CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL MEMO

CLINICAL STUDIES

BLA #:	125522
Supplement #:	
Drug Name:	Repatha (evolocumab)
Indications:	Homozygous familial hypercholesterolemia (HoFH)
Applicant:	Amgen
Dates:	Stamp date: 8/31/2020 Primary review Due date: 1/25/2021 PDUFA date: 2/28/2021
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II
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Keywords: Homozygous familial hypercholesterolemia **(**HoFH)

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Introduction

Repatha (evolocumab) is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with LDLR. FDA had approved evolocumab 420 mg once monthly (QM) dose on August 27, 2015. However, a Complete Response Letter (CRL) was issued for evolocumab 420 mg once every two weeks (Q2W) dose for HoFH patients.

The CRL stated the following deficiency of the original submission:

"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 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."

Amgen has submitted the results of their long term open-label extension (OLE) study, study 20110271 titled, "A Multicenter, Open-label Study to Assess the Long-term Safety, Tolerability, and Efficacy of AMG 145 on LDL-C in Subjects with Severe Familial Hypercholesterolemia", which was ongoing at the time of the original filing. Study 2011027 hereafter will be referred to as study 271.

Study design and results

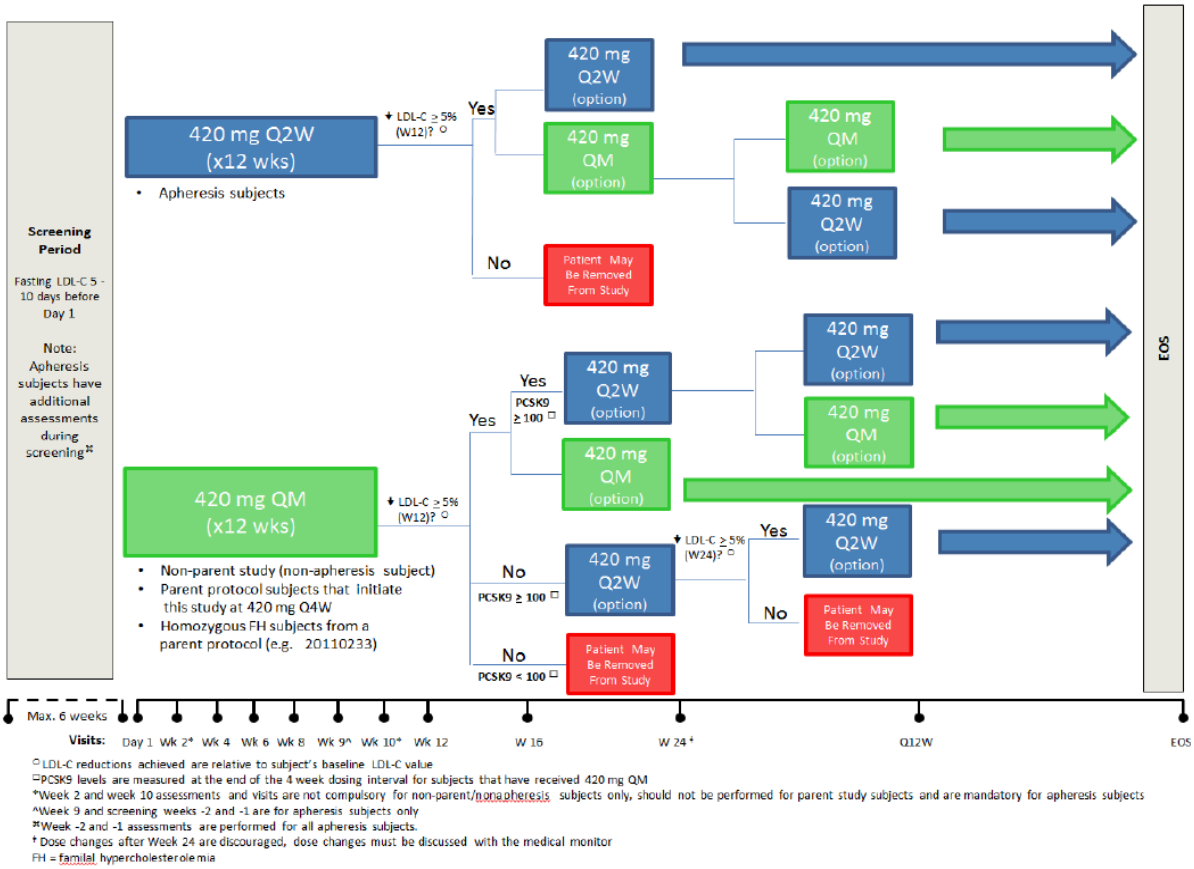
This was a phase 2/3 single arm, OLE study designed to characterize the safety and tolerability of long-term administration of evolocumab to subjects with severe familial hypercholesterolemia (FH): homozygous familial hypercholesterolemia (HoFH) or non-HoFH severe FH. All subjects received evolocumab 420 mg SC, initially administered either QM (non-apheresis subjects) or Q2W (apheresis subjects).

