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RESEARCH**

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Deputy Director Decisional Memo

Date	July 24, 2014
From	Mary H. Parks, MD
Subject	Office Deputy Director Decisional Memo
NDA/BLA #	125559
Supplement #	
Applicant Name	Sanofi
Date of Submission	November 24, 2014
PDUFA Goal Date	July 24, 2015
Proprietary Name / Established (USAN) Name	Praluent (alirocumab)
Dosage Forms / Strength	75 or 150 mg for subcutaneous injection
Approved Indication(s)	as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C
Action:	Approval

Introduction

Alirocumab is a monoclonal antibody of the human IgG1 isotype to the proprotein convertase subtilisin kexin type 9 (PCSK9). PCSK9 binds to the hepatic LDL receptor, facilitating receptor uptake and degradation. Alirocumab binds to PCSK9 and inhibits its interaction with the LDL receptor thereby allowing the LDL receptor to be recycled to the hepatic cell surface for continued clearance of LDL-cholesterol (LDL-C) from the circulation. Alirocumab and other lipid-altering products targeting this pathway in LDL-C metabolism are collectively referred to as PCSK-9 inhibitors, a new class of drugs being developed for the treatment of hypercholesterolemia.

Consideration for approval of this class of drugs carries a notable impact on public health. Not since the approval of the HMG-CoA reductase inhibitors (or statins) from 1987 through 2009, has the scientific and medical community been presented with another class of lipid-altering drugs with a marked degree of cholesterol lowering. However, over the span of 20+ years with the approval of 8 statins and current availability of 7, the statins have also been extensively studied in multiple cardiovascular outcomes trial (CVOT). With the exception for one statin, each of these statins carries labeling supporting a reduction in CV risk based on at least one CVOT conducted with its product. In addition to establishing their benefits, these CVOTs and the extensive post-marketing use of statins have provided a trove of information on the long-term safety of statins. While it could be argued that statins have laid to rest the debate on LDL-C as a reliable marker to target in the treatment of CV disease, it has also been conversely debated whether it is specifically statin therapy or LDL-lowering through any means that leads to CV risk reduction. This debate was heightened with several recently failed CVOTs of non-statin drugs. Notable among the failed programs was the cholesterol-ester transfer protein (CETP) inhibitor,

torcetrapib, whose CV trial and the development program were terminated due to excess CV mortality associated with the drug.¹ This drug was touted for its HDL-raising efficacy but it also lowered LDL-C by approximately 25% when added to a statin. Two clinical trials of the intestinal cholesterol inhibitor, ezetimibe, also failed to show a favorable outcome on carotid intimal medial thickness and CV outcomes in patients with aortic stenosis resulting in a criticism of FDA for not requiring CVOTs be conducted in a timely fashion.^{2,3} Certainly an outcome of these failed trials was a greater appreciation for potential off-target effects of drugs that might counterbalance the expected benefit of LDL-lowering. Another CVOT with ezetimibe called IMPROVE-IT was recently completed and published. According to the authors of the publication, “when added to statin therapy, ezetimibe resulted in incremental lowering of LDL cholesterol and improved cardiovascular outcomes”.⁴

Regardless of which side of the debate one resides, statins have established themselves through strong clinical trial evidence in varied patient populations to be the initial cholesterol lowering drug to be considered as an adjunct to diet, exercise and a healthy lifestyle to reduce CV risk. Consequently, during the IND stage of development, the review division informed Sanofi that a CVOT evaluating the benefit of alirocumab added to statin therapy would need to be conducted. This CVOT, initiated in 2012, is an ongoing 18,000-patient trial in patients with acute coronary syndrome. It is against this backdrop of clinical and scientific evidence for statins that the PCSK9-inhibitors have to be considered in their benefit-risk assessment for treating hypercholesterolemia.

The review team has recommended approval of this BLA and I concur with this recommendation. This is an extensive clinical development program that was discussed at a public advisory committee before the Endocrine and Metabolic Drugs Advisory Committee (EMDAC) on June 9, 2015. There are very detailed, thorough, and lengthy reviews from a multi-disciplinary review team and I refer the reader to these publicly available documents for an appreciation of the scope of this program and the Agency’s extensive review. In particular, I recommend reading Dr. Jim Smith’s exceptional Cross-Discipline Team Leader/Deputy Division Director’s memo which summarizes all review discipline findings and recommendations. My memo will only summarize the key primary efficacy findings, adverse events of special interest (AESI) and issues requiring extended negotiations with Sanofi, including the intended population for use, dosing recommendations, post-marketing requirements to further assess safety, and labeling.

