue for any reason, or an administrative decision to close the study. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP were not to be reported to the investigator prior to Week 8 for subjects coming from a blinded (or blinded portion) of an evolocumab parent protocol, since some laboratory results might inadvertently unblind investigators to treatment assignment in the parent study. Proprotein convertase subtilisin/kexin type 9 (PCSK9) levels were blinded until Week 4. Study participation could be stopped for subjects that did not demonstrate minimal benefit (i.e., subjects that had less than 5% LDL-C reduction from baseline while on therapy). The study had adjudication of deaths and specific cardiovascular events potential endpoints (PEPs) by an independent Clinical Events Committee (CEC).

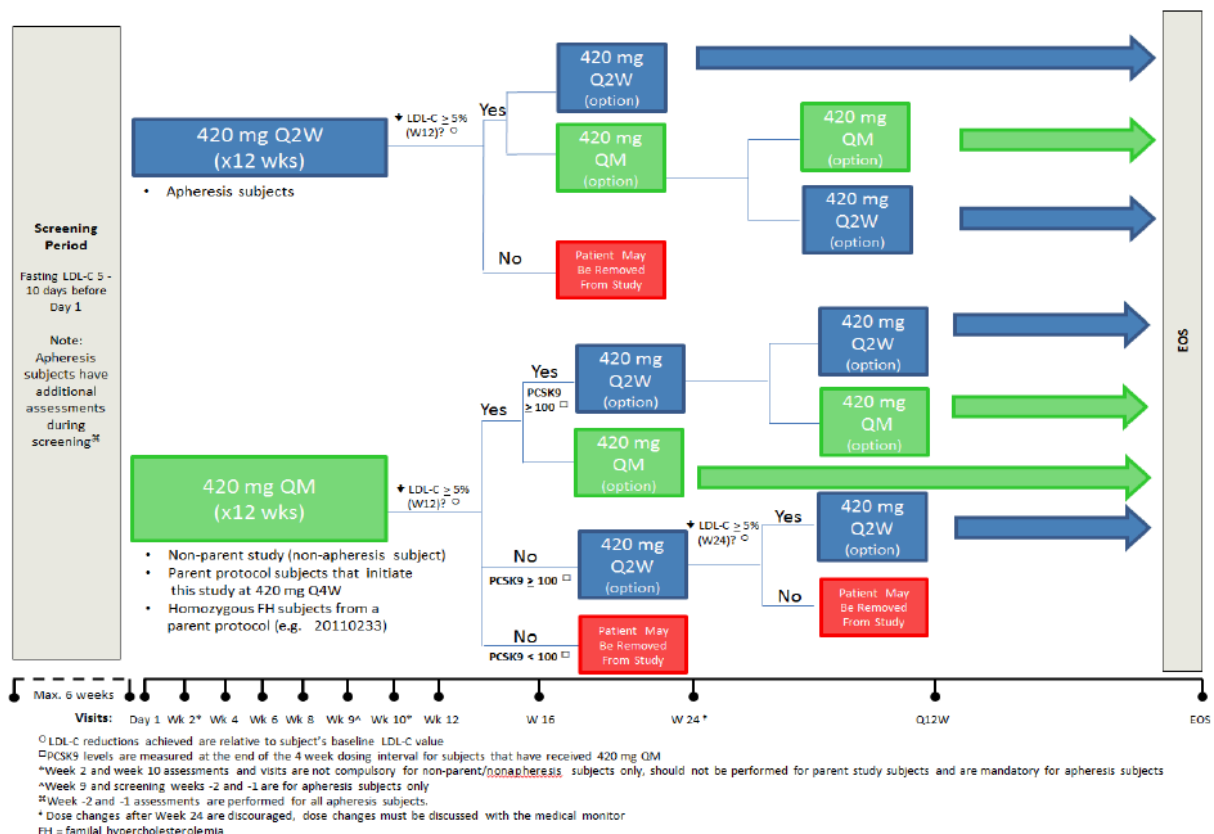
Subjects visited the study center QM (non-apheresis subjects) or Q2W (apheresis subjects) until OLE Week 24, after which they received a 12-week supply of evolocumab if they decided to self-administer evolocumab. Beyond OLE Week 24, these subjects visited the site every 12 weeks for central laboratory tests and to collect information on concomitant medications and adverse events. Subjects who did not want to self-administer evolocumab could continue to visit the study center QM or Q2W to receive treatment.

At OLE Week 12, subjects with < 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL could discontinue evolocumab. If serum unbound PCSK9 was $\geq$ 100 ng/mL with QM dosing, the subject could switch to evolocumab 420 mg Q2W treatment at OLE Week 12. Subjects on apheresis with $\geq$ 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL with Q2W treatment could switch to QM dosing at OLE Week 12 (refer to Figure 1.)

The approximate total number of subjects expected to participate in this study was 310.

This study was conducted at 43 centers in Canada, South Africa, Czech Republic, Netherlands, USA, France, Spain, Italy, Belgium, Australia, New Zealand, United Kingdom, Japan, Israel, Greece, Lebanon, Brazil, and Hong Kong.

Figure 1. Study 20110271: Design and Treatment Schema



EOS = end of study; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = once every 2 weeks; QM or Q4W = once monthly (every 4 weeks); wks = weeks.

Source: Applicant CSR 20110271, Figure 8-1; page 48 of 4704.

Summary of Inclusion Criteria

- Subjects that participated in a qualifying evolocumab parent protocol must have a diagnosis of familial hypercholesterolemia. Subjects must not have experienced an investigational product (IP) treatment related serious adverse event that led to IP discontinuation during their participation in the qualifying evolocumab parent study.
- Subjects with homozygous familial hypercholesterolemia who meet the inclusion and exclusion criteria of study 20110233¹⁸ may enroll after study 20110233 is closed.
- Subjects that have not participated in a qualifying evolocumab parent protocol must:
 - Have a diagnosis of familial hypercholesterolemia.
 - Bodyweight must be 40 kg or greater at screening for subjects age < 18 years.

¹⁸ In 20110233, participants were on background statin therapy with or without ezetimibe and not receiving apheresis. The diagnosis of HoFH was made by genetic confirmation or a clinical diagnosis based on a history of an untreated LDL-C concentration > 500 mg/dL together with either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents.

- c. Receive stable low-fat diet and pre-existing, background lipid-lowering therapy (e.g. statins, cholesterol-absorption inhibitors, bile-acid sequestrants, nicotinic acid, omega 3 fatty acids or combinations thereof) for at least 4 weeks prior to final screening.
- d. Demonstrate a fasting central lab triglyceride concentration ≤ 400 mg/dL and either LDL cholesterol concentration ≥ 100 mg/dL for subjects with CHD or CHD risk equivalent by NCEP ATP III criteria or ≥ 130 mg/dL for subjects that do not have CHD or CHD risk equivalent by NCEP ATP III criteria. Subjects that are receiving apheresis are not required to demonstrate a minimum LDL-C level at baseline due to the fluctuations caused by apheresis therapy.
- e. Male or female ≥ 12 to ≤ 80 years of age

Summary of Exclusion Criteria

1. Use of mipomersen or lomitapide within 5 months of screening or a cholesterylester transfer protein (CETP) inhibitor in the last 12 months;
2. New York Heart Failure Association (NYHA) class III or IV or last known left ventricular ejection fraction $< 30\%$;
3. Cardiac arrhythmia within past 3 months that is not controlled by medication;
4. Systolic blood pressure (SBP) > 180 mmHg or diastolic BP (DBP) > 110 mmHg;
5. Requiring statin up-titration within 4 weeks of screening;
6. Estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73m²; persistent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN), creatine kinase (CK) > 5 x ULN without a known cause;
7. Known major active infection, or major hematologic, renal, metabolic, gastrointestinal or endocrine dysfunction; deep vein thrombosis or pulmonary embolism within 3 months prior to enrollment;
8. History of malignancy in the last 5 years;
9. Subject previously received a non-evolocumab investigational therapy to inhibit PCSK9; currently enrolled in a non-evolocumab investigational device or drug study, or less than 30 days since ending a non-evolocumab investigational device or drug study(s), or receiving other investigational agent(s).
10. Female subjects cannot be pregnant or breast-feeding or planning to become pregnant or breastfeed and premenopausal females of childbearing potential must be willing to use an acceptable method(s) of birth control during treatment with evolocumab (IP) and for an additional 15 weeks after the last dose of evolocumab (IP).

Table 3. Study 20110271: Schedule of Assessments (Non-parent/Non-apheresis Subjects Only)

Study Day / Timepoint	Screening ^a	Day 1 OL ^b	Optional Visits (Weeks 2, 10 ^c)	Interval Visits (Weeks 4, 6, 8, 16, 20)	Quarterly Visits ^d (Every 12 weeks)	EOS/ ET OL
<i>General Procedures</i>						
Informed consent	X					
Vital Signs (HR, BP)	X	X	X	X	X	X
AEs/SAEs	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X
Physical exam	X					X
Body weight	X					X
12 Lead ECG	X					X
<i>Central Laboratory</i>						
Fasting plasma lipids, Lp(a), ApoA1, ApoB ^e	X	X	X	X ^f	X	X
PK samples (AMG 145), PCSK9	X ^g	X	X	X ^f	X	X
Chemistry	X	X			X	X
Hematology	X	X			X	X
HbA1c	X	X			X	X
Coagulation	X	X			X	X
hsCRP		X			X	X
Fasting Vitamin E		X ^h			X ^h	X
Biomarkers (blood)		X			X ⁱ	
Anti-AMG 145 antibodies		X			X ^j	X
Serum pregnancy (women of childbearing potential) and FSH	X ^{k,l}	X ^k			X ^l	X
Urinalysis, eGFR	X ^m	X				X
<i>Investigational Product</i>						
IP administration, QM or Q2W ⁿ		X		X	X	

AE = adverse event; AMG 145 = evolocumab; ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; BP = blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration ratio; EOS = end of study; ET OL = end of treatment, open label; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; HR = heart rate; hsCRP = high sensitivity C-reactive protein; IP = investigational product; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9; Q2W = once every 2 weeks; QM = once monthly; SAE = serious adverse event;

^a Screening was for all non-parent study subjects.

^b D1 = day of first administration of investigational product for the open-label.

^c Week 2 and week 10 assessments and visits were not compulsory. They could be performed according to the subject's availability for non-parent subjects only.

^d Quarterly visits started at wk 12 and occur every 12 wks thereafter. Starting at week 24, all subjects had the option of self-administering evolocumab. Prior to week 24, subjects who were treated with evolocumab 420 mg administered SC Q2W had to self-administer study drug between some visits.

^e Investigators and staff involved with this trial remained blinded to locally obtained lipid panels until the Week 8 visit for all subjects who transitioned from an ongoing blinded (or blinded portion) parent study into this study, in order to avoid potential unblinding of the ongoing parent study.

^f Week 4, 6, 8, 16, and 20 labs were mandatory for all subjects.

^g PCSK9 only.

^h Vitamin E was only collected at EOS Parent/Day 1 and at weeks 12, 24, 48 (year 1), 72, and 96 (year 2).

ⁱ Biomarkers was only collected at month 3 (week 12).

^j After year 1 antibody samples will only be collected at the end of each year.

^k FSH in applicable subjects for study entry only.

^l Pregnancy testing occurred every 6 months and during screening for non-parent subjects.

^m eGFR at screening only.

ⁿ Dose frequency could vary based on titration.

Source: Applicant's Table 8-5 in CSR 20110271

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Eileen Craig, MD
BLA 125522 SD1566
Repatha (evolocumab)

Study Endpoints

Primary Endpoint

- Subject incidence of treatment emergent adverse events

Secondary Endpoints

- Percent change in LDL-C from baseline at each scheduled visit
- Percent change in non-HDL-C from baseline at each scheduled visit
- Percent change in Lp(a) from baseline at each scheduled visit
- Percent change in ApoB from baseline at each scheduled visit
- Percent change in total cholesterol/HDL-C ratio from baseline at each scheduled visit
- Percent change in ApoB/ApoA1 ratio from baseline at each scheduled visit
- Response rate of subjects with 15% or greater reduction in LDL-C by scheduled visit.

Investigational Product Dosage and Administration

Evolocumab was administered at 1 of 2 regimens: 420 mg SC QM or 420 mg SC Q2W.

Evolocumab was available in 1 of 3 presentations based on regional availability;

1. six 1.0 mL vials (70 mg/dL) with doses that can be split into multiple injections (e.g., 3 injections at 2 mL each for 420 mg) with the condition that the full dose is provided at each respective study visit,
2. three 1.0 mL auto injectors (140 mg/dL),
3. one 3.5 mL Personal Injector (PI) (120 mg/dL), based on device availability.

No control group was used in this open-label study.

Parent Study 20110233 Subjects: Subjects coming from parent study 20110233 started with evolocumab 420 mg SC monthly (QM) dosing. After 12 weeks of 420 mg SC QM, if observed LDL-C reduction was > 5% and PCSK9 levels were maximally suppressed (i.e., < 100 ng/mL), subjects could continue QM dosing for the duration of the study. In subjects with PCSK9 levels > 100 ng/mL assessed at the end of a 420 mg SC QM dosing interval (e.g., assessed at Weeks 4 and/or 8), dosing could be changed to 420 mg SC Q2W at the Week 12 visit. If the observed LDL-C reduction from baseline is < 5% and PCSK9 levels was maximally suppressed (i.e., < 100 ng/mL) the subject could be withdrawn from the study at Week 12. Depending on the subject response to 420 mg SC Q2W dosing, these subjects could continue Q2W dosing, return to QM dosing, or be withdrawn from the study at the Week 24 visit.

Apheresis Subjects: Subjects on apheresis were to initiate treatment with evolocumab 420 mg

SC Q2W in this study to correspond with their apheresis schedule, to maximally suppress PCSK9, and to avoid possible apheresis-mediated clearance of evolocumab. For apheresis subjects who initiated this study on 420 mg Q2W dosing, the dosing schedule could be continued or downtitrated to 420 mg QM at the Week 12 visit provided there was evidence of sufficient efficacy (LDL-C reduction of > 5% was considered sufficient efficacy for these subjects) and adequate suppression of PCSK9 (<100 ng/mL). Subjects downtitrating to 420 mg QM dosing at Week 12 could revert to 420 mg Q2W dosing 12 weeks after the initiation of 420 mg QM dosing (e.g., Week 24) if clinically indicated. Dosing changes that did not occur on Week 12 or 24 were permitted in cases where apheresis therapy was discontinued by patients. Dose adjustments after Week 24 were discouraged.

