CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125522Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Clinical Pharmacology Memorandum

BLA Number	125522
Link to EDR	\\CDSESUB1\evsprod\BLA125522\0292
Submission Date	August 31, 2020
Submission Type	Complete Response to the FDA's Complete Response Letter
Brand Name	Repatha
Generic Name	Evolocumab
Dosage Form and Strength	Injectable solution; 140 mg/mL (b) (4) and 420 mg dose, (b) (4) using Pushtronex system
Route of Administration	Subcutaneous
Proposed Indication	• to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease • as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C) • 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
Applicant	Amgen
Associated IND	105188
OCP Primary Reviewer	Sang Chung, Ph.D.
OCP Team Leader	Jayabharathi Vaidyanathan, Ph.D.

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1. EXECUTIVE SUMMARY

The sponsor submitted this complete response to the FDA's Complete Response Letter (CRL) dated August 27, 2015 (see the CRL in Appendix).

The CRL letter was issued regarding the proposed dosing regimen of 420 mg once every 2 weeks (Q2W) for patients with homozygous familial hypercholesterolemia (HoFH) in the original Biologics License Application (BLA). The proposed Q2W dosing regimen was based on preliminary results and 120-day safety update of on-going Study 20110271 as part of the original BLA. 420 mg once monthly (QM) has been approved in patients with HoFH.

The sponsor addressed deficiencies of the CRL in this submission using the final complete study report (CSR) of Study 20110271.

1.1 Recommendations

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.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

The sponsor proposed both 420 mg QM and 420 mg Q2W dosing regimens for patients with HoFH in the original BLA submission. The Q2W dosing regimen in the original BLA was proposed based on the interim CSR of Study 20110271.

The Agency issued the CRL for the Q2W dosing regimen with the following clinical deficiency, due to the preliminary nature of interim CSR;

- *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.*

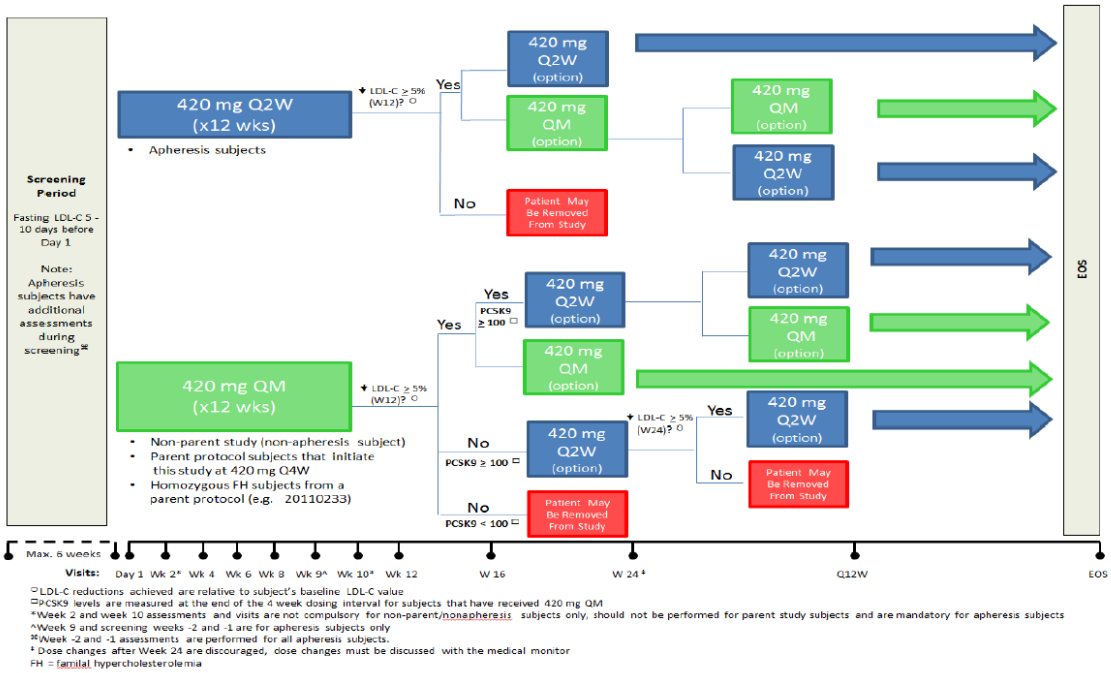
The sponsor addressed deficiencies of the CRL in this complete response using the final CSR.