Intended Population for Use

Sanofi submitted its BLA with the following proposed Indication:

¹ Barter PJ et al. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* 2007; 357:2109-22.

² Kastelein J et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med* 2008; 358:1431-43.

³ Rossebo A et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med* 2008; 359:1343-56.

⁴ Cannon CP et al. Ezetimibe added to statin therapy after acute coronary syndrome. *N Engl J Med* 2015; 372:2387-97.

...the long-term treatment of adult patients with primary hypercholesterolemia or mixed dyslipidemia including patients with type 2 diabetes mellitus, to reduce LDL-C, total cholesterol (Total-C), non-high density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TGs), and lipoprotein (a) (Lp[a]), and to increase HDL-C and apolipoprotein A-1 (Apo A-1).

-Excerpt from Sanofi AC Briefing Document

In addition, approval is sought for alirocumab’s use in combination with a statin, with or without other lipid-modifying therapies (LMT); as monotherapy; or as add-on to other non-statin LMT, including in patients who cannot tolerate statins. This latter group of patients is referred to as the “statin intolerance” population.

To support its proposed indication Sanofi submitted data from ten phase 3 trials in its BLA. The primary efficacy endpoint in all Phase 3 trials was percent change in LDL-C from baseline at Week 24 and there were multiple secondary endpoints evaluated through the testing sequence summarized in Table 6 of Dr. Brad McEvoy’s FDA statistical review. The following table highlights some key characteristics of these 10 trials.

Table 1. Summary of Phase 3 Clinical Trials Submitted in Support of BLA

Trial Name	Patient Population	Dosing regimen	Background Statin use	N
Placebo-controlled				
FH I	HeFH	75/150	MTD	486
FH II	HeFH	75/150	MTD	249
High FH	HeFH	150	MTD	107
Long-term	HeFH High CV risk	150	MTD	2341
COMBO I	Hx of CVD, moderated CKD, or diabetes	75/150	MTD	316
Active-controlled				
COMBO II	Hx of CVD	75/150	MTD	720
OPTIONS I	High or very high CV risk	75/150	Atorvastatin	355
OPTION II	High or very high CV risk	75/150	Rosuvastatin	305
ALTERNATIVE	Statin-intolerant	75/150	No	314
MONO	Moderate CV risk	75/150	No	103

MTD = maximally tolerated dose

Some important observations should be made about the Phase 3 program:

1. Patient Population

With regard to dyslipidemic syndromes, this program was comprised of patients with heterozygous familial hypercholesterolemia (HeFH) and non-familial hypercholesterolemia

(non-FH). Of the 5296 patients in the Phase 3 program, 1257 (25%) had a diagnosis of HeFH. HeFH patients were identified/diagnosed by either genotyping or the Simon Broome criteria or the WHO/Dutch Lipid Network criteria for clinical diagnosis of HeFH. The applicant also identified patients as having mixed dyslipidemia if they had a baseline Tg level \geq 150 mg/dL in addition to the specified LDL-C entry criteria for a particular study (either \geq 70 or 100 mg/dL). Patients with mixed dyslipidemia could fall into either the HeFH or non-FH broad dyslipidemia category.

Patients were also classified by CV risk as moderate, high or very high based on definitions from guidelines in effect at the time the studies were initiated. With exception for the ALTERNATIVE and MONO trials, all patients had high to very high CV risk. From Table 18 in Drs. Golden's and Robert's FDA clinical review, 13.7% of the patients in the ALTERNATIVE trial and 100% of those in MONO trial had moderate CV risk. In other words, this program did not target extensively the moderate CV risk patient population, which made up less than 3% of the Phase 3 population.

2. Use of alirocumab as add-on to statin or monotherapy

Over 90% of the patients in this program received alirocumab on top of background statin therapy +/- another lipid-modifying therapy. Furthermore, 4219 (79.7%) of the patients were on maximally tolerated daily dose of statins at randomization, including 2504 (59%) who were on either atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg. Only 417 (7.9%) of the patients studied were not on background statin therapy (ALTERNATIVE and MONO study). In other words, the Phase 3 program predominantly evaluated alirocumab as an add-on therapy to statins.