Other Subjects: Subjects that were not receiving apheresis were provided with evolocumab 420 mg SC QM. Similar to subjects coming from study 20110233, an option of 420 mg SC Q2W was available to other subjects pending observed LDL-C levels and insufficient suppression of PCSK9 (> 100 ng/mL) at the end of a dosing interval (e.g., assessed at Week 4, 8, etc.). Dosing changes were to occur at Week 12 or 24 if clinically indicated. Dosing changes after Week 24 were discouraged.

Subjects with known insufficient efficacy (e.g., LDL-C reduction < 5% after an adequate trial of evolocumab dosing) could be removed at either the Week 12 or 24 study visit pending a final risk/benefit discussion with Amgen's medical monitor.

Applicant's Rationale for Study Dose

Evolocumab 420 mg QM was initially selected for this study. This dose was the highest dose tested in previous evolocumab studies, including Study 20110233. Because pharmacologic LDL-C reduction in HoFH or severe FH is extremely difficult to manage due to the biology underlying the disease, the applicant believed that only maximum doses of evolocumab were likely to provide a substantial therapeutic benefit in this population. An amendment to the study protocol added administration of evolocumab 420 mg Q2W as the starting dose with apheresis or after dose adjustment in other subjects. In a repeated-dose (SC once weekly) 6-month toxicology study conducted in the cynomolgus monkey (Study 110359), no evidence of toxicity was observed up to the highest dose tested, 300 mg/kg. Based on area under the serum concentration-time curve (AUC), this dose level provides a 156-fold exposure margin relative to a 420 mg Q2W clinical dose. In pharmacokinetic simulations of QM and Q2W dosing for evolocumab 420 mg, evolocumab concentrations at steady state with an extended period of Q2W dosing were not predicted to exceed those with QM dosing.

Statistical Analysis Plan

Statistical analyses in this open label, multicenter single arm study were descriptive in nature.

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For efficacy analyses, the baseline value was defined as:

- Subjects from a qualifying parent study with baseline parent study data: the baseline was defined as the baseline of the parent study
- Subjects not enrolling from a parent study or without baseline parent study data: the baseline was defined as the baseline obtained in study 20110271

For non-efficacy analyses, baseline values for all subjects were defined as the baseline values obtained in this study, 20110271.

The following analysis sets were used:

- The evaluable analysis set (EAS) for the final analysis included all subjects (HoFH and severe HeFH) enrolled in this study.
- The HoFH analysis set (HAS) included all subjects who received at least 1 dose of evolocumab in Study 20110271 and either met clinical criteria of HoFH or who had supportive genetic information.
 - The evolocumab titration analysis set (TAS) was a subset of the HAS and included subjects who were exposed to evolocumab 420 mg QM for at least 12 weeks in Study 20110271 and then to evolocumab 420 mg Q2W for at least 12 weeks in Study 20110271.
 - The adolescent subset was a subset of the HAS and included all adolescent subjects (ages 12 to < 18 years at enrollment in the parent study [for rollover subjects] or in Study 20110271 [all other subjects]) who received at least 1 dose of evolocumab in Study 20110271.
- The severe FH analysis set (SAS) included all subjects who received at least 1 dose of evolocumab in Study 20110271 and were not included in the HAS.
- The pharmacokinetics analysis set included all subjects in the EAS for whom there were unbound evolocumab or unbound PCSK9 results. Pharmacokinetics analyses were conducted separately in HoFH subjects and non-HoFH severe FH subjects.

Blinding: This was an open-label study. For each subject who transitioned from the blinded part of Study 20110233 (phase 3), the investigator and the study team were blinded to lipid levels until OLE Week 8 to preserve blinding in Study 20110233.

There was no imputation for missing data.

Protocol Amendments

Original protocol, dated 15 November 2011 (5 subjects enrolled between this date and the date of the first amendment)

Amendment 1 summary: 17 July 2012 (7 subjects enrolled between this date and the date of

the next amendment)

- Clarify that labs will be blinded for subjects coming from a blinded (or blinded portion) of a parent study
- Add an optional apheresis substudy
- Nonapheresis Subjects: Subjects coming from parent study 20110233 may receive the dose investigated during that study. Subjects that are not receiving apheresis will be provided with evolocumab at 420 mg SC Q4W or an option of 420 mg SC Q2W pending observed insufficient suppression of PCSK9 (> 100 ng/mL) at the end of a 4-week dosing interval.
- Apheresis Subjects: Subjects on apheresis will initiate treatment with 420 mg SC Q2W in this study to correspond with their apheresis schedule. For these subjects, the dosing schedule can be continued or downtitrated to Q4W at the Week 12 visit provided there is evidence of sufficient efficacy (LDL-C reduction of $> 5\%$ is considered sufficient efficacy for these subjects). Subjects downtitrating to Q4W dosing at Week 12 will revert to Q2W dosing at Week 24 if clinically indicated.
- Increase the sample size from 75 subjects to 125 based on new patient interest in the study
- Add a screening period for subjects that either do not come from a parent study or for parent study subjects that do not rollover into 20110271 within 3 days
- Decrease the frequency of anti-evolocumab antibody collection after Year 1
- Update the patient inclusion criteria
- Highlight that anytime there are 2 consecutive LDL-C values below 25 mg/dL for an individual subject that the DMC will be notified.
- Highlight that Vitamin E values will be blinded

Amendment 2 summary: 07 December 2012 (33 subjects enrolled between this date and the date of the next amendment)

- Update the at-home dosing information
- Add an additional secondary endpoint
- Add more flexible dosing language for subjects that enter study 20110271 from study 20110233
- Highlight that lipid lowering concomitant medications cannot be adjusted during the first 12 weeks of the study

Amendment 3 summary: 16 September 2013 (174 subjects enrolled between this date and the date of the next amendment)

- Add Lp(a) as a secondary endpoint
- Update the exploratory endpoints
- Include subjects with severe hypercholesterolemia
- Exclude lomitapide and CETP inhibitors
- Add additional criteria for withholding IP
- Remove the apheresis substudy

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Amendment 4 Summary: 15 April 2014 (81 subjects enrolled between this date and the date of the next amendment)

- Update the sample size
- Update the number of sites
- Update the analyte table

Amendment 5 summary: 11 May 2015 (No subjects enrolled between this date and the date of the next amendment)

- To remove the external Data Monitoring Committee (DMC) following the DMC's expressed preference to not review open-label, uncontrolled safety data. Safety monitoring will continue to be performed by AMGEN. Even though review of this specific study will no longer fall under direct DMC review, the DMC will continue to consider the totality of data from all studies. Any emerging safety considerations identified by AMGEN will be discussed with the DMC and the committee will incorporate that data when making its recommendations to AMGEN.
- To add measurements of height, weight and Tanner staging for adolescent subjects, and to allow for documentation of historical assessments of height, weight and Tanner staging in adolescent subjects. A definition of 'adolescent' was also provided.

Amendment 6 summary: 02 December 2015 (No subjects enrolled)

- Clarify end of study language to specify the study will end when the last patient has completed assessments at Week 260.
- Draw attention to collection of adverse device effects (ADEs) by adding ADEs to the Schedule of Assessments and the general study procedures when reviewing for adverse events (AEs) and serious adverse events (SAEs). This information is already being collected under AEs.
- Update criteria for possible drug-induced liver injury (DILI).
- Allow for additional pregnancy testing at the discretion of the investigator.
- Correct Tanner Staging criteria for males.

After the completion of Study 20110118 (FOURIER), the study was closed as the applicant believed that further collection of data would not contribute meaningfully to the long-term understanding of evolocumab safety. The closing of the study was not related to any safety findings.

Reviewer comment: The applicant's protocol amendments are reasonable, and I do not believe that these modifications had a negative impact on the integrity of the trial or our interpretation of the results.

6.1.2. Study Results

Compliance with Good Clinical Practices

Amgen confirms that this study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and Food and Drug Administration (FDA) regulations/guidelines. The Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs) for this study reviewed the study protocol, amendments, and the informed consent form (ICF). No subjects were recruited into the study and no investigational product was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Financial Disclosure

The applicant submitted financial disclosure information for the HoFH trials (20110233, 20110271) with the original submission in August 2014. This information was reviewed, and the conclusion was that the efficacy and safety studies used multiple investigators (most of whom do not have a disclosable interest), blinding, objective endpoints, or measurements of endpoints by someone other than the investigator to minimize bias. There were no outstanding financial disclosure issues.

Patient Disposition

A total of 246 subjects enrolled directly in Study 20110271 (TAUSSIG) and 54 subjects rolled over from Study 20110233. The database lock date for this final analysis report of Study 20110271 was 13 July 2018.

The evaluable analysis set (EAS) included all 300 (100%) subjects who had enrolled in the study. A total of 106 HoFH subjects comprised the HoFH analysis set (HAS); 48 (20.1%) titration analysis set subjects (TAS) and 14 (4.7%) adolescent subjects were included in the HAS. A total of 194 non-HoFH severe FH subjects (i.e., those subjects with FH who did not meet the study criteria for HoFH) comprised the severe FH analysis set (SAS) (see table and figure below).

Table 4. Analysis Set Disposition in Study 20110271 (All Enrolled Subjects)

	Apheresis subjects (N=61) n (%)	Non- apheresis subjects (N=239) n (%)	Total (N=300) n (%)
Evaluable Analysis Set (EAS) inclusion	61 (100.0)	239 (100.0)	300 (100.0)
HoFH subjects (HAS)	34 (55.7)	72 (30.1)	106 (35.3)

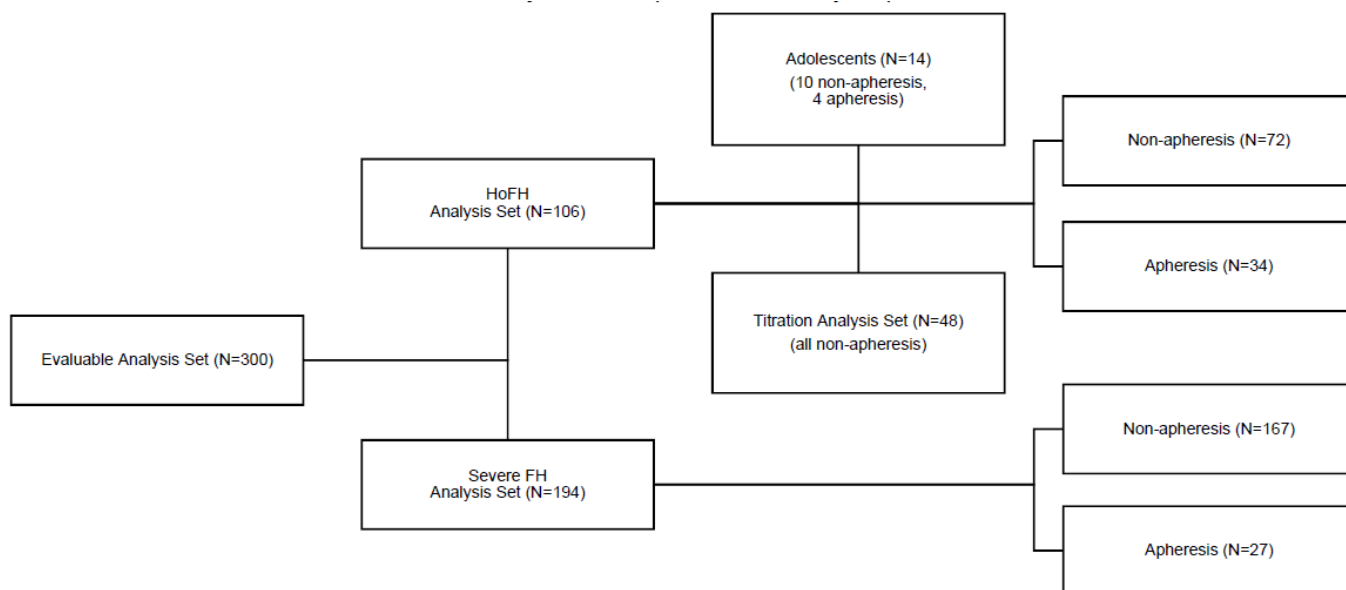
HoFH Evolocumab Titration Analysis Set (TAS) inclusion	0	48 (20.1)	48 (20.1)
HoFH Evolocumab Titration Analysis Set (TAS) exclusion	0	24 (10.0)	24 (10.0)
<i>Exposed to QM less than 12 weeks</i>	0	1 (0.4)	1 (0.4)
<i>Exposed to QM for 12 weeks and remained on QM</i>	0	19 (7.9)	19 (7.9)
<i>Exposed to Q2W less than 12 weeks</i>	0	4 (1.7)	4 (1.7)
Adolescent subgroup	4 (6.6)	10 (4.2)	14 (4.7)
Severe FH subjects (SAS)	27 (44.3)	167 (69.9)	194 (64.7)

N = number of subjects enrolled in Study 20110271; FH = Familial Hypercholesterolemia; HAS = HoFH Analysis Set; HoFH = Homozygous Familial Hypercholesterolemia; IP = investigational product; Q2W = every 2 weeks (subcutaneous); QM = monthly (subcutaneous);

Note: Reasons for exclusion from an analysis set are not mutually exclusive.

Source: Applicant's Table 14-2.1.1 in CSR 20110271

Figure 2. Summary of Analysis Set Disposition Study 20110271 (All Enrolled Subjects)



FH = familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia
Applicant's Figure 9-1 and Table 14-2.1.1 in CSR 20110271

The table below summarizes the patient disposition within several discontinuation reason categories. Approximately 83% of patients (248) continued evolocumab treatment until the end of the study. A total of 52 (17%) patients discontinued evolocumab for reasons other than early study closure; the most common reasons for discontinuation of evolocumab were subject

request (5%) and physician decision (5%), followed by adverse event (2%).

A total of 48 (16%) patients discontinued the study. Eighteen (6%) patients ended the study early due to study closure and had their primary reason for ending study recorded as 'study terminated by sponsor' on eCRF pages; the most common reasons for discontinuation of the study were study termination (6%) and full consent withdrawn (6%), followed by death (3%). Of the 14 adolescent subjects, 3 subjects discontinued the study (withdrew consent).