The Study 20110271 was entitled as '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 – TAUSSIG'. Objectives of the study were;

- to characterize the safety and tolerability of long-term administration of AMG 145 among subjects with severe familial hypercholesterolemia
- to characterize the efficacy of long term administration of AMG 145 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 familial hypercholesterolemia

Initial dosing regimens were Q2W or QM for subjects (12-80 years of age) with or without apheresis, respectively (see Figure 1 for the study design). Dose frequency changes were permitted at week 12, 24, or other visits with approval under the following rules;

- discontinue if < 5% LDL-C reduction from baseline and serum unbound proprotein convertase subtilisin/kexin type 9 (PCSK9) < 100 ng/mL
- switch from QM to Q2W if serum unbound PCSK9 was ≥ 100 ng/mL
- switch from Q2W to QM if subjects on apheresis with ≥ 5% LDL-C reduction from baseline and serum unbound PCSK9 < 100 ng/mL



○LDL-C reductions achieved are relative to subject's baseline LDL-C value
□PCSK9 levels are measured at the end of the 4 week dosing interval for subjects that have received 420 mg QM
*Week 2 and week 10 assessments and visits are not compulsory for non-parent/nonapheresis subjects only, should not be performed for parent study subjects and are mandatory for apheresis subjects
^Week 9 and screening weeks -2 and -1 are for apheresis subjects only
※Week -2 and -1 assessments are performed for all apheresis subjects.
‡ Dose changes after Week 24 are discouraged, dose changes must be discussed with the medical monitor
FH = familial hypercholesterolemia

Figure 1 Study design and treatment scheme (Source; Figure 8-1, CSR)

Reviewer's comments

Evolocumab concentrations were increased (Figure 2) and thus PCSK9 concentrations were decreased when dosing frequency was increased (i.e., from 420 QM to 420 mg Q2W) (Figure 3). The reduction in PCSK9 was expected as the dose frequency change (QM to Q2W) was allowed for subject with a high PCSK9 concentration (i.e., ≥100 ng/mL). However, there was no apparent change in LDL-C reduction during the dosing frequency change (Figure 4). Corresponding relationships among evolucumab, PCSK9 and LDL-C concentrations in adolescent subjects with age ≥12 and <18 (n=14; 4 and 10 with and without apheresis, respectively) were similar (Figure 5, Appendix) to those of adults (n=106 HoFH; 34 and 72 with and without apheresis, respectively, and n=194 severe FH; 27 and 167 with and without apheresis).

In the clinical pharmacology review for the original BLA, it was concluded that the exposure-response relationship was already in the plateau following QM dosing based on the interim study report as follows (see Dr. Sury Sista's review for further details in DARRTS dated on June 1, 2015.);

- "*The 420 mg Q2W regimen appears to offer little additional benefit (~6% addition reduction in LDL-C) to HoFH patients. An analysis of the distribution of the average LDL-C concentrations over the duration of the treatment for (a) those patients that did not switch, (b) before the switch and (c) after the switch for those patients that changed their dosing frequency, showed that patients that did not up-titrate were responding better than those that required titration. There was a mild numerical lowering (6%) in the mean LDL-C concentrations in patients who up-titrated. At the individual level there was a sustaining of effect, but not much improvement was noted. Further, exposure-response data were not available in the HoFH populations. However, the relationship in the HeFH population suggests that the exposures from the QM dose are already in the plateau of the response curve and that dosing higher amounts will not likely provide additional benefit. From an efficacy perspective, the 420 mg Q2W regimen does not appear to offer much additional benefit and from a safety perspective, there may be an insufficient amount of data in patients who received 420 mg Q2W*."
- "*it appears that with the 420 mg Q2W dose aligned with biweekly apheresis, there is negligible evolocumab loss after apheresis, and trough levels are associated with sufficient post apheresis concentrations to maintain PCSK9 suppression*."

Additional exposure data obtained after 12 weeks in the final CSR (descriptive summary in Table 1, Appendix) supports the conclusions of exposure-response in the original BLA review. There was no new proposed labeling related to the clinical pharmacology information in this submission.