From Table 3 of the FDA clinical review, they highlighted that in an April 27, 2012 Advice Letter, Sanofi was informed that inclusion of data from the ALTERNATIVE trial before completion of the CVOT would be a review issue.

3. Active control

All active-controlled trials used ezetimibe as the comparator to alirocumab. Alirocumab's LDL-lowering efficacy was not directly compared to high doses of potent statins.

From Table 3 of the FDA clinical review, they highlighted that at an EOP2 meeting, Sanofi was informed that data from trials comparing alirocumab vs ezetimibe or vs statin up-titration would not be considered for labeling before the CVOT was completed.

From the above observations, the FDA review team has concluded that Sanofi's proposed indication is unacceptable. The major extent of efficacy and safety data for alirocumab was derived from add-on to statin therapy trials, not monotherapy trials. The attempt to carve out a population with an unmet need by defining a statin-intolerant population in whom alirocumab could serve as an alternative, possibly as monotherapy, faced some degree of criticism and skepticism internally and by several members of EMDAC as to whether we can appropriately identify a truly intolerant population to a class of drugs that clearly has an established history of CV benefit.

FDA requested that the ALTERNATIVE trial design include an atorvastatin arm to test the specificity of the diagnosis of statin intolerance. The results of this trial revealed that nearly half of patients deemed ineligible for participation during the run-in period reported a skeletal muscle-related AE while on placebo, questioning how specific these complaints are to statin use. Of those who were eligible and were randomized to atorvastatin (n=63), nearly 70% of these patients were able to complete at least 22 weeks of statin therapy despite being labeled statin-intolerant. While FDA does not dismiss the fact that there are patients who truly cannot take statins, the ALTERNATIVE trial also highlighted that some patients might not actually be intolerant, therefore granting a specific indication for statin-intolerance when there is not a good means for defining and identifying this patient population might result in patients inappropriately prescribed an alternative for which no CV benefit has been established.

The review team also noted that the proposed indication would include a generally broad population identified only as having primary hypercholesterolemia or mixed dyslipidemia. Such a classification does not identify patients based on level of CV risk although Sanofi did recommend that the intended population include patients with Type 2 diabetes. In revising the proposed indication, the clinical review staff considered the currently available lipid-altering therapies, their benefits and risks, and the benefits and risks of alirocumab.

As stated under the **Introduction** of this memo, the benefit-risk assessment of PCSK9 inhibitors will be considered in the setting of the statins with their available long-term safety data and established evidence for CV risk reduction across multiple patient populations, including patients with T2DM. The clinical review staff also took into consideration the discussions from the EMDAC members and patient testimonials during the open public hearing at the June 9th AC meeting. The latter was particularly poignant as the Agency heard from patients with HeFH on maximally tolerated doses of statin but continued to have significantly high cholesterol levels. Given the life-time exposure to markedly elevated cholesterol levels, increased risk for fatal and nonfatal CV events at a young age, and additional LDL-lowering needed despite maximally tolerated statin therapy, FDA clinical reviewers recommended alirocumab to be indicated specifically in adult patients with HeFH.⁵

Across the spectrum of CV risk, the Phase 3 development program had limited data in patients with moderate or low CV risk to support an indication in this patient population. Those categorized as having high to very high CV risk would encompass those with clinical atherosclerotic cardiovascular disease and those with multiple CV risk factors. The majority of non-HeFH patients had established coronary heart disease as summarized in Table 17 of the FDA clinical review (69 to 90% had coronary heart disease in LongTERM, COMBO I and COMBO II studies). Given the absence of evidence for CV risk reduction associated with alirocumab use, the clinical review staff recommended alirocumab in patients with clinical atherosclerotic cardiovascular disease (i.e., history of a CV event such as MI or stroke) who, despite maximally tolerated statin therapy, still require further LDL-lowering therapy. With completion of the CVOT, FDA will have additional efficacy and long-term safety data to better assess the benefit-risk of alirocumab in a broader patient population.