The primary objective was to characterize the safety and tolerability of long-term administration of evolocumab among subjects with severe familial hypercholesterolemia. The secondary objectives were 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 A1 (ApoA1) ratio, and response of LDL-C reduction (15% or greater) in subjects with severe FH.

This summary will focus on the secondary objective pertaining to LDL-C.

Figure 1 below shows the scheme of the study design for study 271.

Figure 1. Study Design



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: Clinical Study Report, Trial 20110271: Figure 8-1, page 48

The evaluable analysis set (EAS) included all 300 (100%) subjects who had enrolled in the study. There was 106 HoFH subjects in the HoFH analysis set (HAS); where 48 (20.1%) of the subjects were in the titration analysis set (TAS) subjects 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).

Table 1 shows the subject disposition.

No formal statistical analysis was planned for this OLE study. Based on input from clinical team, I focused on the 48 subjects in the TAS.

Table 1. Subject Disposition

	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	--	48 (20.1)	48 (20.1)
HoFH Evolocumab Titration Analysis Set (TAS) exclusion	--	24 (10.0)	24 (10.0)
Exposed to QM less than 12 weeks	--	1 (0.4)	1 (0.4)
Exposed to QM for 12 weeks and remained on QM	--	19 (7.9)	19 (7.9)
Exposed to Q2W less than 12 weeks	--	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)
Did not take any dose of IP	0 (0.0)	0 (0.0)	0 (0.0)

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: Clinical Study Report, Trial 20110271: Table 9-1, page 70

The percent change in LDL-C from baseline is shown in the table below. A total of 48 subjects were included to receive evolocumab QM for 12 weeks followed by evolocumab Q2W for another 12 weeks. There were 47 subjects that received evolocumab QM for 12 weeks and 46 subjects that received evolocumab Q2W for 12 weeks.

There was a further reduction in the mean percent change in LDL-C from baseline of evolocumab when subjects switched from QM regimen to Q2W regimen. The mean percent change from baseline was of -19.6% and -29.7% for the QM and Q2W regimens respectively. The further reduction also appears statistically significant based on a paired t-test, which indicates that it is unlikely the reduction occurred purely due to random variation. However, since there was no concurrent control, it is also uncertain whether the reduction could be fully attributable to the up titration.

Table 2. 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 N=48	After 12 weeks of 420 mg evolocumab every 2 weeks N=48
Mean (SD) Baseline value, mg/dL	374.1 (145.1)	374.1 (145.1)
n	47	46
Mean (SD) Change from baseline, mg/dL	-68.9 (82.2)	-104.5 (83.9)
Mean Percent (SD) change from baseline	-19.6 (22.0)	-29.7 (22.6)

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: Statistical reviewer; adlbeff.xpt and adsl.xpt

Summary

The submission relies on results from an open-label, single-arm study. Therefore, it does not seem to satisfy the required evidence from adequate well-controlled study(ies) cited in the CRL. Nevertheless, findings from this study appear to suggest that up titration to Q2W from QM for some subjects could lead to further reduction of LDL-C. However, since there is no concurrent control, it is unclear whether other factors have also contributed to the observed reduction. Clinical insight to this population and proposed dosing regimen will be helpful to further interpret the findings.

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