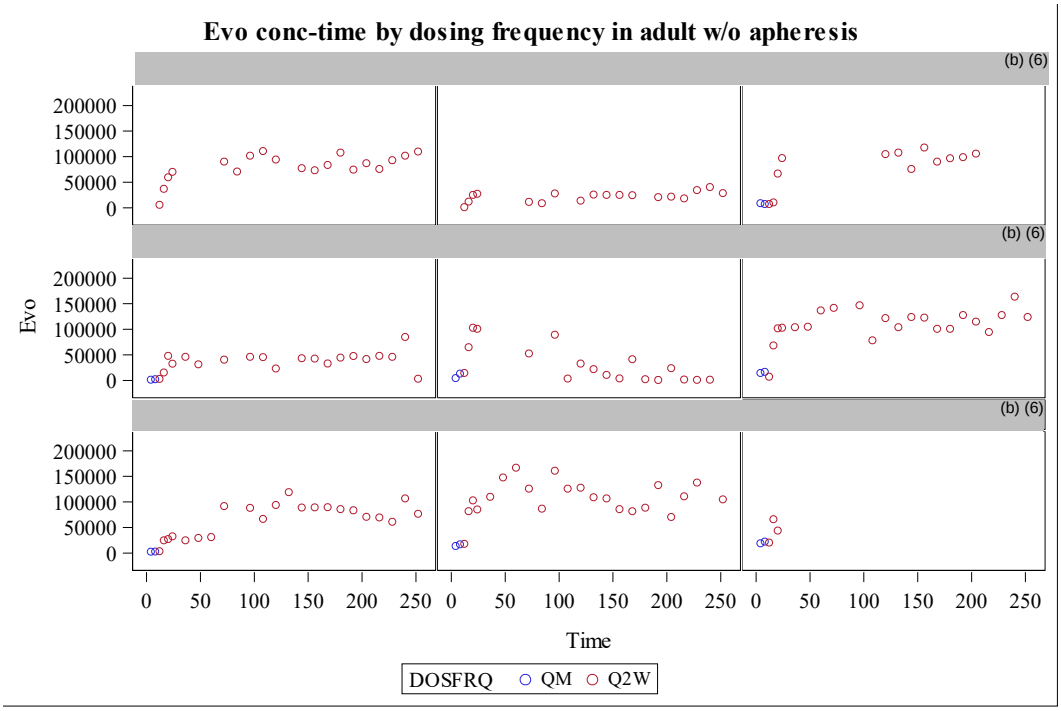


Figure 2 Evolocumab concentration (Evo, ng/mL)-time (Time in weeks) profiles over the treatment period in representative adult subjects with dosing frequency change