I concur with the FDA review staff that the proposed Indications statement be revised to:

⁵ See FDA clinical reviews for discussion of pediatric development program for Praluent (alirocumab)

.....indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or with clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

Clinical Efficacy

Please see Dr. Brad McEvoy's FDA statistical review for a detailed discussion of clinical efficacy findings. The primary efficacy endpoint in all Phase 3 trials was percent change in LDL-C from baseline at Week 24. The mean percent LDL-C reduction in placebo-controlled trials ranged from 36% to 58% and 21% to 31% in ezetimibe-controlled trials. The additional LDL-lowering in the placebo-controlled trials is notable in that these trials enrolled patients on maximally tolerated statins who were considered eligible for additional LDL-lowering based on targeted goals of either < 70 mg/dL or 100 mg/dL, depending on the study protocol. From Table 21 of the FDA clinical review, 46.8 to 88% of patients in the 5 placebo-controlled trials were taking atorva 40 to 80 mg, rosuva 20 to 40 mg, or simva 80 mg daily at screening.

Only the MONO trial evaluated alirocumab as a sole lipid-altering treatment and it was compared to ezetimibe, a modestly effective LDL-lowering drug; hence, it was expected that alirocumab could demonstrate superiority in LDL-lowering from baseline compared to ezetimibe. There are no head-to-head trial data to allow a conclusion that alirocumab will provide greater LDL-lowering efficacy compared to high-intensity statins with their proven benefit on CV risk reduction. However, as noted by Dr. Golden, the LS mean percent change from baseline of alirocumab in the MONO trial was -47.2% (See Table 36 from FDA clinical review) and the mean percent change in LDL-C from baseline for rosuvastatin 5 to 50 mg ranges from -4^(b)₍₄₎ to 63%, as described in its product labeling. While a cross study comparison should be viewed with caution, the overlapping range of LDL reduction from baseline between rosuvastatin and alirocumab monotherapy should also give one pause before concluding that alirocumab as a single agent for LDL-lowering will be more effective than the high-intensity statin.

Dosing Recommendations

Alirocumab will be marketed in two dosage strengths, 75 mg and 150 mg, to be administered subcutaneously every 2 weeks. Two Phase 3 trials (HIGH FH and Long Term) evaluated alirocumab 150 mg SC every 2 weeks throughout the duration of the trials whereas the remainder of the Phase 3 program studied an up-titration dosing scheme wherein patients randomized to alirocumab were initiated at the 75 mg dose every 2 weeks with potential up-titration to 150 mg at Week 12 based on whether the patient achieved a pre-specified LDL-C goal at Week 8. These two doses were not evaluated in parallel, fixed-dose trials to determine a dose-response relationship. They were selected for Phase 3 based on a Phase 2 study suggesting maximal efficacy at the 150 mg dosing and an estimate that 75 mg would provide approximately 50% LDL reduction from a dose-response model.

The applicant is recommending initiation of therapy at 75 mg with up-titration to 150 mg if further LDL-C reduction is needed. This recommendation is supported from the up-titration trials in which patients who required an increase in dose achieved any additional 1.5 to 23.1%

reduction in LDL-C. In addition, the applicant is proposing the 150 mg be considered as a start dose for those with higher baseline LDL-C who may require greater LDL-C reduction.

While there are two studies supporting the safety and efficacy of initiating treatment at 150 mg, there are no data to conclude that 150 mg would better serve a patient over 75 mg as a start dose, nor are there consistent data that a patient with a “high” baseline LDL-C would achieve a desired cholesterol goal with initiation at the 150 mg more likely than the 75 mg dose. What the goal should be is individualized for a patient, which in turn is dependent on his/her baseline LDL-C, risk factors, and the current treatment guideline recommendations. For example, if we were to apply the most recent AHA/ACC treatment guidelines, patients with atherosclerotic cardiovascular disease (secondary prevention) or if ≥ 21 years of age with severe hypercholesterolemia (primary prevention), high intensity statins are recommended to lower LDL-C by $\geq 50\%$.⁶ In the following table obtained from the applicant’s Clinical Summary of Efficacy, the percentage of patients at Week 12 across the 8 up-titration trials reveals that over half of the patients (55%) had at least a 50% reduction in LDL-C with the 75 mg dose.