Table 5. Patient Disposition in Study 20110271 (All Enrolled Subjects)

	Apheresis subjects (N=61) n (%)	Non- apheresis subjects (N=239) n (%)	Total (N=300) n (%)
Evolocumab accounting	61 (100.0)	239 (100.0)	300 (100.0)
Subjects who completed evolocumab	41 (67.2)	207 (86.6)	248 (82.7)
Completed evolocumab per protocol ^a	0	10 (4.2)	10 (3.3)
Study closed out early per sponsor ^b	41 (67.2)	197 (82.4)	238 (79.3)
Subjects who discontinued evolocumab	20 (32.8)	32 (13.4)	52 (17.3)
Full consent withdrawn	1 (1.6)	5 (2.1)	6 (2.0)
Adverse event	0	7 (2.9)	7 (2.3)
Pregnancy	2 (3.3)	0	2 (0.7)
Death	1 (1.6)	4 (1.7)	5 (1.7)
Subject request	5 (8.2)	10 (4.2)	15 (5.0)
Physician decision	11 (18.0)	4 (1.7)	15 (5.0)
Lost to follow-up	0	2 (0.8)	2 (0.7)
Study completion accounting			
Subjects who completed study	43 (70.5)	209 (87.4)	252 (84.0)
Completed study per protocol ^c	2 (3.3)	12 (5.0)	14 (4.7)
Study closed out early per sponsor ^d	41 (67.2)	197 (82.4)	238 (79.3)
Subjects who discontinued study	18 (29.5)	30 (12.6)	48 (16.0)
Full consent withdrawn	7 (11.5)	11 (4.6)	18 (6.0)
Death	2 (3.3)	7 (2.9)	9 (3.0)
Study termination	9 (14.8)	9 (3.8)	18 (6.0)
Lost to follow-up	0	2 (0.8)	2 (0.7)
Other	0	1 (0.4)	1 (0.3)

Number of subjects screened: 326; N = number of subjects enrolled in Study 20110271; eCRF = electronic case report form;

First subject enrolled: 01JUN2012

a Subjects who did not have discontinuation investigational product reasons on eCRF pages.

b Among the subjects who ended the study due to early study closure per Amgen consideration decided on 08 Feb 2018, the subjects also ended their evolocumab due to the same reasons and their primary reason for ending evolocumab were recorded as 'Administrative decision by sponsor' on eCRF pages.

c Subjects who did not have discontinuation study reasons on eCRF pages.

d Subjects who ended the study due to early study closure per Amgen consideration had their primary reason for ending study recorded as 'Study terminated by sponsor' on eCRF pages.

Source: adsl.xpt-JMP; Applicant's Table 14-1.1.1 in CSR 20110271

Protocol Violations/Deviations

A total of 32 (11%) subjects had an important protocol deviation (IPD) and 10 (3%) subjects did not meet the eligibility criteria. The most common reported IPDs were important GCP violations (16 [5%] subjects), followed by received expired or compromised investigational product (8 [3%] subjects), and not on stable lipid therapy or LDL-C entry criteria not met (3 [1%] subjects). In addition, two subjects were pregnant or breastfeeding and one subject had hepatic dysfunction (see table below).

The 16 subjects with important GCP violations included 1 subject who signed an ICF for another study in error at the screening visit and signed the ICF for Study 20110271 at a non-scheduled visit after Week 4, and 15 subjects whose data privacy/confidentiality was not appropriately protected for subject relatives because cholesterol laboratory results for family members were made available to the monitors. These protocol violations were not expected to affect the study results nor lead to significant safety risks for study participants.

Table 6. Study 20110271 Protocol Deviations (All enrolled subjects)

	Apheresis Subjects (N=61) n (%)	Non- apheresis Subjects (N=239) n (%)	Total (N=300) n (%)
Subjects with at least 1 protocol deviation	17 (27.9)	15 (6.3)	32 (10.7)
Important GCP violation	13 (21.3)	3 (1.3)	16 (5.3)
Received expired or compromised IP	1 (1.6)	7 (2.9)	8 (2.7)
Not on stable lipid therapy or LDL-C entry criteria not met	0	3 (1.3)	3 (1.0)
Pregnant or breastfeeding	2 (3.3)	0	2 (0.7)
Female subject requiring contraception	1 (1.6)	0	1 (0.3)
Active liver disease or hepatic dysfunction	1 (1.6)	0	1 (0.3)
Investigational product not withheld per protocol	0	1 (0.4)	1 (0.3)
Randomized with multiple missing labs	0	1 (0.4)	1 (0.3)

N = number of subjects enrolled in Study 20110271; GCP = good clinical practice; LDL-C = low-density lipoprotein cholesterol

Note: Deviation categories are not mutually exclusive. Multiple deviations within the same category are counted once per subject.

Source: addv.xpt-JMP; Applicant's Table 14-3.1.1 in CSR 20110271

Demographic Characteristics

The evaluable analysis set (EAS) included all subjects (HoFH and severe HeFH) enrolled in this study. That study population of 300 individuals consisted of 44% women and the mean (SD) age of all subjects at baseline was 47.5 (16.1) years. The majority of subjects were white (88%), followed by Asian (5%), other (4%), black (2%), mixed race (<1%), and American Indian or Alaskan native (<1%). Ethnicity was Hispanic or Latino for 9% of subjects. Sixty-nine (23%) subjects were from North America [37 (12%) from Canada, 32 (11%) from the USA]; 144 (48%) subjects were from Europe: Belgium (12, 4%), Czech Republic (11, 4%), France (20, 7%), Greece (2, 1%), Israel (5, 2%), Italy (25, 8%), Lebanon (1, <1%), Netherlands (23, 8%), Spain (19, 6%), and United Kingdom (9, 3%); 25 (8%) subjects were from Latin America (Brazil); and 62 (21%) subjects were from Asia Pacific [Australia (10, 3%), Hong Kong (1, <1%), Japan (9, 3%), New Zealand (11, 4%), and South Africa (31, 10%)].

The purpose of this submission is to evaluate the option of a higher dose for the HoFH population: 420 mg SC every 2 weeks (Q2W). Of the 300 subjects in the EAS, 106 subjects were diagnosed with HoFH and are described in more detail in the following table. Of these 106 subjects with HoFH, a subset of 48 subjects were administered evolocumab 420 mg QM for at least 12 weeks and then up-titrated to evolocumab 420 mg Q2W for at least 12 weeks in Study 20110271. These 48 subjects, none of which were on apheresis, had similar demographic and baseline characteristics as the non-apheresis group (N=72) described in the table below.

Table 7. Baseline Demographics Study 20110271 (HoFH Analysis Set)

Demographic Parameters	Apheresis Group (N= 34) n (%)	Non-apheresis Group (N=72) n (%)	Total (N=106) n (%)
Sex			
Male	18 (52.9)	34 (47.2)	52 (49.1)
Female	16 (47.1)	38 (52.8)	54 (50.9)
Age			
Mean years (SD)	34.3 (15.6)	34.3 (13.9)	34.3 (14.4)
Median (years)	32.5	32.5	32.5
Min, max (years)	13, 68	13, 68	13, 68
Age Group			
< 18 years	4 (11.8)	10 (13.9)	14 (13.2)

Demographic Parameters	Apheresis Group (N= 34) n (%)	Non-apheresis Group (N=72) n (%)	Total (N=106) n (%)
≥ 18 years	30 (88.2)	62 (86.1)	92 (86.8)
Weight			
Mean, kg (SD)	69.7 (13.6)	73.5 (19.4)	72.3 (17.8)
BMI (kg/m²)			
Mean, kg (SD)	25.8 (4.30)	25.6 (5.3)	25.7 (5.0)
Race			
White	23 (67.6)	62 (86.1)	85 (80.2)
Black or African American	0	0	0
Asian	7 (20.6)	6 (8.3)	13 (12.3)
American Indian or Alaska Native	1 (2.9)	0	1 (0.9)
Native Hawaiian or other Pacific Islander	0	0	0
Other	3 (8.8)	4 (5.6)	7 (6.6)
Ethnicity			
Hispanic or Latino	2 (5.9)	3 (4.2)	5 (4.7)
Cardiovascular History			
Coronary artery disease	18 (52.9)	32 (44.4)	50 (47.2)
Cerebrovascular or peripheral arterial disease	12 (35.3)	8 (11.1)	20 (18.9)
Diabetes Mellitus	0	3 (4.2)	3 (2.8)
Smoking (current)	1 (2.9)	7 (9.7)	8 (7.5)
Hypertension	6 (17.6)	13 (18.1)	19 (17.9)
Genotype			
Mutations in both LDLR alleles	30 (88.2)	64 (88.9)	94 (88.7)
LDLR defective	12 (35.3)	38 (52.8)	50 (47.2)
LDLR negative	4 (11.8)	4 (5.6)	8 (7.5)
LDLR unclassified	14 (41.2)	22 (30.6)	36 (34.0)
Mutation in single LDLR allele	0	1 (1.4)	1 (0.9)
ApoB mutation	1 (2.9)	2 (2.8)	3 (2.8)
Baseline LDL-C, calculated (mg/dL)			
Mean (SD)	288.5 (102)	348.1 (147)	329.0 (137)
Median (mg/dL)	281.3	337.0	321.3
Min, max (mg/dL)	130, 528	132, 811	130, 811
Baseline HDL-C (mg/dL)			
Mean (SD)	39.6 (13.8)	39.5 (13.2)	39.5 (13.3)
Median (mg/dL)	36.0	38.3	37.0
Min, max (mg/dL)	18, 70	10, 84	10, 84
Baseline Total Cholesterol (mg/dL)			
Mean (SD)	347.7 (97.5)	410.0 (145.4)	390.0 (134.7)

Demographic Parameters	Apheresis Group (N= 34) n (%)	Non-apheresis Group (N=72) n (%)	Total (N=106) n (%)
Median (mg/dL)	342.3	398.3	372.8
Min, max (mg/dL)	164, 591	198, 891	164, 891
Baseline Triglycerides (mg/dL)			
Mean (SD)	97.4 (49.3)	112.0 (58.2)	107.3 (55.7)
Median (mg/dL)	81.8	96.8	93.5
Min, max (mg/dL)	35, 241	44, 342	35, 342
Baseline non-HDL-C (mg/dL)			
Mean (SD)	308.1 (101.9)	370.5 (149.2)	350.5 (138.4)
Median (mg/dL)	312.0	358.8	341.5
Min, max (mg/dL)	145, 546	160, 849	145, 849
Baseline Apolipoprotein B (mg/dL)			
Mean (SD)	179.5 (48.1)	210.7 (76.4)	200.7 (69.9)
Median (mg/dL)	184.8	197.0	190.0
Min, max (mg/dL)	100, 282	105, 465	100, 465
Baseline Lipoprotein-a (nmol/L)			
Mean (SD)	96.3 (83.7)	108.7 (107.9)	104.7 (100.6)
Median	65.5	78.5	77.0
Min, max	5, 305	5, 439	5, 439
Baseline PCSK9 (ng/L)			
Mean (SD)	704.9 (221)	653.9 (190)	670.3 (201)
Median	685.0	639.8	648.8
Min, max	275.5, 1105.0	283.0, 1088.0	275.5, 1105.0
Baseline hsCRP (mg/dL)			
Mean (SD)	0.13 (0.22)	0.20 (0.31)	0.17 (0.29)
Median (mg/dL)	0.04	0.07	0.05
Min, max (mg/dL)	0.02, 0.9	0.02, 1.76	0.02, 1.76

N = number of HoFH subjects enrolled and dosed in study 20110271;

Abbreviations: ApoB = apolipoprotein B; HDL-C = high density lipoprotein cholesterol; 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; PCSK9 =proprotein convertase subtilisin/kexin type 9; GFR=glomerular filtration rate; SD=standard deviation; ASCVD=Atherosclerotic Cardiovascular Disease

Baseline demographics for parent study rollover subjects are defined at the parent study baseline.

Source: adsbl.xpt-JMP; Applicant's Tables 14-2.2.2, 14-2.2.4, 14-2.4.3, 14-2.5.3 in CSR 20110271

There were 14 adolescent patients with HoFH; 10 were not on apheresis at baseline and 4 were receiving apheresis. This population was 36% female and the mean (SD) age of all adolescent subjects at baseline was 14.7 (1.4) years with a range of 13 to 17 years. The majority of subjects were white (79%), followed by other (14%), and American Indian or Alaskan native (7%). Ethnicity was Hispanic or Latino for 14% of adolescent subjects. The mean weight was 57.5 kg

with a range of 41 to 80 kg. The mean calculated LDL-C was 355 mg/dL, mean HDL-C was 34 mg/dL, median TG was 69 mg/dL, mean ApoB of 201 mg/dL, and mean Lp(a) of 72 nmol/L. Four (29%) of subjects had CAD at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall, 96 (91%) of subjects in the HoFH population were on high-intensity statin therapy and 10 (9%) were on moderate-intensity statin therapy as background treatment. Ninety-five (90%) subjects were on background ezetimibe. Forty-six subjects (43%) in the HoFH population were on background atorvastatin 80 mg plus ezetimibe and 29 (27%) subjects in the HoFH population were on background rosuvastatin 40 mg plus ezetimibe.

In the adolescent population, 12 (86%) of subjects in the HoFH population were on high-intensity statin therapy and 2 (14%) were on moderate-intensity statin therapy as background treatment. Four (29%) subjects were on atorvastatin 40 mg plus ezetimibe and 6 (43%) subjects were on atorvastatin 80 mg plus ezetimibe as background therapy.

Efficacy Results – Primary Endpoint

For this submission, the most relevant efficacy endpoint is the change in LDL-C in subjects who titrated from the 420 mg QM to the 420 mg Q2W dose; this is represented by the Titration Analysis Set (TAS).

A total of 48 subjects were included in the TAS; they received evolocumab 420 mg QM for at least 12 weeks in the OLE study and then received evolocumab 420 mg Q2W for at least 12 weeks in the OLE study. None of the subjects in the TAS were receiving lipid apheresis treatment. Seven (15%) of the subjects in the TAS were adolescent subjects. All subjects in the TAS were on a high-dose statin (atorvastatin or rosuvastatin) with ezetimibe 10 mg at baseline.