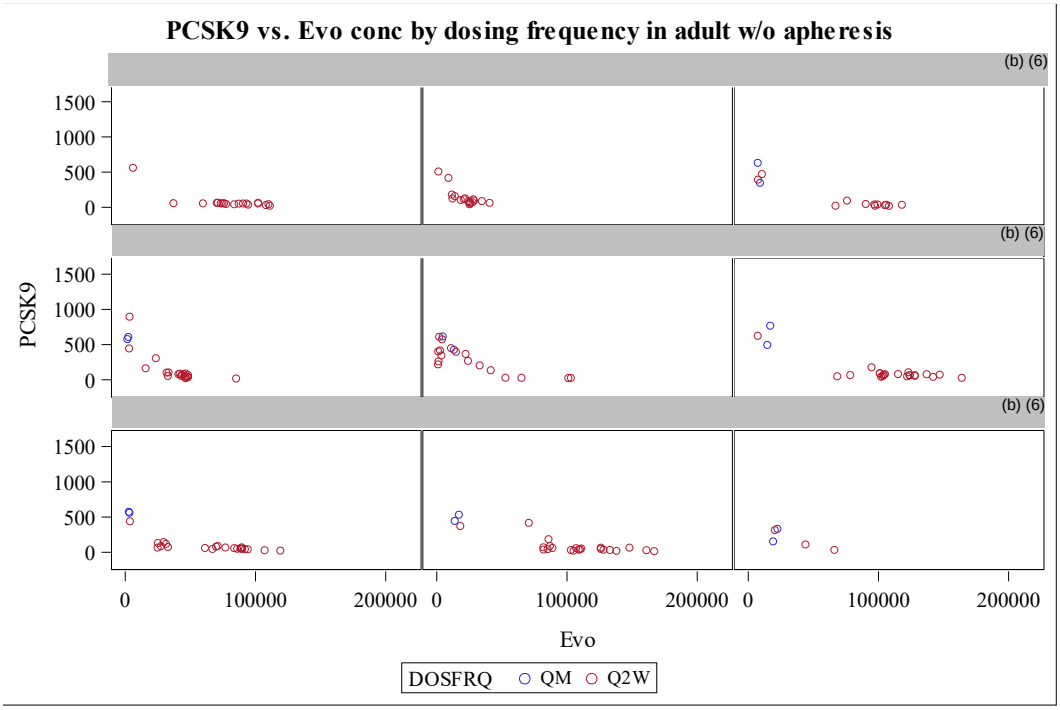


Figure 3 Relationship between PCSK9 (PCSK9, ng/mL) and evolocumab concentration (Evo, ng/mL) in representative adult subjects with dosing frequency change

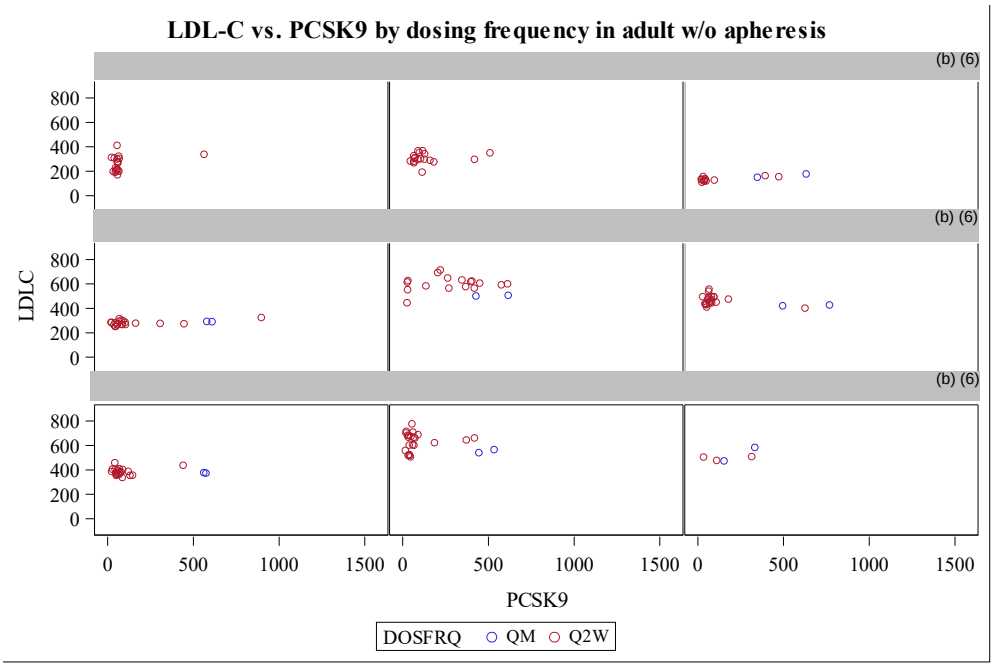


Figure 4 Relationship between LDL-C (LDLC, mg/dL) and PCSK9 (PCSK9, ng/mL) in representative adult subjects with dosing frequency change Note; it is expected a positive correlation between PCSK9 and LDL-C concentrations if the exposure-response relationship is not in the plateau.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

There are no labeling comments reflecting trial designs, results and latest labeling guidances from the clinical pharmacology perspectives:

Current labeling;

HoFH: 420 mg once monthly

Proposed labeling;

(b) (4) with HoFH:

- The initial recommended dosage of REPATHA is 420 mg once monthly administered subcutaneously.
- The dosage can be increased to 420 mg every 2 weeks if a clinically meaningful response is not achieved in 12 weeks.
- Patients on lipid apheresis may initiate treatment with 420 mg every 2 weeks to correspond with their apheresis schedule. Administer REPATHA after the apheresis session is complete.