Table 59 - Proportion of patients randomized to alirocumab achieving a target reduction in calculated LDL-C at Week 12 - Raw data description (On-treatment analysis) - Phase 3 studies with alirocumab 75mg Q2W as initial dose

	FH I (N=321)	FH II (N=166)	COMBO I (N=204)	COMBO II (N=464)	OPTIONS I (N=98)	OPTIONS II (N=99)	ALTERNA TIVE (N=123)	MONO (N=51)	All (N=1526)
Number of patients with calculated LDL-C available at Week 12	303	151	188	439	90	92	109	45	1417
At least 40% reduction	193 (63.7%)	95 (62.9%)	129 (68.6%)	336 (76.5%)	66 (73.3%)	58 (63.0%)	86 (78.9%)	36 (80.0%)	999 (70.5%)
At least 50% reduction	141 (46.5%)	63 (41.7%)	98 (52.1%)	272 (62.0%)	59 (65.6%)	46 (50.0%)	72 (66.1%)	29 (64.4%)	780 (55.0%)
At least 60% reduction	83 (27.4%)	33 (21.9%)	69 (36.7%)	200 (45.6%)	41 (45.6%)	30 (32.6%)	40 (36.7%)	15 (33.3%)	511 (36.1%)
At least 70% reduction	36 (11.9%)	12 (7.9%)	35 (18.6%)	109 (24.8%)	23 (25.6%)	16 (17.4%)	8 (7.3%)	4 (8.9%)	243 (17.1%)
At least 80% reduction	8 (2.6%)	2 (1.3%)	11 (5.9%)	39 (8.9%)	9 (10.0%)	8 (8.7%)	1 (0.9%)	0 (0.0%)	78 (5.5%)

PGM=PRODOPS/SAR236553/OVERALL/POOL_2014_01/REPORT/PGM/ALL_eff_tdesc_ldlw12_target_m_t.sas OUT=REPORT/OUTPUT/ALL_eff_tdesc_ldlw12_target_m_t_i.rtf (21OCT2014 - 9:11)

Source: Page 219 of Applicant’s Clinical Summary of Efficacy

The review team evaluated characteristics of patients requiring up-titration to determine if there were baseline factors which could identify who would eventually require up-titration to recommend these patients be initiated on therapy at the maximal dose. These explorations and analyses are post-hoc and in post-randomized subgroups and interpretation of a characteristic’s predictive value for up-titration or need for initiation with the 150 mg dose should be made with extreme caution. Surprisingly, the baseline PCSK-9 levels were not significantly different between the two dosing groups. Additional analyses of PCSK-9 levels at Week 8 (decision point for up-titration) did not reveal that those requiring up-titration had higher PCSK-9 level than patients who remained on 75 mg.

It could be argued that the proposal to allow a statement that initiation at 150 mg is recommended for those with higher baseline LDL-C is benign because differences in AEs were not discernable between the two doses and 150 mg is clearly efficacious. However, given that we have no trial which prospectively assessed whether there is a dose-response between the 75

⁶ Stone, NJ et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic CV Risk in Adults.

and 150 mg doses, the 75 mg dose was clearly effective in the majority of patients, and there is no evident risk to waiting 4 to 8 weeks to determine how a patient has responded to 75 mg before deciding to increase the dose, it would seem prudent to recommend the 75 mg dose as the initial start dose while we await additional data from ongoing trials with alirocumab, including plans to evaluate other dosing regimens. This step-wise recommendation would also minimize the risk of some patients achieving too low of an LDL-C (e.g., < 25 or 15 mg/dL).

Clinical Safety

In addition to a general review of overall safety, the clinical reviewer delved further in several adverse events of special interest (AESI) identified based on the mechanism of action of the PCSK9-inhibitors, safety concerns with other lipid-altering drugs, and signals identified from non-clinical data. Pages 170-233 of the FDA clinical review covers the following AESIs: injection site reactions; allergic events; neurocognitive events, including demyelination and peripheral neuropathies; musculoskeletal events, including elevated CPKs; hepatic disorders and elevated LFTs; diabetes; CV safety; fat-soluble vitamin deficiencies; and safety concerns associated with very low LDL-C. Dr. Mary Roberts has provided a very detailed analysis of each of these events. Overall, there was no concerning finding of a serious event directly related to alirocumab treatment or an imbalance unfavorable to treatment that precluded a recommendation for approval. I will highlight the AESIs that were considered in labeling and will be further evaluated in required postmarketing trials.