As shown in the table below, increasing the dosing frequency of evolocumab to every 2 weeks in 48 patients not on apheresis resulted in approximately mean 10% further reduction in LDL cholesterol.

Table 8. Change and Percent Change from Baseline in Calculated LDL-C in mg/dL at OLE Week 12 on QM and OLE Week 12 on Q2W; Study 20110271 (Evolocumab Titration Analysis Set)

Calculated LDL-C	After 12 weeks of 420 mg evolocumab every month	After 12 weeks of 420 mg evolocumab every 2 weeks
Mean (SD) Baseline value, mg/dL	374.1 (145.1) N=48	374.1 (145.1) N=48
Mean (SD) Change from baseline, mg/dL	-68.9 (82.2) n=47	-104.5 (83.9) n=46

Mean Percent (SD) change from baseline	-19.6 (22.0) n=47	-29.7 (22.6) n=46
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Abbreviations: N = number of subjects at baseline; n= number of subjects at different timepoints in study 20110271; OLE = Open-Label Extension; QM = Monthly; Q2W = Every 2 weeks; SD = standard deviation
Baseline LDL-C for parent study rollover subjects are defined at parent study baseline.
Source: FDA statistical reviewer, Kiya Hamilton, PhD.

As shown in the previous table, at the Week 12 on 420 mg QM timepoint, there is LDL data on only 47 of 48 subjects. One subject (Subject (b) (6)) attended the Week 12 visit and had samples drawn for laboratory assessments; however, no LDL-C results corresponding to this visit are available. This subject did have LDL-C assessments at the Week 8 and Week 16 visits. This subject's baseline LDL-C was 205 mg/dL (in parent Study 20110233). At Week 8, which reflects 8 weeks of treatment with evolocumab 420 mg QM, the LDL-C value was 109 mg/dL (-47% change from baseline). The dose frequency was changed to 420 mg SC Q2W at the Week 12 visit. The LDL-C value at Week 16, which reflects 4 weeks of Q2W treatment, was 132 mg/dL (-36% change from baseline). At an unscheduled visit performed 2 weeks prior to Week 24, the LDL-C value was 123 mg/dL (-40% change from baseline). At week 24, after 12 weeks of treatment with evolocumab 420 mg Q2W, the LDL-C value was 165 mg/dL (-19% change from baseline). This subject's LDL values were variable, which is often seen in patients with HoFH, but increasing the dose to 420 mg Q2W does not seem to have provided any additional LDL-C reduction.

As shown in the previous table, at the Week 12 on 420 mg Q2W timepoint, there are LDL data on only 46 of 48 subjects; 2 subjects ((b) (6) and Subject (b) (6)) were missing assessments at that timepoint.

- Subject (b) (6) switched to evolocumab 420 mg SC Q2W dosing at Week 16 of open-label extension Study 20110271 so did not have 12 weeks of 420 mg Q2W dosing by Week 24. Labs were drawn at Weeks 24 and 36. This subject's baseline LDL-C value was 446 mg/dL (in parent Study 20110233). At week 24, which reflects 8 weeks of treatment with evolocumab 420 mg Q2W, the LDL-C value was 371 mg/dL (-17% change from baseline). At week 36, the LDL-C value was 486 mg/dL (+9% change from baseline).
- Subject (b) (6) switched from evolocumab 420 mg SC QM dosing to 420 mg SC Q2W dosing at Week 12 of open-label extension Study 20110271. This subject's baseline calculated LDL-C value was 233 mg/dL. The Week 12 calculated LDL-C value, which reflects 12 weeks of treatment with 420 mg QM dosing, was 188 mg/dL (-19% change from baseline). The Week 16 calculated LDL-C value, after 4 weeks of treatment with 420 mg Q2W dosing, was 195 mg/dL (-16% change from baseline). This subject did not have a calculated LDL-C value at Week 24 (after 12 weeks of 420 mg Q2W dosing) due to high triglycerides (488 mg/dL). However, an LDL-C value measured by preparative ultracentrifugation (UC) is available. The baseline UC LDL-C value was 250 mg/dL. The UC LDL-C value at Week 12 was 193 mg/dL (-23% change from baseline). At

Week 24, which reflects 12 weeks of treatment with 420 mg Q2W dosing, the UC LDL C value was 166 mg/dL (-34% change from baseline). This patient's LDL value was lower after 12 weeks of 420 mg Q2W as compared to 12 weeks at 420 mg QM.

Additional details on the mean, median and range of calculated LDL values on 420 mg QM and then 420 mg Q2W are shown in the table below. In summary, median percent changes from baseline in calculated LDL-C in the TAS were -16.3% at Week 12 of QM treatment and -29.3% at Week 12 of Q2W treatment. Mean percent changes from baseline in calculated LDL-C in the TAS were -19.6% at Week 12 of QM treatment and -29.7% at Week 12 of Q2W treatment. The median change in LDL-C from baseline was -62 mg/dL at Week 12 of QM treatment and -103 mg/dL at Week 12 of Q2W treatment.

Table 9. Change and Percent Change from Baseline in Calculated LDL-C (mg/dL) at OLE Week 12 on QM and OLE Week 12 on Q2W in Study 20110271 (HoFH Titration Analysis Set)

Primary Efficacy Endpoint	Non-apheresis Subjects (N=48)
<i>Baseline (mg/dL)</i>	
Number of HoFH subjects	48
Mean	374
Median	375
Min, Max	149, 811
<i>Week 12 on 420 mg QM (mg/dL)</i>	
Number of HoFH subjects	47
Mean	309
Median	284
Min, Max	70, 783
<i>Change from baseline to week 12 on 420 mg QM (mg/dL)</i>	
Number of HoFH subjects	47
Mean	-69
Median	-62
Min, Max	-247, 106
<i>Percent change from baseline to week 12 on 420 mg QM (%)</i>	
Number of HoFH subjects	47
Mean	-20
Median	-16
Min, Max	-62, 23
<i>Week 12 on 420 mg Q2W (mg/dL)</i>	
Number of HoFH subjects	46

Mean	271
Median	258
Min, Max	50, 616
<i>Change from baseline to week 12 on 420 mg Q2W (mg/dL)</i>	
Number of HoFH subjects	46
Mean	-105
Median	-103
Min, Max	-242, 157
<i>Percent change from baseline to week 12 on 420 mg Q2W (%)</i>	
Number of HoFH subjects	46
Mean	-30
Median	-29
Min, Max	-71, 34

N = number of subjects that were on QM for ≥ 12 weeks and then titrated to Q2W for ≥ 12 weeks in study 20110271;

Abbreviations: QM = Monthly; Q2W = Every 2 weeks; OLE = Open-Label Extension.

Baseline LDL-C for parent study rollover subjects are defined at parent study baseline.

Source: adlbeff.xpt-JMP and Applicant's csr-20110271 Table 14-4.22.4.1

Reductions observed for ApoB were similar in direction to LDL-C. Median (Q1, Q3) percent changes from baseline in ApoB in the TAS were -12% (-29%, 0%) at Week 12 of QM treatment and -24% (-36.7%, -11.8%) at Week 12 of Q2W treatment. Mean percent reductions from baseline in ApoB in the TAS were -14% at OLE Week 12 of QM treatment and -24% at Week 12 of Q2W treatment. The median change in ApoB from baseline was -27 mg/dL at Week 12 of QM treatment and -55 mg/dL at Week 12 of Q2W treatment.

The following table displays the LDL-C reduction observed at the time of the 120-day safety update of Study 20110271 from the original BLA in comparison to the data observed at the time of the final CSR report at study conclusion.

Table 10. Change and Percent Change from Baseline in Calculated LDL-C (mg/dL) after 12 Weeks of 420 mg QM and 12 Weeks of 420 mg Q2W in Study 20110271 (HoFH Titration Analysis Set: 120-day safety update vs final update)

Calculated LDL-C	120-day TAS (N = 28)	Final TAS (N = 48)
Median (Q1, Q3) % Reduction in LDL-C		
After 12 Weeks 420 mg QM Dosing	15.8% (2.9, 28.5)	16.3% (3.2, 37.3)
After 12 Weeks 420 mg Q2W Dosing	21.5% (7.3, 34.7)	29.3% (13.7, 44.1)
Incremental % reduction of Q2W vs. QM	6%	13%

Median Reduction in LDL-C (mg/dL)		
After 12 Weeks 420 mg QM Dosing	66	62
After 12 Weeks 420 mg Q2W Dosing	80	103

Responders (≥ 15% Reduction in LDL-C) – n (%)		
After 12 Weeks 420 mg QM Dosing	15 (54%)	26 (55%)
After 12 Weeks 420 mg Q2W Dosing	18 (64%)	34 (74%)

CSR=clinical study report; HoFH=hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; Q2W=every 2 weeks; QM=once monthly; TAS=titration analysis set.

Source: Applicant's Table 14-4.22.4.1, Table 14-4.22.4.3 of Final Study 20110271 CSR; Table 14-4.22.4.1, Table 14-4.22.4.7 of 120-day Study 20110271 CSR.

Overall, subjects that increased the dosage of evolocumab from 420 mg QM to 420 mg Q2W experienced approximately mean 10% and median 13% greater reduction in LDL-C. The incremental LDL-C reduction associated with increasing the frequency of the 420 mg dose from QM to Q2W in subjects with HoFH in this study was small but similar to what has been described for doubling the dose of rosuvastatin in patients with HoFH at the time of approval in August 2003:

- Crestor Package Insert, 9/2020:

“14.5 Homozygous Familial Hypercholesterolemia

Dose-Titration Study: In an open-label, forced-titration study, homozygous FH patients (n=40, 8-63 years) were evaluated for their response to CRESTOR 20 to 40 mg titrated at a 6-week interval. In the overall population, the mean LDL-C reduction from baseline was 22%. About one-third of the patients benefited from increasing their dose from 20 mg to 40 mg with further LDL lowering of greater than 6%.”

Details of a rosuvastatin dose-titration study in patients with HoFH¹⁹ are provided below:

Table 11. Baseline levels and percent changes from baseline in lipids in patients with HoFH who received daily treatment with rosuvastatin 20 mg (first 6 weeks) and 40 mg (Week 6-12)

	Baseline		Percentage change from baseline	
	Mean (S.D.) (mmol/L) (n = 41)	Median (range) (mmol/L) (n = 41)	Week 6 (obs), rosuvastatin 20 mg; mean (S.D.) (n = 41)	Week 12 (obs), rosuvastatin 40 mg; mean (S.D.) (n = 37)
LDL cholesterol ^a	13.3 (3.0)	13.2 (7.6–20.5)	–18.8 (15.8)***	–22.5 (15.3)***
Total cholesterol	15.0 (3.2)	15.0 (8.8–23.9)	–17.7 (12.5)***	–20.9 (12.3)***
HDL cholesterol	0.93 (0.27)	0.91 (0.52–1.7)	+5.1 (24.5) NS	+4.2 (17.2) NS
Triglycerides	1.6 (1.4)	1.1 (0.5–6.1)	–7.5 (29.7) NS	–9.6 (26.9)*

¹⁹ Marais AD, Raal FJ, Stein EA, Rader DJ, Blasetto J, Palmer M, Wilpshaar W. A dose-titration and comparative study of rosuvastatin and atorvastatin in patients with homozygous familial hypercholesterolaemia. Atherosclerosis. 2008 Mar;197(1):400-6. doi: 10.1016/j.atherosclerosis.2007.06.028. Epub 2007 Aug 28.

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Eileen Craig, MD
BLA 125522 SD1566
Repatha (evolocumab)

Abbreviations: obs=observed values at the timed measurement; LDL= low-density cholesterol; HDL-C=high-density cholesterol; NS=not statistically significant.

* $p < 0.05$; *** $p < 0.0001$.

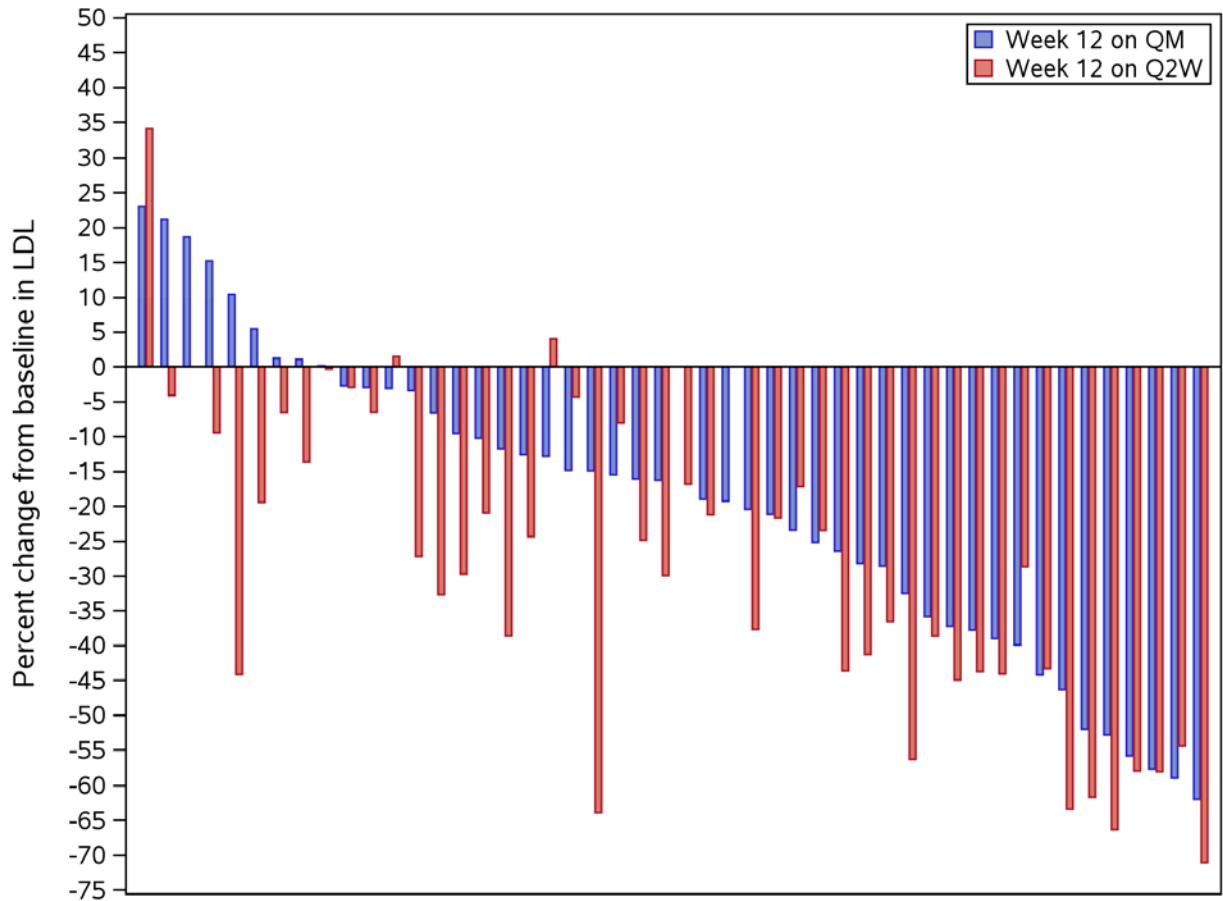
^a $n=40$ for baseline

As detailed in Table 1, adding a second agent, such as ezetimibe or lomitapide, would likely yield a greater reduction in LDL-C than increasing the evolocumab dose to 420 mg Q2W.