12.1 Mechanism of Action

Evolocumab is a human monoclonal IgG2 directed against human proprotein convertase subtilisin kexin 9 (PCSK9). PCSK9 (b) (4) binds to (b) (4) the low-density lipoprotein (LDL) receptor (LDLR) on the surface of hepatocytes to promote , (b) (4) LDLR degradation within the liver (b) (4). By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.

3. APPENDICES

3.1 Complete Response Letter by the Agency dated August 27, 2015

(b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125522/ Original 2

COMPLETE RESPONSE

Amgen, Inc.
Attention: Marc Kubasak, PhD
Senior Manager, Regulatory Affairs
One Amgen Center Drive, Mail Stop 17-2-B
Thousand Oaks, CA 01320-1799

Dear Dr. Kubasak:

Please refer to your Biologics License Application (BLA) dated and received August 27, 2014, submitted under section 351(a) of the Public Health Service Act for Repatha (evolocumab), 140 mg/mL.

We acknowledge receipt of your amendments dated September 16, 23, 24, and 29, October 10, 13, 22, 23, 27, 28, and 31, November 3, 5, 24 (2), December 11 and 16 (2), and 17, 2014, and January 8, 12, and 29, February 17, and 26 (2), March 2, 5 (2), 16 (2), 24, 25, 27, and 30, April 2, 3 (2), 8, 9, 20, 21, 23, 24 (2), and 27, May 5, 7 (2), 8, 13, 14, 18, and 22 (2), June 1, 3, 4 (2), 5(2), 8, 9, 10, 15, 17, 22, 24 (2), 26, July 8, 15, and 20, August 11, 14(2), 18, 25(5), and 26(3), 2015.

BLA 125522 provides for the use of Repatha (evolocumab) for the following indications which, for administrative purposes, we have designated as follows:

- BLA 125522/Original 1 - Repatha is indicated 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, who require additional lowering of LDL-C. Repatha is also indicated 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. This application only includes a 420 mg once monthly dosing regimen for the HoFH indication.
- BLA 125522/Original 2 – Repatha is indicated 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. This application only includes a 420 mg every two weeks dosing regimen.

The subject of this action letter is BLA 125522/Original 2. A separate action letter will be issued for BLA 125522/Original 1.

All future submissions to BLA 125522/Original 1 and BLA 125522/Original 2 should specify the BLA number and the Original number to which each submission pertains.

We have completed the review of BLA 125522/Original 2, as amended, and have determined that we cannot approve this application in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

CLINICAL

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.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 601.14(b)]in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update. The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

   - Present new safety data from the studies for the proposed indication using the same format as the initial submission.
   - Present tabulations of the new safety data combined with the initial data.
   - Include tables that compare frequencies of adverse events in the initial data with the retabulated frequencies described in the bullet above.

- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the initial data.

6. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before BLA 125522/Original 2 may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf

The drug product may not be legally marketed for the 420 mg dose administered every 2 weeks in patients with homozygous familial hypercholesterolemia who require additional lowering of LDL-C until you have been notified in writing that this application is approved.

If you have any questions, call Kati Johnson, Senior Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Table 1 Descriptive Statistics of Serum Unbound Evolocumab Concentration-Time Data (Source; Table 11-2, CSR)

Evolocumab 420 mg QM in subjects with HoFH

	Nominal Time (week)															
Subject	DAY 1 pre	WEEK 2	WEEK 4 pre	WEEK 6	WEEK 8 pre	WEEK 10	WEEK 12 pre	WEEK 16 pre	WEEK 20 pre	WEEK 24 pre	WEEK 36 pre	WEEK 48 pre	WEEK 60 pre	WEEK 72 pre	WEEK 84 pre	WEEK 96 pre
N	21	6	56	58	60	9	72	70	71	68	65	65	64	62	62	62
Mean	0.00	37.1	8.59	34.9	12.7	54.3	13.1	36.3	44.3	52.5	52.9	67.1	64.6	66.9	63.5	82.3
SD	0.00	14.9	6.73	19.4	10.8	18.4	10.8	29.7	36.9	45.9	39.3	55.7	54.4	54.0	52.2	72.8
Min	0.00	22.4	0.981	1.71	0.00	22.9	0.00	0.00	0.837	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Median	0.00	33.6	6.19	31.4	9.71	48.3	10.4	25.8	32.5	37.6	49.1	57.3	58.5	61.1	68.8	81.6
Max	0.00	64.9	31.1	82.6	52.8	80.0	47.9	109	137	211	139	187	203	232	219	288
CV%	NR	40.1	78.4	55.6	84.9	33.8	82.6	81.9	83.2	87.4	74.3	83.0	84.3	80.7	82.2	88.4