Allergic Reactions

Treatment emergent allergic reactions, excluding injection site reactions, were summarized by Dr. Roberts in the combined placebo-controlled trials and ezetimibe-controlled trials. In both comparisons, the rates of TEAEs were slightly higher in alirocumab-treated patients compared to the control arms but the rates of events coded as serious were similar. None of these events were fatal. Discontinuation rates due to allergic reactions were slightly higher in the alirocumab group. The following table from the FDA clinical review highlights these findings for allergic events.

Table 88. Overview of TEAE allergic events (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Allergic events	Placebo-controlled			Ezetimibe-controlled		
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	HR ¹ (95% CI)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)	HR ¹ (95% CI)
TEAE	99 (7.8)	213 (8.6)	1.10 (0.87-1.40)	33 (5.3)	59 (6.8)	1.31 (0.85–2.02)
Treatment emergent SAE	5 (0.4)	9 (0.4)		2 (0.3)	1 (0.1)	
TEAE leading to death	0	0		0	0	
TEAE leading to discontinuation	2 (0.2)	14 (0.6)		2 (0.3)	7 (0.8)	

Source: ISS Table 21, ISS appendix 1.4.1.2.4

Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)

Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

MedDRA 17.0. The selection of PTs is based on the Standardized MedDRA Queries (SMQs): 'hypersensitivity' (broad + narrow) excluding the following PTs ('infusion/injection site dermatitis', 'infusion/injection site hypersensitivity', 'infusion/injection site rash', 'infusion/injection site urticaria' and 'injection site vasculitis')

1. Calculated using a Cox model stratified on the study

There were 3 patients in the alirocumab group who experienced angioedema and none in the control group. All three had resolution of symptoms after receiving appropriate medical therapy (e.g., steroids or anti-histamines) and two had treatment discontinued. There was one report of anaphylaxis requiring intubation that was reported with the 4-month safety update. This patient was in an ongoing trial investigating alirocumab 300 mg Q4 wk dosing and the event occurred 1 ½ years after the first dose and 11 days after the dose prior to the event. The patient was rechallenged with a single dose after recovery from the event and did not have signs and symptoms but treatment was discontinued nonetheless.

Table 91 from the clinical review summarizes the serious TEAEs. Although the incidence rates were similar across treatment groups, several of the alirocumab cases resulted in hospitalization. The majority of alirocumab cases had a history of allergies or asthma and anti-drug antibody was positive in some patients. All control cases were ADA negative.

Allergic reactions will be described under the Warnings and Precautions and Adverse Reactions sections of labeling. In addition, under the Contraindications section, reference will be made to the serious hypersensitivity reactions described under Section 5.0.

Local Injection Site Reactions

In the combined Phase 2 and 3 clinical trials, more patients in the alirocumab group reported injection site reactions compared to controls (6.1% vs 4.1%). There were no serious injection site reactions although more patients on alirocumab vs placebo reported the event as a moderate reaction and the mean duration of reaction tended to be longer in the drug arm. Permanent treatment discontinuation rates due to injection site reactions were similar between alirocumab and control arms (0.2% vs 0.3%) and with exception of one patient whose outcome is unknown, symptoms resolved with all others who discontinued.

These reactions will be described under the Adverse Reactions section of labeling.

Neurocognitive (b) (4) Events

Neurocognitive concerns related to statins and theoretical concerns related to very low LDL-C levels affecting myelination formed the basis for evaluating neurocognitive and neurologic events as AESIs.

Neurocognitive events related to terms such as delirium, cognitive and attention disorders and disturbances, dementia and amnesic conditions, disturbances in thinking and perception, mental impairment disorders were evaluated. The overall incidence of neurocognitive events was low across all treatment groups. Among the placebo-controlled trials the incidence was 0.8% for alirocumab vs 0.7% for placebo patients with confusional state and memory impairment occurring at a higher rate for alirocumab patients (0.2%) than placebo (<0.1%). In the ezetimibe pool, memory impairment was reported in 3 alirocumab patients and none in ezetimibe arm. Dr. Roberts has summarized the narratives of these events in Table 98 of the FDA clinical review.