In the TAS, treatment response ($\geq 15\%$ reduction in calculated LDL-C from baseline) was seen for 26 out of 47 (55%) subjects at Week 12 of 420 mg QM treatment and for 34 out of 47 (72%) subjects at Week 12 of 420 mg Q2W treatment.

The waterfall plot, shown below, of the percent change from baseline in calculated LDL-C for each of the 48 subjects with HoFH in the TAS illustrates the LDL-C reduction at Week 12 with 420 mg QM of evolocumab and Week 12 of 420 mg Q2W evolocumab.

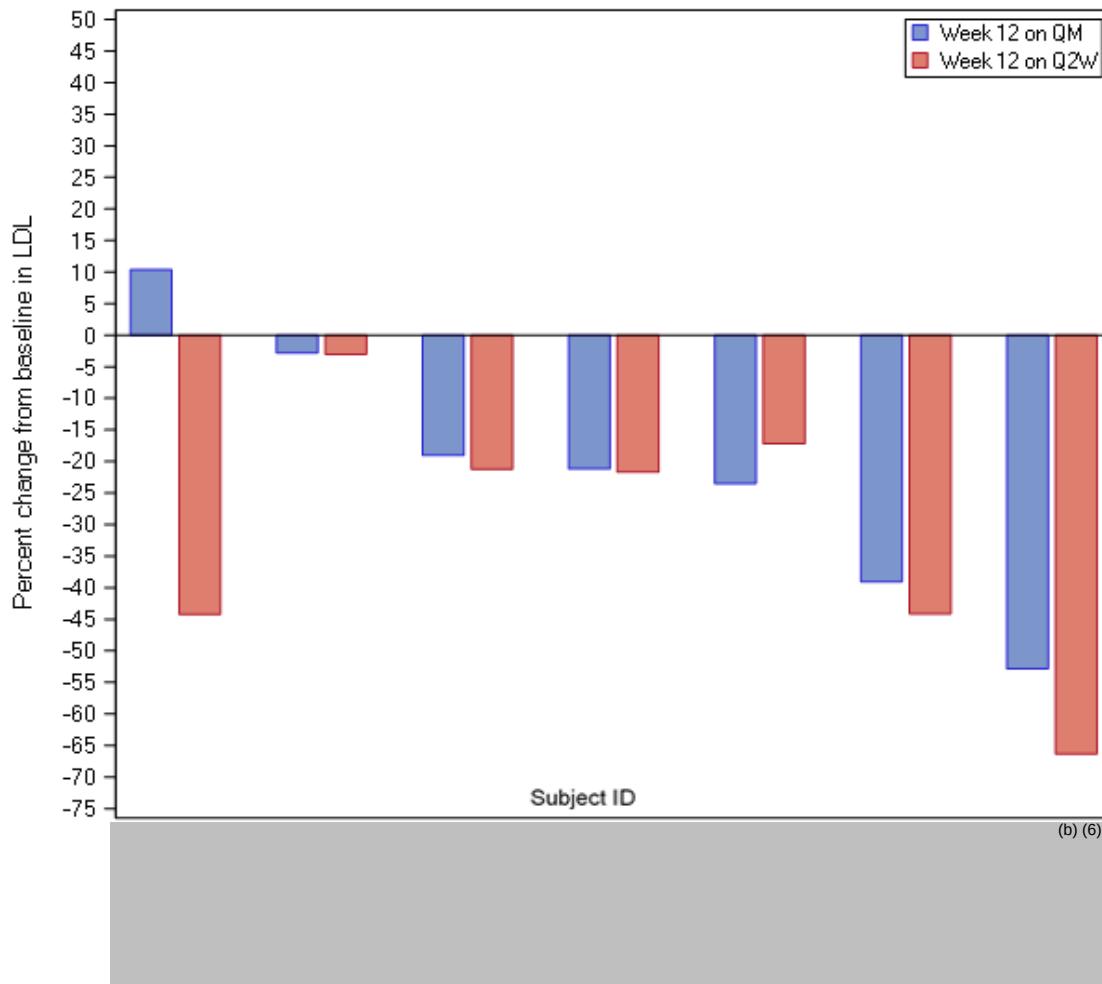
Figure 3. Waterfall Plot of Percent Change from Baseline LDL-C at OLE Week 12 on 420 mg QM and OLE Week 12 on 420 mg Q2W in Calculated LDL-C in Patients with HoFH; Study 20110271 (Evolocumab Titration Analysis Set)



OLE = Open-Label Extension; QM = Monthly; Q2W=Every 2 weeks;
Plot is based on observed data and no imputation is used for missing values.
Source: Applicant's csr-20110271 Figure 14-4.22.4.4

The waterfall plot, shown below, of the percent change from baseline in calculated LDL-C for each of the 7 pediatric subjects with HoFH in the Evolocumab Titration Analysis Set illustrates the LDL-C reduction at Week 12 with 420 mg QM of evolocumab and Week 12 of 420 mg Q2W evolocumab.

Figure 4. Waterfall Plot of Percent Change from Baseline LDL-C at OLE Week 12 on 420 mg QM and OLE Week 12 on 420 mg Q2W in Calculated LDL-C in Pediatric Patients with HoFH; Study 20110271 (Evolocumab Titration Analysis Set)



N=number of subjects in the analysis set aged <18 years at baseline; OLE=Open-Label Extension;
QM=Monthly; Q2W=Every 2 weeks;
Plot is based on observed data and no imputation is used for missing values.
Source: Applicant's response to FDA 12/3/20 Information Request

Reviewer comment: The two waterfall plots demonstrate that the treatment response to the increased dose of evolocumab was notably modest and variable in this subset of the HoFH population. However, as supported by the responder analysis (treatment response $\geq 15\%$ reduction in calculated LDL-C from baseline), some individuals, after 12 weeks of 420 mg Q2W dosing, did experience a likely clinically meaningful improvement in LDL reduction with an increase in the dose of evolocumab. As LDL levels are easy to obtain, a health care provider can assess whether an individual patient is or is not responding to an increase in the dose of

evolocumab and adjust treatment accordingly.

Data Quality and Integrity

The study 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 study results. Subject retention and study completion were acceptable (84%). 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 study has generated data that are interpretable and supportive of the proposed indication.

Efficacy Results – Secondary and other relevant endpoints

Efficacy Results for the HoFH Analysis Set (HAS)

Median percent reductions from baseline in calculated LDL-C in HoFH subjects were stable between OLE Week 4 and Week 216 and were 25.5%, 22.5%, 28.3%, 30.1%, and 32.2% at OLE Weeks 48, 96, 144, 192, and 216, respectively. Mean percent reductions from baseline in calculated LDL-C in HoFH subjects were 24.8%, 25.0%, 27.7%, 27.4%, and 24.0% at OLE Weeks 48, 96, 144, 192, and 216, respectively.

Rates of treatment response ($\geq 15\%$ reduction in calculated LDL-C from baseline) in HoFH subjects at OLE Weeks 48, 96, 144, 192, and 216 were 60% (56 of 93 subjects), 66% (54 of 82 subjects), 72% (57 of 79 subjects), 66% (49 of 74 subjects), and 71% (48 of 68 subjects), respectively.

HoFH subjects had reductions from baseline in LDL-C, non-HDL-C, Lp(a), ApoB, and total cholesterol, and increases from baseline in HDL-C from OLE Week 4 through OLE Week 216. There were no consistent changes in triglycerides or hsCRP. Lipid parameter results at later visits were limited by the smaller number of subjects who had completed these visits.

Reviewer comment: The observed changes in Lp(a) and HDL are of unclear clinical significance,

(b) (4)

Table 12. Change from Baseline to OLE Week 48 in Study 20110271 (HoFH Analysis Set)

Secondary Efficacy Endpoints	Apheresis Subjects (N= 34)	Non-apheresis Subjects (N=72)	Total (N=106)
Percent Change in calculated LDL-C			
Number of HoFH subjects	29	64	93

Mean	-18.7	-27.6	-24.8
Median	-13.7	-27.7	-25.5
Min, Max	-75.6, 46.9	-74.2, 157.2	-75.6, 157.2
Percent Change in non-HDL-C			
Number of HoFH subjects	29	65	94
Mean	-17.8	-25.3	-23.0
Median	-13.9	-26.8	-24.1
Min, Max	-71.8, 43.6	-63.6, 153.7	-71.8, 153.7
Percent Change in ApoB			
Number of HoFH subjects	29	65	94
Mean	-12.5	-20.3	-17.9
Median	-7.7	-23.7	-15.9
Min, Max	-67.9, 49.1	-59.2, 152.7	-67.9, 152.7
Percent Change in Total Cholesterol			
Number of HoFH subjects	29	65	94
Mean	-14.7	-21.3	-19.2
Median	-11.0	-23.9	-19.2
Min, Max	-67.7, 34.3	-58.6, 129.2	-67.7, 129.2
Percent Change in HDL-C			
Number of HoFH subjects	29	65	94
Mean	6.7	7.9	7.5
Median	6.0	6.0	6.0
Min, Max	-30.4, 79.5	-41.8, 86.1	-41.8, 86.1
Percent Change in Triglycerides			
Number of HoFH subjects	29	65	94
Mean	-6.1	6.3	2.5
Median	-3.3	-6.3	-5.2
Min, Max	-45.3, 27.5	-48.8, 402.6	-48.8, 402.6
Percent Change in hsCRP			
Number of HoFH subjects	29	65	94
Mean	76.2	69.1	71.3
Median	0	0	0
Min, Max	-95.8, 1346.5	-96.5, 1275.8	-96.5, 1346.5
Percent Change in Lp(a)			
Number of HoFH subjects	29	65	94
Mean	-7.0	-15.8	-13.1
Median	-6.2	-16.1	-13.2
Min, Max	-67.7, 100.0	-70.0, 57.1	-70.0, 100.0

N =number of HoFH subjects enrolled and dosed in Study 20110271;

Abbreviations: HoFH=Homozygous Familial Hypercholesterolemia; OLE = Open-Label Extension.; LDL-C = low-density lipoprotein cholesterol; ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; hsCRP = high sensitivity C-reactive protein; Lp(a) = lipoprotein(a); non-HDL-C = non-high-density lipoprotein cholesterol;

Baseline LDL-C for parent study rollover subjects are defined at parent study baseline.

Source: Applicant's CSR 20110271 Tables 14-4.22.5.1, 14-4.23.5.1., 14-4.24.5.1., 14-4.25.5.1., 14-4.29.5.1., 14-4.31.5.1., 14-4.32.5.1., 14-4.33.5.1.

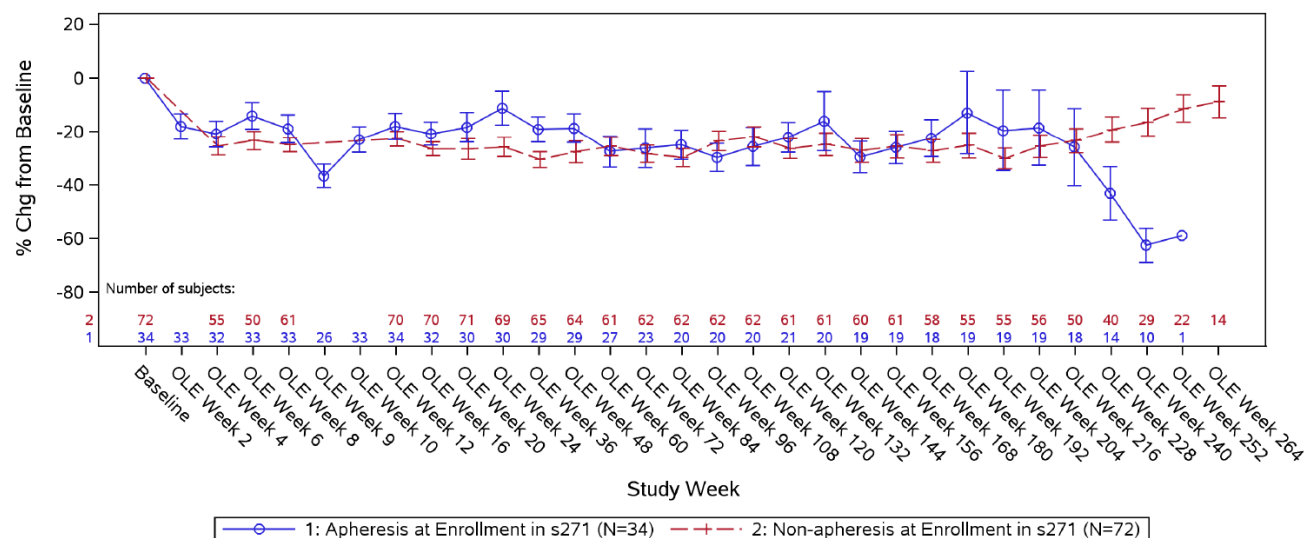
Efficacy Results in Adolescent Patients with HoFH

In the 14 adolescent patients (age 13 to 17 years) with HoFH; 10 were not on apheresis at baseline and 4 were receiving apheresis. The mean calculated LDL-C was 355 mg/dL at baseline; 12 (86%) patients were on high-intensity statin therapy and 2 (14%) were on moderate-intensity statin therapy as background treatment. Median (Q1, Q3) percent change from baseline in calculated LDL-C at OLE Weeks 12, 24, 48, 96, 144, 192, and 216 were -5.4% (-23.5%, 1.5%); -19.2% (-37.9%, 1.8%); -13.3% (-56.2%, -3.7%); -8.1% (-28.1%, -5.1%); -8.7% (-26.2%, 16.6%), -9.5% (-21.2%, 7.4%), and -20% (-42.6, 22.4%), respectively. Of note, the data is limited by the small number of subjects especially at the later weeks in the study. The treatment response to evolocumab was notably modest and variable in this adolescent subset of the HoFH population. This 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.