	Nominal Time (week)												
Subject	WEEK 108 pre	WEEK 120 pre	WEEK 132 pre	WEEK 144 pre	WEEK 156 pre	WEEK 168 pre	WEEK 180 pre	WEEK 192 pre	WEEK 204 pre	WEEK 216 pre	WEEK 228 pre	WEEK 240 pre	WEEK 252 pre
N	62	61	61	61	60	57	55	55	53	41	30	23	21
Mean	66.9	62.0	66.8	64.3	63.7	67.2	61.8	63.0	60.0	65.0	70.4	92.3	74.7
SD	55.6	54.8	55.8	65.1	56.7	56.7	49.1	50.3	51.1	52.1	51.9	63.6	49.1
Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Median	56.8	57.8	59.1	55.8	61.5	67.3	67.1	54.7	49.3	65.0	70.3	90.5	76.9
Max	242	270	189	380	243	244	167	172	212	196	166	228	145
CV%	83.1	88.4	83.5	101.3	89.0	84.4	79.4	79.9	85.1	80.3	73.7	68.9	65.7

Evolocumab 420 mg Q2W in subjects with HoFH

Subject	Nominal Time (week)															
	DAY 1 pre	DAY 1 post	WEEK 2 pre	WEEK 2 post	WEEK 4 pre	WEEK 4 post	WEEK 6 pre	WEEK 6 post	WEEK 8 pre	WEEK 8 post	WEEK 9 post	WEEK 10 pre	WEEK 10 post	WEEK 12 pre	WEEK 12 post	WEEK 16 pre
N	34	34	33	33	32	31	34	31	34	30	29	34	30	34	28	32
Mean	0.00	0.00	33.5	23.0	51.3	33.1	60.3	41.6	68.5	48.9	106	69.2	49.3	76.0	56.7	71.2
SD	0.00	0.00	16.7	12.7	23.9	16.3	24.4	21.9	26.7	22.5	26.0	25.2	22.3	32.2	29.2	36.7
Min	0.00	0.00	5.86	4.49	15.6	9.48	11.3	10.1	17.0	12.3	70.3	11.6	9.48	10.1	8.63	19.8
Median	0.00	0.00	33.1	20.5	47.3	30.7	59.1	39.1	60.8	45.0	98.6	64.8	43.7	78.8	54.0	63.4
Max	0.00	0.00	82.2	62.5	129	81.6	109	102	119	96.1	163	117	101	140	116	145
CV%	NR	NR	49.7	55.0	46.6	49.3	40.5	52.7	39.1	46.0	24.4	36.4	45.3	42.3	51.5	51.6

Subject	Nominal Time (week)															
	WEEK 16 post	WEEK 20 pre	WEEK 20 post	WEEK 24 pre	WEEK 24 post	WEEK 36 pre	WEEK 36 post	WEEK 48 pre	WEEK 48 post	WEEK 60 pre	WEEK 60 post	WEEK 72 pre	WEEK 72 post	WEEK 84 pre	WEEK 84 post	WEEK 96 pre
N	27	30	26	31	27	29	26	27	23	25	21	23	17	20	17	20
Mean	54.2	69.4	54.7	73.7	60.6	69.8	54.7	71.9	53.8	67.2	48.1	53.7	47.3	71.7	52.8	65.4
SD	34.6	41.3	35.4	42.6	34.6	41.7	36.7	45.2	38.6	44.8	38.7	51.9	50.8	66.5	54.1	48.9
Min	11.6	11.6	7.83	0.00	11.8	7.07	5.31	9.84	7.02	2.00	1.53	0.00	0.00	0.00	0.00	0.00
Median	45.9	64.9	48.8	64.2	58.0	82.8	54.4	66.7	43.3	61.4	45.3	47.7	24.6	58.2	34.9	63.3
Max	159	151	113	166	123	154	119	185	142	144	134	175	151	268	206	162
CV%	63.9	59.6	64.8	57.8	57.1	59.8	67.2	62.8	71.7	66.7	80.4	96.6	107.3	92.8	102.3	74.8