The overall incidence of neurologic TEAE was similar between alirocumab and placebo groups (3.5% for both) in the pool of placebo-controlled trials and 3.4% in alirocumab vs 2.4% in

ezetimibe in the active-controlled trials. Incidences of serious neurologic TEAEs were low (<0.1-0.2%) and none were fatal. Among the neurologic AEs related to demyelination, there were four cases in the alirocumab group which received closer scrutiny (optic neuritis, Miller-Fisher syndrome, demyelination suspicious of multiple sclerosis, and transverse myelitis). The Division of Neurology Products was consulted to provide their expert assessment of alirocumab's potential risk for a specific neurologic adverse event or syndrome. Overall, their consult "did not find compelling evidence to support the notion that alirocumab...is associated with a specific neurological adverse event or syndrome as a result of drug treatment". The consult also considered the 4 cases noted above and the reviewer observed that "Miller Fisher syndrome and transverse myelitis are so rare that a single case of either is unexpected in this clinical trial population". Each case was lacking in evidence to implicate alirocumab; however, the consult recommended demyelinating adverse events as AESI for enhanced investigation and reporting.

There will be a section under the Adverse Reactions section of labeling describing the rate of neurocognitive events in treatment and control groups. As causality could not be attributed to alirocumab for the 4 cases of interest among the neurologic AEs, these will not be included under the Adverse Reactions section of labeling in accordance with the 201.57(c)(7).

Liver Enzyme Abnormalities

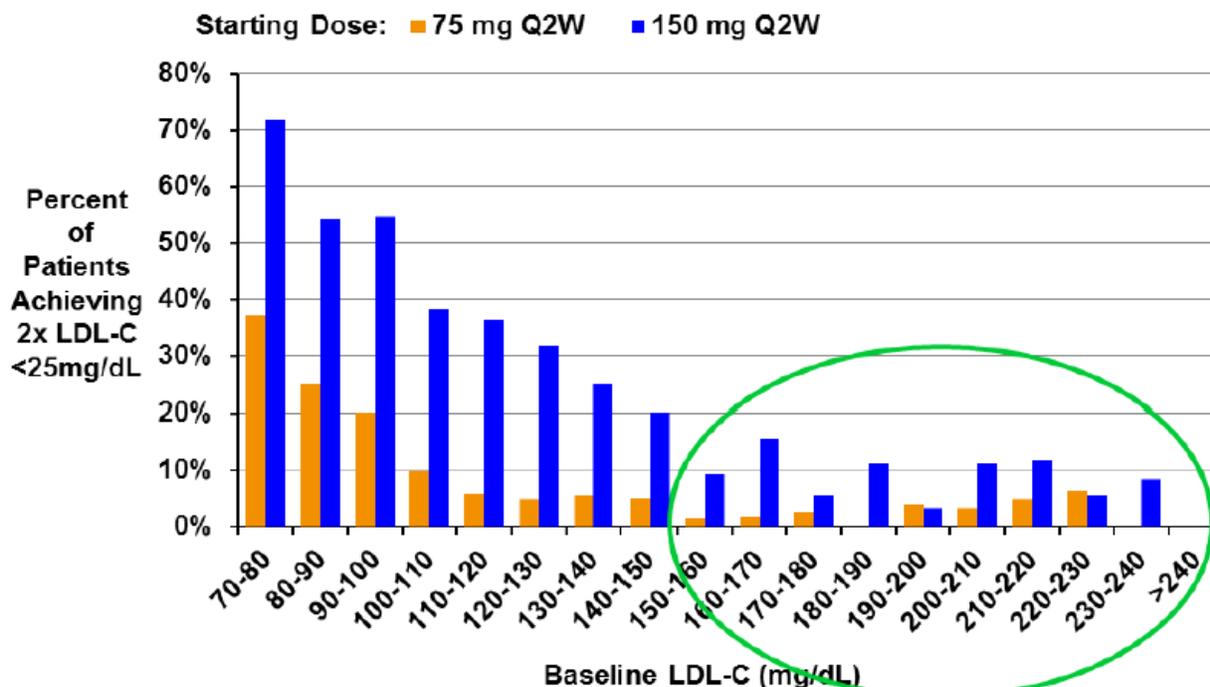
Imbalances in liver test abnormalities were noted in the controlled trials and a slightly higher percentage of alirocumab-treated patients discontinued therapy as a result. There were 3 cases of elevated transaminases with total bilirubin > 2 ULN, one in alirocumab and 2 in placebo-treated patients. None of these met the criteria for Hy's Law as alternative etiologies for the laboratory abnormalities were identified.