Durability of Response

In the HoFH analysis set (N=106: 34 on apheresis and 72 not on apheresis), the durability of the treatment effect on LDL-C over time is illustrated in the figure below. While the LDL-C reduction is modest in this HoFH population, it does appear to be maintained over 4 years.

Figure 5. Mean Percent Change from Baseline in Calculated LDL-C by Scheduled Visit and Cohort Study 20110271 (HoFH Analysis Set)



N = number of HoFH subjects enrolled and dosed in Study 20110271; HoFH=Homozygous 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.

Source: CSR 20110271 Figure 14-4.22.5.3

7. Integrated Review of Effectiveness

7.1. Additional Efficacy Considerations

7.1.1. Considerations on Benefit in the Postmarket Setting

In the postmarket setting, evolocumab is anticipated to have a similar treatment effect on LDL-C reduction to that observed within the context of clinical trials. The enrolled trial population was generally reflective of the HoFH population encountered in clinical practice.

The majority of efficacy data was contributed from sites outside of the U.S. However, no exposure or PK differences were observed based on race/ethnicity, and HoFH treatment is generally consistent worldwide given its rare disease nature. Thus, it is reasonable to expect that efficacy results will be similar in a U.S.-based postmarket setting.

7.2. Integrated Assessment of Effectiveness

The Applicant provided sufficient clinical data to demonstrate evidence that evolocumab 420mg Q2W dosing reduces LDL-C in some adults and adolescents with HoFH when added to other LDLC-lowering therapies.

The data to support the new dose constitute substantial evidence of effectiveness, even though the applicant is relying on a single additional trial, with an uncontrolled, open-label design in this application. The approval decision for the new dose may rely on the previous finding of effectiveness for evolocumab 420 mg QM in the same population, which was supported by one randomized, placebo-controlled trial plus confirmatory evidence from open-label trials. Because HoFH is a serious disease with high unmet need, in a rare population, a second randomized, controlled trial to evaluate the effect of 420 Q2W versus 420 mg QM in patients with HoFH would most likely not have been feasible. Furthermore, the incremental effect of 420 mg Q2W observed after open-label dosing cannot be attributed to other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation, considering the natural history of HoFH. In summary, the totality of the data, including the randomized, controlled trial of evolocumab 420 mg QM, open-label trial data with evolocumab 420 mg QM, and open-label trial data with titration from evolocumab 420 mg QM to 420 mg Q2W in the subset of patients who did not have suppression of PCSK9 (<100 ng/mL) demonstrating incremental benefit constitute substantial evidence for the 420 mg Q2W dose.

Study 20110271 provides supportive, open-label data on the durability of evolocumab's LDL-C lowering effect in patients with HoFH with continued treatment to at least 4 years.

The treatment response to the increased dose of evolocumab 420 mg Q2W was notably modest and variable in this subset of the HoFH population. However, some individuals, after 12 weeks of 420 mg Q2W dosing, did experience a likely clinically meaningful improvement in LDL reduction with an increase in the dose of evolocumab. A health care provider can assess LDL-C levels and decide whether an individual patient is or is not responding to an increase in the dose of evolocumab and adjust treatment accordingly.

8. Review of Safety

8.1. Safety Review Approach

The safety of the evolocumab 140 mg Q2W (hyperlipidemia population) and 420 mg QM (hyperlipidemia and HoFH populations) dosing regimens has already been established. For the non-HoFH population, this placebo-controlled database includes 2651 patients treated with evolocumab (median treatment duration of 12 weeks with 515 exposed for 1 year) and a cardiovascular outcomes trial (FOURIER, NCT01764633) involving ~13,780 patients exposed to evolocumab (median treatment duration of 24.8 months with ~91% exposed for ≥ 12 months and ~54% exposed for ≥ 24 months). For the HoFH population, this database included a placebo-controlled study in 33 patients treated with evolocumab 420 mg QM for 12 weeks and open-label, uncontrolled studies with a median treatment exposure of 9 months.

The primary focus for this review is the safety profile of the 420 mg Q2W dosing regimen in patients with familial hypercholesterolemia. In the original BLA, 31 patients with FH, not on apheresis (30 HoFH and 1 severe FH) had their dose up-titrated from 420 mg QM to 420 mg Q2W in OLE Study 20110271. At the time of the 120-day Safety Update, this increased to 43 patients with FH, not on apheresis (41 HoFH and 2 severe FH). In the final analysis of Study 20110271, which is submitted in this complete response application, 80 patients with FH, not on apheresis (53 HoFH and 27 severe FH) had their dose up-titrated from 420 mg QM to 420 mg Q2W during the study.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The exposure to evolocumab in OLE Study 20110271 by dosing subgroups is summarized in the following table.

Table 13. Evolocumab Exposure by Dosing Subgroup in Patients with HoFH and Severe FH in Study 20110271 (Final Analysis)

	420 mg Q2W only	420 mg Q2W & QM	420 mg QM only	Total
HoFH				
No. subjects	29	58	19	106
Median IP exposure (months)	36	53	49	50
IP exposure (patient-years)	74	228	63	365
<i>Adolescent subjects</i>				
No. subjects	4	9	1	14
Median IP exposure (months)	29	59	3	54
IP exposure (patient-years)	10	35	0.2	45
Severe FH				
No. subjects	17	37	140	194
Median IP exposure (months)	41	47	49	48
IP exposure (patient-years)	57	142	530	728

Source: Applicant's Response to FDA Advice letter/Information Request (08 July 2020), Table 14
IP=investigational product (evolocumab); FH=familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia;
Q2W=once every 2 weeks; QM=once monthly.

The exposure to study drug (evolocumab) and study drug devices in the HoFH population is detailed below.

Evolocumab Exposure in HoFH Population:

For the HoFH population in the OLE Study 20110271, the duration of exposure to evolocumab was 365 patients-years, mean (SD) duration of exposure of 41 (20) months and median (min, max) duration of exposure of 50 (3, 60) months.

- Exposure to evolocumab in adolescent patients with HoFH was 45 patient-years, mean (SD) duration of exposure was 39 (25) months and median (min, max) duration of exposure of 54 (3, 59) months.

Device Exposure in HoFH Population:

- Autoinjector/pen (AI/pen): Evolocumab was administered with the AI/pen at least once by 96 of 106 (90.6%) subjects with HoFH. The mean (SD) duration of exposure to the AI/pen device was 37 (14) months and median (min, max) duration of exposure was 45 (1, 51) months.
 - Eleven of 14 adolescent subjects (79%) used the AI/Pen at least once. The mean (SD) duration of exposure to the AI/pen device was 38 (17) months and median (min, max) duration of exposure was 45 (1, 49) months.

- Automated mini-doser (AMD): Evolocumab was administered with the AMD at least once by 5 of 106 (4.7%) subjects with HoFH. The mean (SD) duration of exposure to the AMD device was 15 (7) months and median (min, max) duration of exposure was 19 (4, 20) months. No adolescent subject used the AMD.

8.2.2. Relevant characteristics of the safety population:

The demographic and baseline disease characteristics of the HoFH population are described in Section 6.1.2.

8.2.3. Adequacy of the safety database:

The safety database to evaluate the 420mg Q2W dosing regimen includes:

- Patients with HoFH on apheresis who received the 420 mg Q2W dose initially and remained on that dose. These subjects may have safety issues related to apheresis itself that need to be considered during the safety assessment.
- Patients with HoFH on apheresis who received the 420 mg Q2W dose initially and switched to 420 mg QM PLUS patients with HoFH not on apheresis who received the 420 mg QM dose initially and switched to 420 mg Q2W. These subjects, in most cases, received Q2W dosing for 12 weeks or longer.
- Patients with HoFH not on apheresis who only received 420 mg QM and can provide a comparator for the Q2W groups.
- Patients with severe HeFH who received the Q2W dosing.

Table 14. Safety Database for Evolocumab 420 QM and 420 mg Q2W Dosing Regimen in Study 20110271

	As of 01 April 2014 (Original BLA) (N = 198)	As of 13 July 2018 (Final Analysis) (N = 300)
HoFH Analysis Set^a	96	106
TAS ^b	25	48 ^c
HoFH Q2W Only	27	29
HoFH QM and Q2W ^d	34	58
HoFH QM Only	35	19
Severe FH Analysis Set	102	194
Severe FH Q2W only	3	17
Severe FH QM and Q2W	1	37
Severe FH QM only	98	140

BLA=Biologics Application; FH=familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; Q2 =every 2 weeks; QM = once monthly; TAS=titration analysis set.

a Includes apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM; these subjects were excluded from the TAS, the HoFH Q2W Only group, and the HoFH QM Only group.

b TAS: non-apheresis subjects who switched from their initial dose of 420 mg QM after at least 12 weeks to 420 mg Q2W for the remainder of their study participation.

c Included 7 adolescent subjects.

d Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.

While not blinded or placebo-controlled, this limited safety database for an orphan population, which is exploring the option of one increased dosing regimen, is acceptable.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no important issues regarding data quality or the quality of the overall submission that had an effect on the safety review. The submission was well organized, information was relatively easy to find, and requests for additional information from the Applicant were responded to in a timely and complete manner.

8.3.2. Categorization of Adverse Events

The applicant's definition of adverse events (AEs) included worsening of a pre-existing medical condition (i.e., has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome). A pre-existing condition that had not worsened during the study or involved an intervention such as elective cosmetic surgery or a medical procedure while on study, was not considered an AE.

An adverse device effect (ADE) was any AE related to the use of a medical device, which included AEs resulting from inadequate instructions for use, any malfunction of the device, use error or intentional misuse of the device.

AEs were coded using Version 21.0 of the Medical Dictionary for Regulatory Activities (MedDRA). The adverse event grading scale used was the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) grading scale. When an AE could not be graded by NCI-CTCAE, the following severity grade could be used:

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity
4	LIFE-THREATENING: Refers to an event in which the patient was, in the view of the investigator, at risk of death at the time of the event. (This category is not to be used for an event that hypothetically might have caused death if it were more severe.)
5	FATAL

A serious adverse event (SAE) was defined as an AE that met at least 1 of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An AE met the criterion of “requires hospitalization”, if the event necessitated an admission to a health care facility (e.g., overnight stay).

Treatment emergent adverse events were those reported during the investigational product exposure period (i.e., within 28 days [QM] or 14 days [Q2W] of the subject’s last dose of evolocumab or by their EOS date. Adverse events reported at any time during the OLE study were also reported.

Adverse events of special interest included those AEs associated with injectable protein therapies (i.e., injection site reactions), potential hypersensitivity reactions, or potential hepatitis C infections. These AEs were evaluated using standardized MedDRA queries or Amgen narrow search strategies.

Events of death by any cause, cardiovascular death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, stroke, TIA, and hospitalization for heart failure were adjudicated by an independent CEC.

The Applicant’s approach for recording, coding and categorizing AEs, as well as their safety analyses, were reasonable and appropriate.

8.3.3. Routine Clinical Tests

All on-study laboratory samples were to be processed and sent to the central laboratory. Central laboratory results of the lipid panel, ApoA1, ApoB, Lp(a), and hsCRP were not to be reported to the investigator prior to Week 8 for subjects coming from a blinded (or blinded

portion) of a parent study, since some laboratory results may inadvertently unblind investigators to treatment assignment in the parent study. The laboratory tests to be conducted are listed below and one of the schedules of assessments is shown in Table 2.

<u>Chemistry</u>	<u>Coagulation</u>	<u>Urinalysis</u>	<u>Hematology</u>	<u>Other Labs</u>
Sodium	PT/INR	Specific gravity	Hemoglobin	Fasting lipids
Potassium		pH	Hematocrit	• Total cholesterol
Chloride		Blood	MCV	• HDL-C
Bicarbonate		Protein	MCH	• LDL-C
Total protein		Glucose	MCHC	• Triglycerides
Albumin		Bilirubin	RDW	• VLDL
Calcium		WBC	Platelets	• Non-HDL-C
Magnesium		RBC	RBC	ApoA1
Phosphorus		Epithelial cells	WBC	ApoB
Glucose		Bacteria	Differential	ApoB/ApoA1 ratio
BUN or Urea		Casts	• Neutrophils	Total Cholesterol/HDL-C
Creatinine		Crystals	• Bands	hsCRP
Uric acid			• Eosinophils	Lp(a)
Total bilirubin			• Basophils	Anti-AMG 145 antibodies
Direct bilirubin			• Lymphocytes	AMG 145 (PK)
CK			• Monocytes	PCSK9
ALP				HbA1c
LDH				FSH
AST (SGOT)				Fasting Vitamin E
ALT (SGPT)				eGFR (calculated)
				Serum HcG

Antibody Testing Procedures

Blood samples were collected quarterly during the first year and yearly thereafter from all subjects for the measurement of anti-evolocumab (also defined as AMG 145) binding antibodies. These samples were assayed for binding and, if positive, neutralizing antibodies.

The safety assessment methods and time points that were described in the protocol were adequate for the population, disease, and increased dosing regimen that were being investigated.

8.4. Safety Results

8.4.1. Deaths

Study 20110271 included a total of 300 subjects (HoFH and severe FH). Deaths occurred in 7 (2.3%) subjects (2 HoFH subjects and 5 non-HoFH severe FH subjects). These included 1 event each of myocardial infarction, cardiogenic shock, colon cancer metastatic, small cell lung cancer, adenocarcinoma pancreas, sepsis, and subarachnoid hemorrhage. No adolescent subjects had a fatal adverse event. Two additional subjects died (1 event each of cardiac failure

acute and multiple organ dysfunction syndrome) > 30 days after the last dose of evolocumab and were not defined as treatment-emergent adverse events per the SAP definition.

My review of these narratives did not reveal any new safety findings related to evolocumab. There was no discernible pattern as all causes of death occurred in single patients only and was largely consistent with the enrolled population, in which all were at high CV risk.