Subject	Nominal Time (week)										
	WEEK 96 post	WEEK 108 pre	WEEK 108 post	WEEK 120 pre	WEEK 120 post	WEEK 132 pre	WEEK 132 post	WEEK 144 pre	WEEK 144 post	WEEK 156 pre	WEEK 156 post
N	17	19	17	19	16	18	15	17	13	18	14
Mean	51.4	66.4	43.8	73.7	44.6	63.5	43.2	68.5	49.7	76.9	51.2
SD	41.4	49.5	39.2	50.2	40.0	47.7	36.9	45.9	43.1	52.5	40.8
Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	4.83	3.75	7.46	8.40
Median	42.0	53.3	24.7	58.9	24.8	54.6	34.2	59.8	32.2	64.8	30.3
Max	108	136	109	147	117	167	118	143	121	155	129
CV%	80.5	74.6	89.4	68.1	89.9	75.1	85.5	67.1	86.7	68.3	79.6

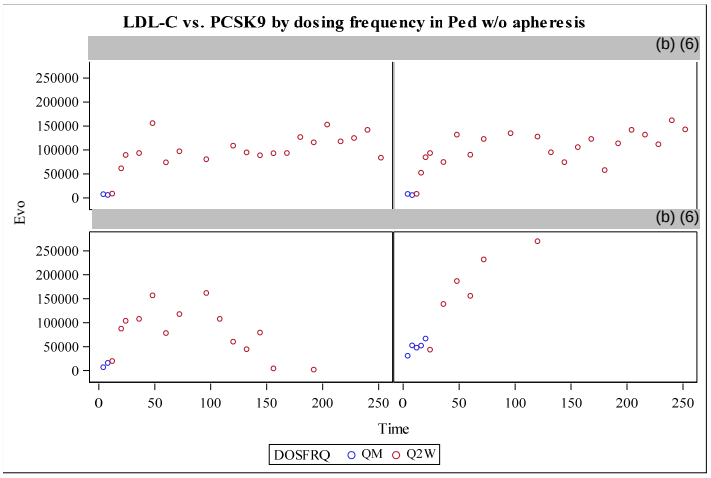
Subject	Nominal Time (week)										
	WEEK 168 pre	WEEK 168 post	WEEK 180 pre	WEEK 180 post	WEEK 192 pre	WEEK 192 post	WEEK 204 pre	WEEK 204 post	WEEK 216 pre	WEEK 216 post	WEEK 228 pre
N	17	10	19	14	18	12	17	11	14	10	10
Mean	75.8	63.9	68.8	56.2	75.8	51.5	63.6	44.4	52.2	38.2	55.2
SD	50.4	43.0	46.2	41.0	59.2	44.1	57.6	45.7	46.7	36.7	38.9
Min	5.49	7.33	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Median	67.8	62.8	79.9	55.1	75.4	38.3	44.5	28.4	44.9	29.2	48.0
Max	159	136	141	112	197	127	162	120	142	111	105
CV%	66.6	67.2	67.1	73.0	78.1	85.7	90.6	102.7	89.5	96.0	70.4

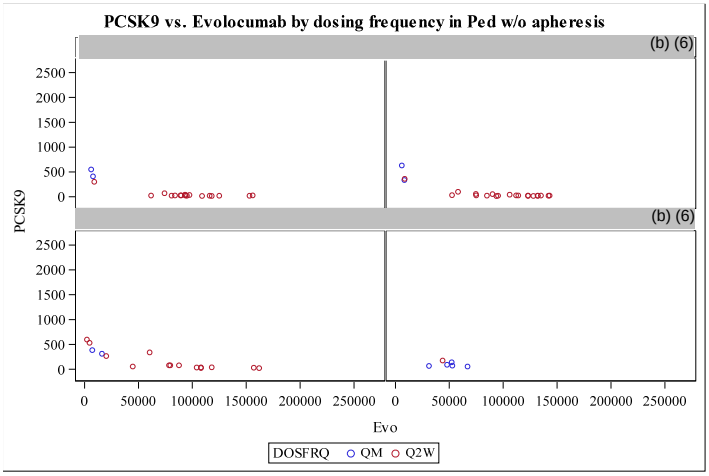
Evolocumab 420 mg QM in subjects with Non-HoFH Severe FH

