

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125522Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	August 27, 2015
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	125522
Applicant Name	Amgen
Proprietary / Established (USAN) Names	Repatha Evolocumab
Dosage Forms / Strength	Subcutaneous (SC) injection 140 mg SC every 2 weeks or 420 mg SC every month
Proposed Indication(s)	Lipid-altering therapy: (1) Primary hyperlipidemia/Mixed Dyslipidemia: to reduce LDL-C, TC, ApoB, non-HDL-C, TC/HDL-C, ApoB/ApoA1, VLDL-C, TG and Lp[a], and to increase HDL-C and ApoA1 in combination with other lipid lowering therapies and as monotherapy; (2) HoFH: to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies
Action:	<i>Approval</i>

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding evolocumab and I refer the reader to the other reviews in the action package for a more detailed discussion. Evolocumab is a human monoclonal immunoglobulin that binds to human proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a protein that binds to low-density lipoprotein receptor (LDLR) inducing LDLR degradation. The LDLR degradation results in decreased metabolism of low-density lipoprotein cholesterol (LDL-C). Therefore, evolocumab targets and inactivates PCSK9 which ultimately results in increased cell surface LDLR levels and increased removal of LDL-C from the blood. Evolocumab is the second monoclonal immunoglobulin product to have a regulatory action as Praluent (alirocumab), which also binds PCSK9, has recently been approved.

Presently, the agency accepts that drug-induced reduction in LDL-C is a surrogate for reduction of risk of cardiovascular (CV) ischemic events. The validity of LDL-C reduction as a surrogate for CV reduction has been demonstrated repeatedly for statins in numerous cardiovascular outcome trials (CVOTs). However, the use of LDL-C as a surrogate for non-statin drugs has been somewhat controversial. A CVOT evaluation of torcetrapib, a cholesteryl ester transfer protein inhibitor which reduced LDL-C by 25%, demonstrated an increase in CV events.¹ These results caused speculation as to whether decreasing LDL-C was predictive for all classes of agents besides statins as some have speculated that statins may have pleomorphic effects other than LDL-C lowering accounting for CV benefit, or, if a drug could have off-target effects that

¹ Barter PJ, et al. N Engl J Med 2007;357:2109-22

would circumvent the salutatory effect one might expect from lowering LDL-C. The results of the torcetrapib trial were then followed by two trials for ezetimibe (ENHANCE, SEAS) where predicted effects, either on objective CV endpoints or other surrogate markers felt to predict CV benefit, were not demonstrated.^{2, 3} However, the controversy surrounding ezetimibe may have been tempered somewhat with the published results of the IMPROVE-IT trial demonstrating CV benefit of an amount commensurate with the amount of LDL-C decrease as demonstrated in numerous statin trials.⁴ Therefore, for this program, while it was agreed that use of LDL-C as a surrogate would allow for review of an application, the magnitude of benefit on clinical outcomes may be uncertain. This will be discussed further in the summary section.

In the six phase 3 pivotal studies, evolocumab reduced LDL-C compared to control (ezetimibe or placebo). In the non-HoFH populations, the reductions in LDL-C were statistically significant and 37% to 47% greater compared to ezetimibe and 55% to 76% greater compared to placebo. The findings were consistent across different populations and background therapies. The amount of LDL-C lowering demonstrated by evolocumab is impressive and is in the same range as that demonstrated by high-dose statin agents. Should this amount of LDL-C decrease correlate to CV benefit as demonstrated by statins (commonly quoted as 22% reduction in major vascular events per 40 mg/dL reduction), drugs in the PCSK9 category have the potential to be very important additions from a public health perspective, welcomed by practitioners, and beneficial to patients. Evolocumab also demonstrated statistically significant decreases in LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) of 31% compared to placebo.

The safety evaluation of evolocumab has not revealed any concerning signals that would prohibit approval. However, considering that this could be life-long therapy in millions of patients, there also has not been a great deal of exposure either in terms of numbers of unique patients or length of exposure. Therefore, completion of the ongoing cardiovascular outcome trial (CVOT) will be quite welcomed and necessary [REDACTED] (b) (4)

The review team is recommending approval, and I agree.

Efficacy

This has been thoroughly covered in reviews authored by Drs. Sinks, Craig and Smith. Four 12-week trials and one 52-week trial were submitted to support the primary hyperlipidemia indication. One open-label, 8-patient pilot study (Part A) followed by a randomized, double-blind placebo-controlled trial (Part B), was submitted to support the safety and efficacy of evolocumab compared with placebo in subjects with HoFH. The particulars of each trial for evolocumab (known as AMG during development) are summarized in the table below from Dr. Sinks' review (Page 9).