8.4.2. Serious Adverse Events

The subject incidence of serious adverse events (SAEs) among subjects in the 3 dosing subgroups (Q2W only dosing in patients on apheresis, QM and Q2W dosing, and QM only dosing in patients not on apheresis) is shown in the following table. Most of these SAEs are cardiovascular events which are expected in this patient population with HoFH. There are a higher percentage of patients with one or more events in the QM/Q2W group; it is unknown if this is due in part to the larger sample size and slightly longer treatment duration in this group. These SAEs are not likely to be associated with increased evolocumab dosing. If an increased dose was causing increased side effects, one would anticipate AEs already known to be associated with evolocumab, such as hypersensitivity reactions, injection site reactions, flu-like symptoms, musculoskeletal symptoms, or upper respiratory tract infection/nasopharyngitis type symptoms. Additionally, the percentage of patients with one or more events was lowest in the Q2W Only group.

Table 15. Serious Adverse Events in Study 20110271 by Dosing Regimen (Q2W only, QM and Q2W, QM only) Occurring in ≥ 2% of Subjects in Any Dosing Group (HoFH Analysis Set)

	Final Analysis for Study 20110271		
	Q2W Only ^a	QM and Q2W ^b	QM Only ^c
Total No. of HoFH subjects	29	58	19
Median exposure to evolocumab (months)	36	53	50
Number of subjects reporting ≥ 1 AE – n(%)	4 (14)	21 (36)	4 (21)
Preferred Term			
Angina Pectoris	0	4 (7)	0
Aortic Stenosis	0	3 (5)	0
Coronary Artery Disease	0	3 (5)	0
Acute Myocardial Infarction	0	2 (3)	0
Alanine Aminotransferase Increased	0	1 (2)	1 (5)

Source: Applicant's Response to FDA Advice letter/Information Request (08 July 2020), Table 8

AE=adverse event; HoFH=homozygous familial hypercholesterolemia; Q2W=once every 2 weeks; QM=once monthly.

a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.

b Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.

c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM.

Adolescent Patients with HoFH

There were 4 (29%) adolescents with HoFH reporting SAEs. This included 3 subjects with 1 serious adverse event each of pleuritic pain, coronary artery occlusion, ovarian germ cell teratoma, and 1 subject with 4 serious adverse events (non-cardiac chest pain, appendicitis, aortic stenosis, and nephrolithiasis). My review of these narratives did not reveal any new safety findings plausibly related to evolocumab.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The overall incidence of AEs leading to discontinuation of evolocumab in Study 20110271 was low. No subjects in the Q2W only and QM only HoFH subgroups reported AEs leading to discontinuation of evolocumab. In the subgroup who received both QM and Q2W dosing, 3 subjects experienced 5 adverse events leading to discontinuation of evolocumab. This included events of eczema and infected eczema (both in 1 subject), myocardial infarction and rash (both in 1 subject), and rash (1 adolescent subject, grade 3 non-serious AE). The 2 events of rash were considered related to evolocumab by the investigator while the other 3 events were considered not related to evolocumab. As allergic reactions/rash were AEs seen in the evolocumab development program, it is reasonable to contribute these AEs to evolocumab; although it is hard to draw conclusions, based on the small sample size, whether the higher incidence of AEs leading to discontinuation could be dose-related.

Some of the patients with severe HeFH in study 20110271 were also treated with 420 mg Q2W of evolocumab. No subjects in the Q2W only severe FH subgroup reported AEs leading to discontinuation of evolocumab. In the subgroup who received both QM and Q2W dosing, one subject (4%) reported myalgia. In the subgroup who received QM only dosing, 7 subjects (5%) reported AEs that led to discontinuation, such as cancer (pancreatic and metastatic colon), cholelithiasis, injection site pain, malaise, and hyperhidrosis. In summary, there was no evidence of a dose-related trend of AEs leading to discontinuation in the severe HeFH cohort.

8.4.4. Significant Adverse Events

Adverse events of special interest included injection site reactions, potential hypersensitivity reactions, or potential hepatitis C infections. In the total of 300 subjects (HoFH and severe FH) in Study 20110271, no subject had a potential hepatitis C event, 32 (11%) subjects had potential hypersensitivity events (all non-serious), and 36 (12%) subjects had potential injection site reaction events. Two adolescents (14%) reported potential hypersensitivity reactions, such as rash, urticaria and allergic rhinitis.

Adjudicated cardiovascular endpoint events were reported for 32 out of 300 (11%) HoFH and severe FH subjects, including 12 (11%) HoFH subjects and 20 (10%) non-HoFH severe FH subjects, respectively). Most events were coronary revascularizations (22 [7%] subjects), followed by death (9 [3%] subjects; including 5 cardiovascular disease and 4 non-cardiovascular disease) and myocardial infarction (7 [2%] subjects). No adolescent subject had a positively adjudicated cardiovascular endpoint adverse event.

Non-coronary revascularization occurred in 5 out of 300 (2%) HoFH and severe FH subjects, including percutaneous (3 [1%] subjects), surgical (1 [$<1\%$] subjects) and unknown (1 [$<1\%$] subjects) non-coronary revascularizations. Non-coronary revascularizations were not adjudicated by the CEC.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The subject incidence of the most common AEs among subjects in the 3 dosing subgroups (Q2W only dosing in patients on apheresis, QM and Q2W dosing, and QM only dosing in patients not on apheresis) is shown in the following table. Overall, the percentage of patients experiencing one or more events was similar in the QM Only and QM/Q2W groups and numerically lower in the Q2W Only arm, where median exposure was substantially shorter. There was a higher incidence of injection site pain/erythema in the Q2W only group but that may be in part due to getting injections every 2 weeks for the entire study period. There were more cases of CPK increased in the QM/Q2W group; this increase does not appear dose related as no subjects in the Q2W only group reported AEs of CPK increase. Overall, the AEs reported in patients with HoFH receiving evolocumab 420 mg Q2W were similar to those reported in patients receiving the approved 420 mg QM dose of evolocumab.

Table 16. Treatment-Emergent Adverse Events in Study 20110271 by Dosing Regimen (Q2W only, QM and Q2W, QM only) Occurring in $> 10\%$ of Subjects in Any Dosing Group (HoFH Analysis Set)

	Final Analysis for Study 20110271		
	Q2W Only ^a	QM and Q2W ^b	QM Only ^c
Total No. of HoFH subjects	29	58	19
Median exposure to evolocumab (months)	36	53	50
Number of subjects reporting ≥ 1 AE – n(%)	23 (79)	54 (93)	17 (90)
Preferred Term			
Nasopharyngitis	6 (21)	7 (12)	4 (21)
Headache	5 (17)	9 (16)	4 (21)
Influenza	5 (17)	10 (17)	2 (11)
Injection Site Pain	5 (17)	0	1 (5)

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Fatigue	4 (14)	3 (5)	1 (5)
Injection Site Erythema	4 (14)	0	0
Vomiting	4 (14)	1 (2)	0
Anaemia	3 (10)	2 (3)	0
Back Pain	3 (10)	4 (7)	2 (11)
Cough	3 (10)	2 (3)	0
Nausea	3 (10)	1 (2)	1 (5)
Neck Pain	3 (10)	1 (2)	0
Oropharyngeal Pain	3 (10)	0	1 (5)
Rash	3 (10)	2 (3)	0
Upper Respiratory Tract Infection	3 (10)	13 (22)	2 (11)
Anxiety	1 (3)	9 (16)	0
Angina Pectoris	1 (3)	7 (12)	0
Blood Creatine Phosphokinase Increased	0	7 (12)	0
Sinusitis	0	7 (12)	0
Hypertension	1 (3)	6 (10)	2 (11)
Abdominal Pain	2 (7)	2 (3)	3 (16)
Alanine Aminotransferase Increased	1 (3)	3 (5)	3 (16)
Aspartate Aminotransferase Increased	1 (3)	2 (3)	3 (16)
Muscle Spasms	0	1 (2)	3 (16)
Arthralgia	1 (3)	3 (5)	2 (11)
Blood Pressure Increased	0	0	2 (11)
Carotid Intima-Media Thickness Increased	1 (3)	1 (2)	2 (11)
Chest Pain	1 (3)	2 (3)	2 (11)
Dental Caries	0	1 (2)	2 (11)
Epistaxis	0	0	2 (11)
Gastroenteritis	1 (3)	3 (5)	2 (11)
Myalgia	1 (3)	3 (5)	2 (11)
Pyrexia	2 (7)	0	2 (11)
Tendonitis	0	2 (3)	2 (11)
Urinary Tract Infection	2 (7)	4 (7)	2 (11)

Source: Applicant's Response to FDA Advice letter/Information Request (08 July 2020), Table 8

AE=adverse event; HoFH=homozygous familial hypercholesterolemia; Q2W=once every 2 weeks; QM=once monthly.

a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.

b Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.

c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM.

Adverse Events Associated with the 420 mg Q2W Dose Increase

One of the issues in this application is whether there were any clinically meaningful adverse reactions that were associated with the 420 mg Q2W dosing regimen as compared to the 420 mg QM dosing regimen.

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In Study 20110271, 80 patients with FH, not on apheresis (53 HoFH and 27 severe FH) had their dose up-titrated from 420 mg QM to 420 mg Q2W during the study. Of these 80 subjects, 9 (11%) subjects down-titrated their dose back to 420 mg QM. Investigators were not required to report the reason for up- or down-titration, but the applicant reports that 7 out of 9 of these subjects had little or no improvement in LDL-C following up-titration to the 420 mg Q2W dose.

As shown in the following table, there does not appear to be any adverse event(s) that is driving the decision to decrease dosing to 420 mg QM. Four of the 9 patients had an adverse event within 30 days after up-titration or 30 days before down-titration. None of the adverse events were serious, none were considered by the investigator to be related to evolocumab or to lead to a dose change, and all of the events were grade 1 or 2 in severity.

Table 17. Adverse Events Among Non-apheresis Subjects Uptitrating and Subsequently Downtitrating Evolocumab in Study 20110271 (Final Analysis)

Subject	LDL-C With QM Dosing ^a			LDL-C With Q2W Dosing ^b			Adverse Event(s) After Up-titration/Before Down-titration ^c					
	Day (Wk) of Up-titration	Change from Baseline	Value mg/dL	Day (Wk) of Down-titration	Change from Baseline	Value mg/dL	Adverse Event Preferred Term	Start Day of AE	CTCAE Grade ^e	SAE ^e	Related to EvoMab ^e	Action Taken With EvoMab ^e
(b) (6)	87 (12)	-12.9%	480	169 (24)	4.0%	573	Sinusitis	105	2	No	No	None
	85 (12)	-2.8%	437	169 (24)	-3.0%	436	Acne	112	2	No	No	None
	421 (60)	-44.3%	136	841 (120)	-40.2%	146	N/A	-	-	-	-	-
	505 (72)	-41.0%	167	1010 (144)	-45.6%	154	N/A	-	-	-	-	-
	505 (72)	-27.3%	242	1016 (144)	-49.9%	167	N/A	-	-	-	-	-
	113 (16)	-35.9%	271	169 (24)	-40.9%	250	N/A	-	-	-	-	-
	169 (24)	-61.9%	65	253 (36)	-51.3%	83	Sinusitis	183	1	No	No	None
	169 (24)	-41.1%	149	1004 (144)	-41.9%	147	N/A	-	-	-	-	-
	87 (12)	-38.8%	141	164 (24)	-62.7% ^f	86 ^f	Epistaxis	87	1	No	No	None
							Dyspnoea	138	1	No	No	None

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; N/A = not applicable; OLE = open-label extension; Q2W = once every 2 weeks; QM = once monthly; SAE = serious adverse event; Wk = week.

^a The most recent LDL-C value obtained (on QM dosing) prior to administration of the first dose of the new Q2W dose.

^b The most recent LDL-C value obtained (on Q2W dosing) prior to the administration of the down-titrated QM dose.

^c Adverse events reported in Study 20120271 within 30 days after up-titration or 30 days before down-titration.

^d This subject also had an unscheduled visit at OLE week 24 on day 155 at which time their calculated LDL-C was 511 mg/dL, equivalent to a - 7.3% change from baseline.

^e Per investigator report.

^f This visit occurred approximately 1 week early; thus, the LDL-C concentration was recorded approximately 1 week after the most recent dose of evolocumab 420 mg Q2W. The subject also had an unscheduled visit at week 24 (day 177) at which time their calculated LDL-C was 82 mg/dL, equivalent to a - 64.4% change from baseline.

Source: Applicant's Response to FDA Advice letter/Information Request (08 July 2020), Table 4.

There were 15 apheresis subjects in the final analysis of Study 20110271 who initiated the study on Q2W dosing, per protocol, and subsequently had their dose down-titrated to QM dosing. A listing of LDL-C values and adverse events occurring within 30 days prior to the down-titration for each of the 15 apheresis HoFH subjects who down-titrated to 420 mg QM dosing from 420 mg Q2W dosing is provided in the table below. Five of the 13 subjects had an adverse event within 30 days prior to down-titration. However, in only one of these 5 subjects (Subject (b) (6), a 54-year-old white female) was an action taken in association with the down-titration. This subject had serious adverse events (grade 4 chest pain and aortic stenosis) on study day 145 and the action taken following these events was 'dose altered or withheld'; however, the events were considered unrelated to evolocumab by the investigator. A review of the narrative does not indicate that evolocumab dosing was changed because of the AEs. There does not appear to be any adverse event(s) that is driving the decision to decrease dosing to 420 mg QM in these 15 subjects on apheresis.