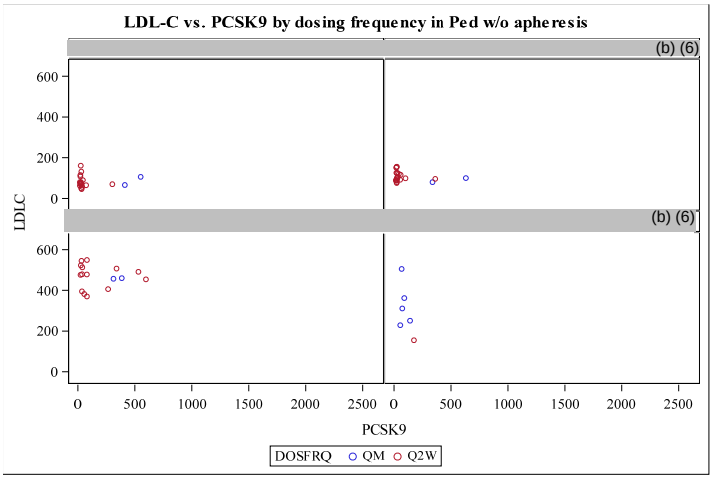
Subject	Nominal Time (week)																
	SCREENING	DAY 1 pre	WEEK 2	WEEK 4 pre	WEEK 6	WEEK 8 pre	WEEK 10	WEEK 12 pre	WEEK 16 pre	WEEK 20 pre	WEEK 24 pre	WEEK 36 pre	WEEK 48 pre	WEEK 60 pre	WEEK 72 pre	WEEK 84 pre	WEEK 96 pre
N	2	158	46	163	152	160	42	162	161	161	165	163	160	162	162	161	157
Mean	0.00	0.00	27.8	4.89	29.8	7.71	35.8	10.5	12.3	14.3	14.4	17.0	20.0	20.5	19.7	21.8	24.3
SD	NR	0.00	13.9	5.22	20.7	8.55	19.1	11.0	15.4	19.5	18.9	20.9	22.7	27.0	21.1	25.5	27.7
Min	0.00	0.00	5.34	0.00	1.11	0.00	2.78	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Median	0.00	0.00	26.2	3.09	26.9	5.13	31.8	6.92	7.04	8.17	7.97	9.53	12.1	12.1	12.6	13.2	13.9
Max	0.00	0.00	57.6	34.9	122	55.0	82.6	69.0	104	117	113	99.4	126	174	101	124	119
CV%	NR	NR	50.0	106.7	69.3	110.9	53.2	104.7	125.6	136.6	131.1	123.3	113.7	132.1	107.0	116.9	113.9

Subject	WEEK 108 pre	WEEK 120 pre	WEEK 132 pre	WEEK 144 pre	WEEK 156 pre	WEEK 168 pre	WEEK 180 pre	WEEK 192 pre	WEEK 204 pre	WEEK 216 pre	WEEK 228 pre	WEEK 240 pre	WEEK 252 pre	EOS Post 12 Weeks
N	156	161	160	159	158	146	136	118	107	13	7	3	3	149
Mean	22.7	22.5	20.8	22.6	23.4	21.2	24.0	23.1	23.0	17.5	18.2	12.4	22.9	19.3
SD	26.8	25.2	24.9	25.6	26.7	23.5	25.9	24.9	25.2	23.1	16.4	17.8	28.8	21.3
Min	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.57	1.98	1.10	0.00
Median	11.9	13.8	12.7	12.7	12.8	13.2	15.1	14.8	14.4	14.4	19.2	2.30	12.0	12.0
Max	117	107	137	142	140	110	121	134	136	86.6	46.6	33.0	55.5	102
CV%	117.9	112.0	119.4	113.3	114.2	110.7	108.0	107.8	109.4	131.8	89.8	143.4	125.9	110.8

Figure 5 Representative profiles of evolocumab (ng/mL)-time (week) (upper), PCSK9 (ng/mL) vs. evolocumab (ng/mL) (middle), and LDL-C (LDLC, mg/dL) vs PCSK9 (PCSK9, ng/mL) in adolescent subjects with dosing frequency change







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/s/

SANG M CHUNG
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