² Kastelein JJP, et al. N Engl J Med 2008; 358:1431-43.

³ Rossebo AB, et al. N Engl J Med 2008; 359:1343-56.

⁴ Cannon CP, et al. N Engl J Med 2015; 372:2387-97.

Table 1 Summary of Study Designs and Endpoints

Trial No.	Study Population	Phase and Design	Primary Endpoint	# of subjects per Arm	Treatment period
Indication: Primary Hyperlipidemia or Mixed Dyslipidemia					
20110114	Subjects with a 10-year Framingham risk score of 10% or less	Phase 3, R, DB, DD, PG, placebo and ezetimibe-controlled, multicenter	Co-primary endpoints: Percent change from baseline in LDL-C at Week 12; Mean percent change from baseline in LDL-C at weeks 10 and 12	AMG 145 140mg Q2W and PO QD (n=153); AMG 145 420mg QM and PO QD (n=153); Placebo SC Q2W and 10mg ezetimibe QD (n=77); Placebo SC QM and 10mg ezetimibe QD (n=77); Placebo SC Q2W and PO QD (n=77); Placebo SC QM and PO QD (n=78)	12 weeks
20110115	Subjects with hyperlipidemia	Phase 3, R, DB, DD, placebo and ezetimibe-controlled, multicenter, with statin background therapy	Co-primary endpoints: Same as above	2 step randomization: Atorvastatin 80mg (n=439), Atorvastatin 10mg (n=442), Rosuvastatin 40mg (n=310), Rosuvastatin 5mg (n=343), Simvastatin 40mg (n=295). For each statin dose cohort and dose frequency, the allocation ratio is approximately 2:1 for AMG 145 vs control (see details in Table 3)	12 weeks
20110116	Hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor	Phase 3, R, DB, DD, PG, ezetimibe-controlled	Co-primary endpoints: Same as above	AMG 145 140mg SC Q2W and PO QD (n=103); AMG 145 420 mg SC QM and PO QD (n=102); Placebo SC Q2W and ezetimibe 10mg QD (n=51); Placebo SC QM and ezetimibe 10mg QD (n=51)	12 weeks
20110117	HeFH on a stable dose of a statin	Phase 3, R, DB, PG, placebo-controlled, multicenter	Co-primary endpoints: Same as above	AMG 145 140 Q2W (n=110); AMG 145 420mg QM (n=110); Placebo Q2W (n=54); Placebo QM (n=55)	12 weeks
20110109	Subjects with hyperlipidemia	Phase 3, R, DB, placebo-controlled, multicenter	Percent change in LDL-C from baseline at week 52	AMG 145 420mg QM (n=599); Placebo QM (n=302)	52 weeks
Indication: Homozygous Familial Hypercholesterolemia (HoFH)					
20110233	Subjects with homozygous familial hypercholesterolemia	Part A (phase 2): open label, single arm, multicenter pilot study; Part B (phase 3): R, DB, placebo-controlled	Percent change in LDL-C from baseline at week 12	Part B: AMG 145 420 mg QM (n=34), placebo QM (n=17)	12 weeks

R-randomized; DB - double-blind; PG- parallel group; DD - double-dummy; Q2W - every 2 weeks; QM - every month; PO - placebo oral; QD- Daily; SC - subcutaneous
 Note that 20110109 was a phase 2 study which Amgen re-classified as a phase 3 study

Below are a series of tables from Dr. Sinks' review demonstrating efficacy in the four 12-week studies and one 52-week study in the primary hyperlipidemia studies (Pages 14-18).

Table 2 Primary Analysis of Percent Change in Reflexive LDL at Week 12 in Studies 20110114, 20110116, and 20110117