Table 18. Adverse Events Among Apheresis Subjects Downtitrating Evolocumab in Study 20110271 (Final Analysis)

Subject	Study Day (Wk) of Down-titration	LDL-C With Q2W Dosing Prior to Downtitration ^a		Adverse Event(s) Before Downtitration ^b					
		Change From Baseline	Value mg/dL	Adverse Event Preferred Term	Study Start Day	CTCAE Grade ^c	SAE ^c	Related to EvoMab ^c	Action Taken With EvoMab ^c
(b) (6)	89 (12)	-30.1%	93	N/A	-	-	-	-	-
	88 (12)	-8.3%	133	N/A	-	-	-	-	-
	85 (12)	-27.2%	134	N/A	-	-	-	-	-
	86 (12)	-80.1%	39	Muscle Spasms	59	1	No	Yes	None
	85 (12)	-68.6%	61	N/A	-	-	-	-	-
	86 (12)	-73.3%	40	N/A	-	-	-	-	-
	91 (12)	-67.6%	74	N/A	-	-	-	-	-
	85 (12)	-75.6%	51	Bronchitis	57, 62, 71	1	No	No	None
	113 (16)	-68.1%	43	N/A	-	-	-	-	-
	84 (12)	-79.1%	35	N/A	-	-	-	-	-
	85 (12)	-92.3%	10	Nasopharyngitis	78	2	No	No	None
	85 (12)	-89.7%	22	N/A	-	-	-	-	-
	141 (20)	-85.6%	21	Tooth Extraction	121	1	No	No	None
	169 (24)	-69.5%	41	Chest Pain	145	4	Yes	No	Dose Alt or WH
				Aortic Stenosis	155	4	Yes	No	Dose Alt or WH
	169 (24)	-85.0%	26	N/A	-	-	-	-	-

Alt = altered; CTCAE = Common Terminology Criteria for Adverse Events; EvoMab = evolocumab; LDL-C = low-density lipoprotein cholesterol; N/A = not applicable; OLE = open-label extension; Q2W = once every 2 weeks; QM = once monthly; SAE = serious adverse event; Wk = week; WH = withheld.

^a The most recent LDL-C value obtained prior to the administration of the down-titrated QM dose.

^b Adverse events reported in Study 20120271 within 30 days prior to downtitration.

^c Per investigator report.

Source: Applicant's Response to FDA Advice letter/Information Request (08 July 2020), Table 5.

Adverse Events in Adolescent Patients

The most frequently reported adverse events ($\geq 10\%$) in the adolescent subgroup were anxiety, migraine, upper respiratory tract infection (3, 21% each), and acne, increase in blood creatine phosphokinase, influenza, non-cardiac chest pain, rash, and urinary tract infection (2, 14% each).

8.4.6. Laboratory Findings

My review of the chemistry, hematology and urinalysis results did not find any new, clinically significant laboratory abnormalities in this study. Notable findings for creatine kinase and liver enzyme tests are described in more detail below.

Creatine Kinase

Among subjects in the EAS, CK $> 5 \times \text{ULN}$ and $> 10 \times \text{ULN}$ at any postbaseline visit occurred in 22 (7%) subjects and 15 (5%) subjects, respectively. In adolescent subjects, 2 (14%) subjects had CK $> 10 \times \text{ULN}$ at any postbaseline visit, as summarized below.

- Subject (b) (6) CK elevations $> 10 \times \text{ULN}$ reported at scheduled visits at Week 36 (CK 63xULN, AST 7xULN, ALT 2.8xULN with normal bilirubin and INR) and Week 108 (10.8xULN). In both instances, the adolescent participant with HoFH engaged in vigorous exercise prior to the study visit/blood draw. Treatment emergent adverse events of liver function test abnormal and increased blood creatine phosphokinase were reported at the Week 36 visit for this subject; both events resolved after 11 days.
- Subject (b) (6) CK elevations were reported at scheduled visits at Week 36 (21.5 x ULN), Week 48 (8 x ULN), and Week 132 (10.7 x ULN). The adolescent participant with HoFH had engaged in vigorous exercise prior to the study visit/blood draw at Week 36 and Week 48. Treatment emergent adverse events of increased blood creatine phosphokinase were reported at the Week 36 and Week 48 visits; the events resolved after 11 and 10 days, respectively. At Week 132, the subject reported feeling well with no muscle symptoms, and the CK elevation was considered not clinically significant by the investigator.

In both subjects, CK values returned to normal or near normal by the subsequent unscheduled visit or by the next scheduled visit. The treatment emergent adverse events were nonserious, CTCAE grade 1 in severity by the investigators, and were not considered related to evolocumab. No action was taken with study drug as a result of the adverse events and both subjects continued evolocumab treatment. In conclusion, there was no evidence of drug-associated myopathy.

Table 19. Subject Incidence of Creatine Kinase > 5 x ULN or > 10 x ULN; Study 20110271 (Evaluable Analysis Set, HoFH Analysis Set)

HoFH + Severe HeFH Population	Apheresis Subjects (N= 61) n (%)	Non-apheresis Subjects (N=239) n (%)	Total (N=300) n (%)
Baseline			
Subjects with at least one baseline CK test, n	61	239	300
CK > 5 x ULN	0	1 (<1)	1 (<1)
CK > 10 x ULN	0	0	0
Any Postbaseline visit			
Subjects with at least one post-baseline CK test, n	61	239	300
CK > 5 x ULN	4 (7)	18 (8)	22 (7)
CK > 10 x ULN	2 (3)	13 (5)	15 (5)
HoFH Only Population			
Baseline			
Subjects with at least one baseline CK test, n	34	72	106
CK > 5 x ULN	0	0	0
CK > 10 x ULN	0	0	0
Any Postbaseline visit			
Subjects with at least one post-baseline CK test, n	34	72	106
CK > 5 x ULN	4 (12)	9 (13)	13 (12)
CK > 10 x ULN	2 (6)	6 (8)	8 (8)
HoFH Adolescent Population			
Baseline			
Subjects with at least one baseline CK test, n	4	10	14
CK > 5 x ULN	0	0	0
CK > 10 x ULN	0	0	0
Any Postbaseline visit			
Subjects with at least one post-baseline CK test, n	4	10	14
CK > 5 x ULN	0	2 (20)	2 (14)
CK > 10 x ULN	0	2 (20)	2 (14)

N = number of subjects enrolled in Study 20110271; CK = Creatine Kinase; ULN = upper limit of normal
For parent study rollover subjects, baseline is defined at parent study baseline.
Post-baseline for all subjects is defined as post-baseline in Study 20110271.
The percentage is based on the total n at the given visit.
Source: Tables 14-7.44.1.1, 14-7.44.2.1, and 14-7.44.4.1

Liver Enzyme Tests

In all subjects, HoFH and severe FH, ALT or AST > 5 x ULN at any postbaseline visit occurred in 8 out of 300 (3%) subjects. Three (1%) subjects had total bilirubin > 2 x ULN at any postbaseline visit. Two (0.7%) subjects had (ALT or AST > 3 x ULN) and (total bilirubin > 2 x ULN or INR > 1.5) at any postbaseline visit. One subject had a history of aortic valve replacement and was on warfarin with a therapeutic INR (>1.5) and had transient increased AST and CK at week 108. One subject had a history of hepatic steatosis and hepatic fibrosis with increased INR (>1.5 and mildly elevated AST/ALT at baseline, and lab criteria ([ALT or AST > 3 x ULN] and [total bilirubin > 2 x ULN or INR > 1.5]) was met at Week 12 in the context of diarrhea and flu; all labs had normalized by Week 24.

In adolescent subjects, one subject (7%) reported an ALT or AST > 5 x ULN at any postbaseline visit (refer to the narrative for Subject (b) (6) with CK elevations). In conclusion, there was no evidence of drug-associated hepatic injury.

8.4.7. Vital Signs

The applicant had instructions in the protocol to help standardized the measurement of vital signs, such as: blood pressure (BP) and heart rate (HR) should be measured at each visit; BP should be measured, with an appropriate size cuff, in the same arm as in the parent study; the diastolic blood pressure (DBP) should be recorded as the pressure noted when sound disappears (Korotkoff Phase V); BP and HR should be determined after the subject has been seated for at least 5 minutes; and the subject's pulse should be measured for 30 seconds and the number should be multiplied by 2 to obtain heart rate.

There were no notable changes from baseline in vital signs in the HoFH and severe FH population.

8.4.8. Electrocardiograms (ECGs)

In all subjects, 11 (4%) subjects and 1 (<1%) subject had a QTcB or QTcF value > 450 msec and > 480 msec postbaseline, respectively; no subject had QTcB or QTcF value > 500 msec postbaseline. Seven (2.3%) subjects had an increase of > 30 msec in QTcB or QTcF; no subject had an increase of > 60 msec in QTcB or QTcF. There was no evidence to suggest a proarrhythmic effect of evolocumab.

8.4.9. Immunogenicity

Eight out of 300 (3%) subjects with HoFH or severe FH tested positive for anti-evolocumab binding antibodies at any time. Three of these subjects tested positive at or before Study 20110271 baseline or parent study baseline for rollover subjects; 5 of these subjects had transient results, defined as a negative result at the subject's last timepoint tested within the study period. No subjects tested positive for anti-evolocumab neutralizing antibodies. No adverse events were associated with a positive antibody result.

8.5. Safety in the Postmarket Setting

The safety profile of evolocumab in the postmarket setting is based on a global clinical development program and post-marketing experience. As of January 2020, the total exposure to evolocumab in clinical trials is 28,207 subjects, and an estimated 662,102 patients (515,656 patient years) have been exposed to evolocumab in the postmarketing setting. As of July 2020, Repatha has been approved in 77 countries worldwide; the 420 mg Q2W dosing regimen has been approved in 65 of those countries without restrictions for use in patients 12 years and older with HoFH.

The applicant reports that while adverse events in the post-marketing setting are routinely reviewed and monitored for safety signal detection, information on the specific indication (HoFH vs non-familial hyperlipidemia), patient age, and dosing regimen are not always reported. Thus, the postmarketing exposure in patients with HoFH, including children, and the dosing regimen they were administered are unknown. The applicant reviewed cumulative post-marketing data through 17 January 2020; a total of 1033 post-marketing adverse events have been received for patients with a reported indication available of HoFH. Based on the information included in these adverse event reports, 55 events occurred in patients receiving the 420 mg Q2W dose, including 5 pediatric patients. The applicant provided a table of these adverse events, including, when known, gender, age, MedDRA preferred term, seriousness of event, event outcome and time to onset. My review of this listing of adverse events did not result in any unexpected or new safety findings. Adverse events listed for pediatric patients included CPK increased, drug ineffective, injection site erythema, and injection site swelling.

8.6. Integrated Assessment of Safety

The focus of this safety review is evaluating the 420 mg Q2W dosing regimen of evolocumab as compared to the 420 mg QM dosing regimen in patients with HoFH. The 106 patients with HoFH were divided into 3 groups: 29 (27%) apheresis subjects who received only Q2W dosing,

58 (55%) subjects who received both QM and Q2W dosing, and 19 (18%) non-apheresis subjects who received only QM dosing.

In general, there were no notable differences in the incidence of adverse events among the 3 dosing groups, but a higher percentage of patients treated with evolocumab both QM and Q2W experienced SAEs and AEs leading to drug discontinuation than patients in the other 2 groups. These events occurred in only a handful of patients, and the number of subjects exposed and treatment duration differs among the 3 groups. As discussed in Section 8.4.2 and 8.4.3, these SAEs and AEs that led to discontinuation were not likely to be associated with increased evolocumab dosing.

Table 20. Overview of Treatment-Emergent Adverse Events in Study 20110271 by Dosing Regimen (Q2W only, QM and Q2W, QM only) (HoFH Analysis Set)

	Final Analysis for Study 20110271		
	Q2W Only ^a	QM and Q2W ^b	QM Only ^c
Total No. of HoFH subjects	29	58	19
Median exposure to evolocumab (months)	36	53	50
Number of subjects reporting event – n(%)			
Adverse events (AEs)	23 (79)	54 (93)	17 (90)
Serious AEs	4 (14)	21 (36)	4 (21)
AEs leading to discontinuation of evolocumab	0	3 (5)	0

Source: Applicant's Response to FDA Advice letter/Information Request (08 July 2020), Table 6

AE=adverse event; HoFH=homozygous familial hypercholesterolemia; Q2W=once every 2 weeks; QM=once monthly.

a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.

b Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.

c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM.

Adolescent Patients with HoFH

In adolescent patients, at least 1 adverse event was reported for 12 (86%) subjects; 9 (64%) were grade ≥ 2 and 5 (36%) were grade ≥ 3 in severity. There were 4 (29%) subjects reporting SAEs; a review of the SAE narratives did not reveal any safety findings likely to be caused by evolocumab. One subject out of 14 (7%) discontinued evolocumab due to a rash (Grade 3 non-serious) that was likely related to evolocumab. There were no fatal events and no device-related adverse events.

Based on the safety data for the 420 mg Q2W dosing regimen from Study 20110271 and the postmarket setting, there is reasonable safety experience to support the use of the 420 mg Q2W dose in patients with HoFH who are 13 years of age or older.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

Some changes were made to the PI, as was done with other recent label changes for the lipid-lowering therapies, to be consistent with best labeling practices, such as:

- In Section 1: Indications: removing the numbered subsections as they are unnecessary and are needed only when it is necessary to clearly identify/differentiate indicated populations (e.g., when there are different prescribing audiences for each).
- In Section 1, removing the listing of the specific other LDL-lowering therapies used in combination with evolocumab in the primary hyperlipidemia indication
- Simplifying the language in Section 2, where needed.
- Added clarifying information to Dosage and Administration: The analysis of lipid levels is part of standard clinical practice for the management of hyperlipidemia. However, when a provider should analyze lipid levels is specific to evolocumab and the pharmacodynamic profile of evolocumab.
- Updated Section 8.1 to include language that was submitted (b) (4) regarding pregnancy.
- Updated Section 14 to be consistent with best labeling practices (such as removed numbered sections and replaced with headings).

Changes made that are specific to the HoFH indication or the 420 mg Q2W dosing regimen:

- Remove ‘who require additional lowering of LDL-C’ from the HoFH indication as it is not necessary information in this patient population with very high LDL levels and replace it with “to reduce LDL-C”.
- Adding information to 2.1 regarding when the 420 mg QM dose, if the LDL-C response is inadequate, can be up-titrated to Q2W.
- Clarifying that patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule and to be administered after apheresis is complete.
- Adding information to Section 6 that describes Study 20110271 (TAUSSIG) and that safety profile of REPATHA in adolescent patients was similar to that described for adult patients with HoFH.
- Updated Section 8.4 Pediatric Use to comply with current pediatric labeling guidance.
- Adding information to Section 14 that describes the efficacy findings from Study 20110271 (TAUSSIG)

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

/s/

EILEEN M CRAIG
02/24/2021 06:26:46 PM

JOHN M SHARRETT
02/25/2021 09:11:57 AM

I concur with the findings and conclusions of this review. This review serves as the decisional memorandum for the supplementary application.