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach		
				LS Mean: % Change	Difference: Evolocumab -control (95% [†] CI)	LS Mean: % Change	Difference: Evolocumab -control (95% [†] CI)	
20110114—Monotherapy								
Every 2 weeks (Q2W) [†]								
AMG 145 SC Q2W 140 MG + PO QD	142	153	133	-57		-54		
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	143	77	70	-18	-39 (-43,-35)	-18	-36 (-41,-32)	
PLACEBO SC Q2W + PLACEBO PO QD	140	76	69	-0	-57 (-61,-53)	-0	-54 (-59,-49)	
Monthly (QM) [†]								
AMG 145 SC QM 420 MG + PO QD	144	153	136	-56		-55		
PLACEBO SC QM + EZETIMIBE QD 10 MG	144	77	69	-19	-38 (-41,-34)	-19	-37 (-41,-32)	
PLACEBO SC QM + PLACEBO PO QD	144	78	70	-1	-55 (-58,-51)	-1	-54 (-59,-50)	
20110116—In "statin-intolerant" subjects								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG + PO QD	192	103	98	-56		-55		
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	195	51	49	-18	-38 (-44,-33)	-18	-37 (-42,-31)	
Monthly (QM)								
AMG 145 SC QM 420 MG + PO QD	192	102	96	-53		-53		
PLACEBO SC QM + EZETIMIBE QD 10 MG	195	51	45	-15	-37 (-42,-32)	-16	-37 (-42,-31)	
20110117—In HeFH subjects on a stable dose of a statin								
Every 2 weeks (Q2W)								
AMG 145 SC Q2W 140 MG	161	110	104	-61		-61		
PLACEBO SC Q2W	151	54	51	-2	-59 (-65,-53)	-2	-59 (-66,-52)	
Monthly (QM)								
AMG 145 SC QM 420 MG	154	110	103	-56		-56		
PLACEBO SC QM	152	55	46	5	-61 (-69,-55)	4	-60 (-67,-53)	

Note: [†] 97.5% CL for study 20110114; N- number of subjects with baseline data; N* --- number of subjects with week 12 data
Q2W - every 2 weeks; QM - every month; PO - placebo oral; QD - Daily; SC - subcutaneous

Table 3 Primary Analysis of Percent Change in Reflexive LDL at Week 12 in Study 20110115

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab -control (95% † CI)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
20110115--ATORVASTATIN 10MG ADD-ON							
Every 2 weeks (Q2W) †							
AMG 145 SC Q2W 140 MG + PO QD	124	110	103	-62		-60	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	127	56	49	-22	-40 (-47,-32)	-20	-40 (-47,-33)
PLACEBO SC Q2W + PO QD	123	56	51	10	-71 (-78,-64)	9	-69 (-76,-62)
Monthly (QM) †							
AMG 145 SC QM 420 MG + PO QD	126	110	101	-58		-56	
PLACEBO SC QM + EZETIMIBE QD 10 MG	119	55	52	-17	-41 (-49,-33)	-18	-39 (-46,-32)
PLACEBO SC QM + PO QD	124	55	51	1	-59 (-67,-51)	0	-57(-64,-49)
20110115--ATORVASTATIN 80MG ADD-ON							
Every 2 weeks (Q2W) †							
AMG 145 SC Q2W 140 MG + PO QD	94	109	102	-62		-61	
PLACEBO SC Q2W + EZETIMIBE QD 10 MG	99	56	50	-15	-47 (-59,-35)	-14	-46 (-57,-36)
PLACEBO SC Q2W + PO QD	100	55	46	14	-76 (-88,-64)	12	-72 (-83,-62)
Monthly (QM) †							
AMG 145 SC QM 420 MG + PO QD	94	110	100	-59		-57	
PLACEBO SC QM + EZETIMIBE QD 10 MG	92	54	52	-20	-39 (-50,-28)	-20	-38 (-48,-28)
PLACEBO SC QM + PO QD	95	55	51	12	-71 (-81,-60)	12	-69 (-79,-59)
20110115--ROSUVASTATIN 40MG ADD-ON							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	89	102	95	-57		-55	
PLACEBO SC Q2W	77	53	50	10	-68 (-77,-58)	7	-62 (-72,-52)
Monthly (QM)							
AMG 145 SC QM 420 MG	87	104	98	-52		-52	
PLACEBO SC QM	104	51	47	2	-55 (-66,-44)	1	-54 (-63,-44)
20110115--ROSUVASTATIN 5MG ADD-ON							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	119	113	100	-60		-56	
PLACEBO SC Q2W	116	58	52	8	-68 (-75,-62)	7	-63 (-71,-56)
Monthly (QM)							
AMG 145 SC QM 420 MG	123	115	104	-59		-57	

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab -control (95% † CI)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
PLACEBO SC QM	120	57	55	5	-64 (-71,-58)	5	-63 (-70,-55)
20110115--SIMVASTATIN 40MG ADD-ON							
Every 2 weeks (Q2W)							
AMG 145 SC Q2W 140 MG	114	98	95	-65		-63	
PLACEBO SC Q2W	110	49	45	5	-70 (-76,-63)	4	-67 (-76,-59)
Monthly (QM)							
AMG 145 SC QM 420 MG	124	99	90	-56		-54	
PLACEBO SC QM	109	49	43	4	-60 (-69,-51)	4	-58 (-67,-50)

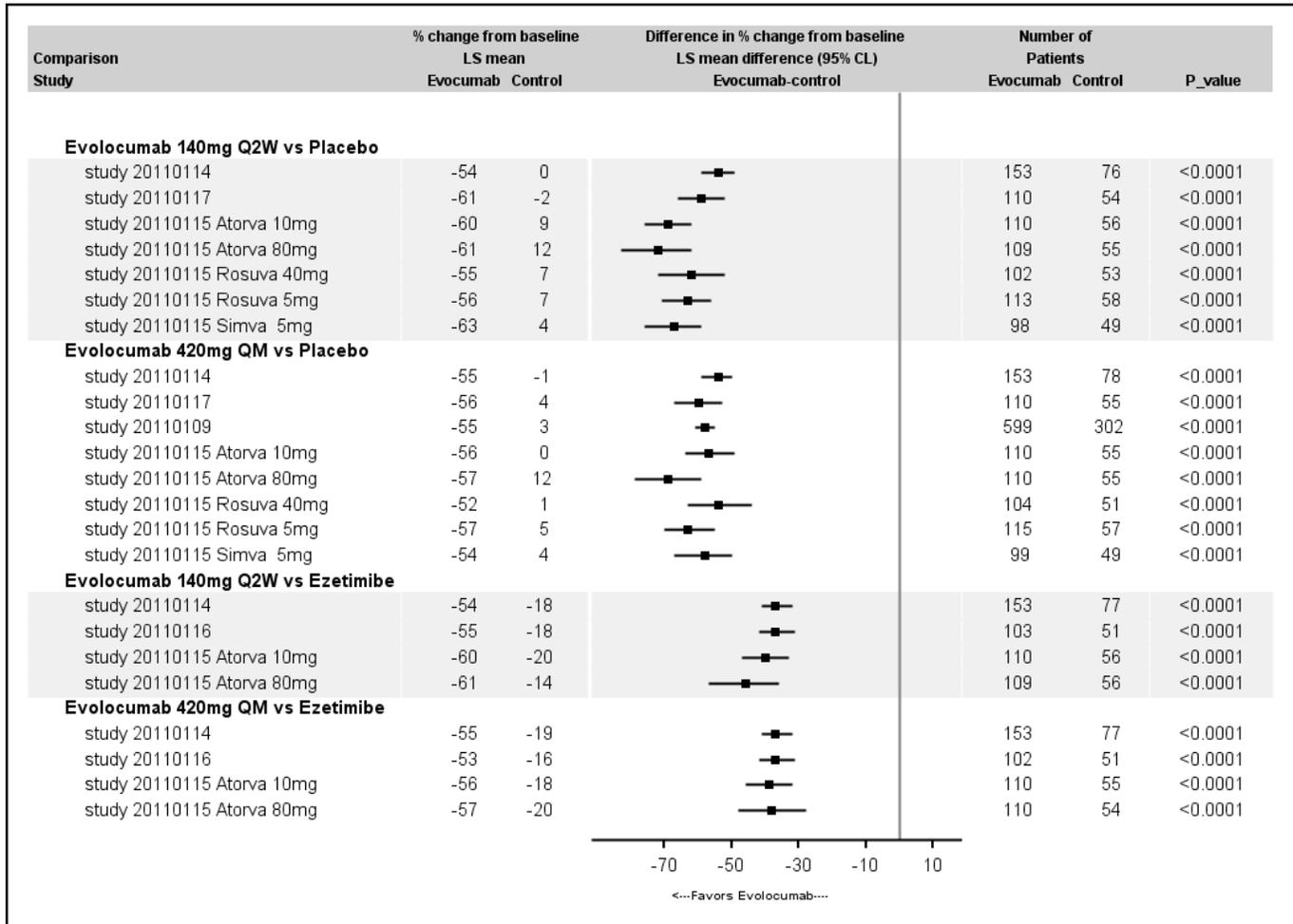
Note: † 97.5 CL for atorvastatin cohorts; N- number of subjects with baseline data; N* --- number of subjects with week 12 data
Q2W - every 2 weeks; QM - every month; PO - placebo oral; QD - Daily; SC - subcutaneous

Table 4 Primary Analysis of Ultracentrifugation LDL Percent Change in Study 20110109 (Long-term study: 52 weeks)

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab -control (95% CI)	LS Mean: % Change	Difference: Evolocumab -control (95% † CL)
20110109							
Week 12							
AMG 145 SC QM 420 MG	104	599	582	-54		-53	
PLACEBO SC QM	104	302	294	-4	-58 (-61,-54)	4	-56 (-59,-53)
Primary endpoint: Week 52							
AMG 145 SC QM 420 MG	104	599	542	-50		-55	
PLACEBO SC QM	104	302	264	7	-57 (-61,-53)	3	-58(-61,-55)

N* --- number of subjects with week 12 or week 52 data; QM - every month; SC - subcutaneous

Figure 1 Summary of Primary Analysis Results (FAS; Based on FDA’s Approach)



Secondary endpoints of non-LDL-C biomarkers tested generally reflected theoretical favorable changes. The ability of the changes of non-LDL-C secondary endpoints to predict clinical benefit has not been proven.

One study was conducted in HoFH subjects. The results are presented in the table and graph from Dr. Sinks’ review (Page 22).

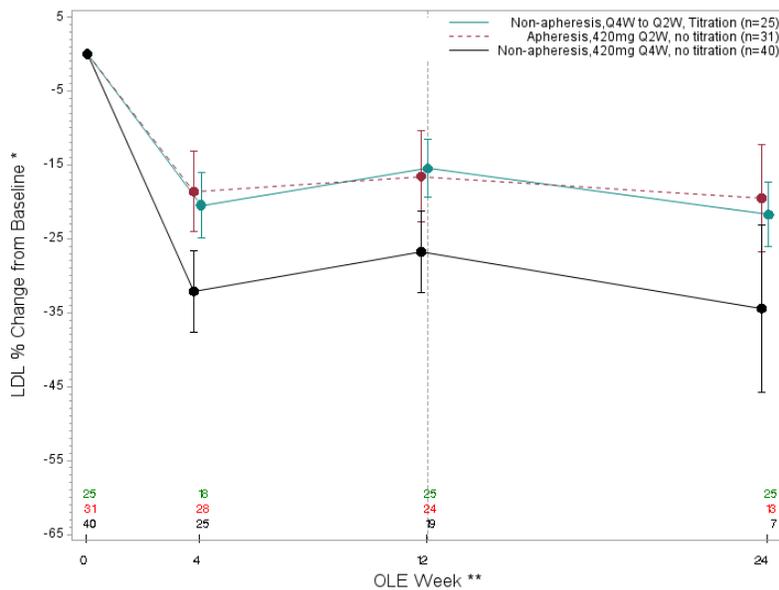
Table 5 Primary Analysis of Percent Change in UC LDL at Week 12

	Baseline (mg/dL)	N	N*	Applicant’s Approach		FDA’s Approach	
				LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
20110233 –HoFH							
FAS (N=49)							
AMG 145 SC QM 420 MG	356	33	29	-23		-22	
PLACEBO SC QM	336	16	15	8	-31 (-44,-18)	8	-30 (-42, -16)

	Baseline (mg/dL)	N	N*	Applicant's Approach		FDA's Approach	
				LS Mean: % Change	Difference: Evolocumab-control (95% CL)	LS Mean: % Change	Difference: Evolocumab-control (95% CL)
Subgroup: LDLR indeterminate or negative (N=21)							
AMG 145 SC QM 420 MG	331	13	11	-11		-13	
PLACEBO SC QM	235	8	7	5	-16 (-41,9)	6	-20 (-47,7)
Subgroup LDLR-defective (N=28)							
AMG 145 SC QM 420 MG	372	20	18	-30		-27	
PLACEBO SC QM	437	8	8	11	-41 (-53,-28)	11	-37 (-52,-21)

N*-- number of subjects with week 12 data; QM - every month; SC – subcutaneous

Figure 2 Percent Change of LDL over Time among HoFH



* Baseline refers to previous study baseline or OLE baseline for new enrollees
 ** Does not correspond to # of weeks on treatment with study medication

One patient identified as LDLR-negative did not show a reduction in LDL-C. The estimated effect of evolocumab was greater in the LDLR-defective group than the LDLR-indeterminate or –negative group. Based on FDA’s analysis approach, the LDL-C reduction was 30% greater on evolocumab, with 95% confidence interval (-42, -16). The estimated mean percent change for evolocumab was -22%, and for the placebo group was 8%. In subset of participants who had minimal reductions in LDL-C with 420mg every month, increasing the dosing frequency from 420 mg every month to every two weeks resulted in approximately 6% greater reduction of LDL-C. However, whether this change represents a true finding has been question by the review team. (b) (4)

The trials above demonstrated efficacy and were conducted in heterogeneous and different populations. As an example, populations included low CV risk not on background statin therapy, higher risk on background statin therapy, HeFH, what the sponsor has termed 'statin-intolerant', and HoFH. Evolocumab provided additional LDL-C lowering of varying degree in all populations studied. Dosing of 140 mg every two weeks and 420 mg every month both proved efficacious with about the same amount of mean reduction, although the pharmacodynamics pattern was different in that the monthly dose resulted in a 'sawtooth' pattern of LDL-C change compared to a relatively stable reduction with every two week dosing.

Evolocumab resulted in LDL-C reductions of approximately 60% compared to placebo in all trials except for HoFH. In those with HoFH, reductions of approximately 30% were demonstrated compared to placebo. If this amount of LDL decrease ultimately is proven to result in CV benefit as may be predicted by statin CVOTs, this will be a valuable addition to drug therapy.

Safety

There were 5416 subjects exposed to any dose of evolocumab with 1824 subjects exposed for at least 12 months, and 614 exposed for two years or more. There were limited numbers of deaths and nonfatal serious adverse events. Those that occurred did so more often in the evolocumab group, but the numbers were too small to draw any conclusions.

There were slightly increased numbers of common adverse events of nasopharyngitis, upper respiratory tract infection, back pain and nausea in evolocumab treated subjects compared to those on placebo or comparator.

There were seven participants with 8 events of pancreatitis. Six of the events occurred in participants receiving evolocumab.

In the long term safety study, there was a slight increase in the incidence of new onset diabetes in subjects receiving evolocumab with impaired fasting glucose, but not in those with normoglycemia, compared to placebo.

In the integrated trials, there was a slight increase in neurocognitive adverse events in the control group (0.3%) compared to those receiving evolocumab (0.1%). The converse was noted in the first year of the open-label safety study for evolocumab, (0.6%) compared to control group (0.2%).

There was a limited incidence of hypersensitivity. No subjects developed neutralizing antibodies. The incidence of injection site reaction was low (approximately 3% across studies).

Advisory Committee Meeting

An advisory Committee meeting was held on June 10, 2015. When asked whether the applicant had sufficiently established that the LDL-C lowering benefit of evolocumab exceeded its risk to support approval in one or more patient populations, the committee voted 11 ‘yes’ and 4 ‘no’. Those voting ‘no’ mostly felt the trials were too short and small to adequately assess safety and some felt uncomfortable, that while the sponsor was voluntarily conducting a CVOT, there was not a regulatory option of requiring a CVOT with efficacy as the goal. Those voting ‘yes’ felt the efficacy to safety considerations were appropriate for patients populations with HeFH, high CV risk or secondary prevention prior to completion of a CVOT.

Regarding approval for HoFH, the committee voted 15 ‘yes’ and 0 ‘no’.

2. Conclusions and Recommendations

Evolocumab was effective in decreasing LDL-C by amounts that are reminiscent of those demonstrated by high-dose statins without any overt disturbing safety signals. However, LDL-C is being used as a surrogate for presumed CV benefit. For the statin class, the validity of LDL-C as a surrogate to predict benefit of CV outcomes has been proven by several different statins and different CVOTs to be sturdy with uniformly predictable decreases in CV events with given amounts of LDL-C lowering. However, there has been some caution regarding whether this can be extrapolated to all drug classes. There are good reasons for this concern as noted with the torcetrapib experience. Torcetrapib is not an isolated case either as similar unanticipated results have been seen with drugs that lowered LDL-C yet either did not have a salutatory effect or caused harm (niacin, estrogen plus progestin).^{5,6} Whether these disparate results are due to off-site effects of the non-statin drugs, or pleomorphic effects of statins is unknown, although the published results of IMPROVE-IT may suggest the former.

If PCSK9 drugs were demonstrated to decrease CV events commensurate with changes in LDL-C as demonstrated by the multiple trials in statin drugs (without the discovery of some unknown consequential severe adverse event), the potential impact to public health and individual patients could be substantial. It therefore seems reasonable to allow access of evolocumab to those most in need (e.g. HeFH, HoFH, secondary prevention).

Therefore I believe this application should receive an approval action with appropriate labeling.

⁵ Landray MJ, et al. N Engl J Med 2014; 3:203-212.

⁶ Rossouw JE, et al. JAMA 2002; 288:32133.

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/s/

CURTIS J ROSEBRAUGH
08/27/2015