Dr. Smith describes a case of symptomatic hepatitis with jaundice submitted as a 15-day safety report to the IND near the end of the review cycle. This case was of obvious concern and immediate consultation with FDA hepatologists ensued and follow-up information from the applicant was requested. Additional information attributed this event to acute hepatitis E and unlikely due to alirocumab.

Low LDL-C Values

Given the magnitude of LDL-lowering on top of statins, it was anticipated that very low LDL-C would be observed with alirocumab treatment. Approximately 20 and 40% of alirocumab treated patients had at least one LDL-C below 15 and 25 mg/dL, respectively. Not surprisingly, the lower the baseline LDL-C is when initiating therapy with alirocumab, the higher the percentage of patients experiencing a very low LDL-C. The following graph presented by the applicant at the AC meeting would suggest that in addition to baseline LDL-C, initiation at the higher dose of 150 mg also resulted in a higher percentage of patients with very low LDL-C levels.

Baseline LDL-C and Starting Dose Predict LDL-C <25



Source: from Sanofi's AC presentation on June 9, 2015

Dr. Roberts evaluated adverse events related to low LDL-C levels using the thresholds of LDL < 25, 15, and on more than one occasion. The following table summarizes adverse events by these thresholds for alirocumab patients versus the overall control population. These comparisons are not between randomized populations and any conclusion is tenuous.

Table 140. Overview of adverse event profile in patients achieving low LDL-C levels on alirocumab (safety population) - global pool

	Alirocumab			Total Alirocumab ¹ N=3340 n (%)	Total Control ¹ N=1894 n (%)
	1 LDL-C <25 N=1371 n (%)	2 LDL-C <25 N=796 n (%)	2 LDL-C <15 N=288 n (%)		
Any TEAE	908 (66.2)	543 (68.2)	193 (67.0)	2483 (74.3)	1396 (73.7)
SAE	175 (12.8)	104 (13.1)	28 (9.7)	453 (13.6)	251 (13.3)
TEAE leading to death	4 (0.3)	3 (0.4)	0	15 (0.4)	18 (1.0)
Treatment d/c due to TEAE	56 (4.1)	28 (3.5)	14 (4.9)	207 (6.2)	125 (6.6)

Source: ISS Appendix 1.4.5.1, 1.4.5.9, 1.4.6.1, 1.4.9.2

LDL-C calculated

Pbo controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361). Ezetimibe controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Only TEAEs that occurred, worsened or became serious the day or after the first of the 2 consecutive LDL-C <25 mg/dL are considered. Consecutive defined as values separated by at least 21 days

1. Includes patients that achieved LDL-C <25 mg/dL

Dr. Roberts reviewed selected adverse events, in particular, neurocognitive events, and no obvious safety concern could be identified; however, both the applicant and FDA acknowledge that safety data on low LDL-C from double blind trials are limited beyond 1 year.

The number of patients with low LDL-C levels by the threshold of < 25 and 15 mg/dL will be described in the Adverse Reactions section of the label. This section is intended to relay to prescribers that such low levels were observed and while no safety signal was observed in these patients, the long-term effects of sustained low levels is unknown.

Immunogenicity

In the 10 Phase 3 trials, anti-drug antibodies (ADA) were detected in 4.8% of alirocumab patients versus 0.6% in the control arms. The most common AE occurring at a higher rate in ADA-positive patients versus ADA-negative patients was injection site reaction, and as already discussed, none of these reactions were serious and few required discontinuation. Serious TEAEs were reported in 16.3% of ADA-positive patients vs 14.1% of the ADA-negative patients; however, there were no events reported in greater than 2 ADA-positive patients (See Table 131 of FDA clinical review).

Dr. Golden in the FDA clinical review and Dr. Amy Rosenberg, from the Division of Biotechnology Review and Research, summarized 8 patients with high titer ADA who may have had transient diminished efficacy and two patients with ADA who may have had enhanced efficacy as a result of the ADA.

Overall, development of ADA does occur with alirocumab and appears to be transient with no serious safety outcome. One postmarketing commitment has been requested of the applicant to develop an algorithm for decision-making in the presence of loss of efficacy due to antibody response.

Other safety findings

Dr. Roberts has carefully reviewed cases of diabetes, glucose intolerance and shifts in glycemic control given the recent finding for statins. There was no consistent finding of excess risk for developing diabetes, meaningful change in HbA1c or fasting plasma glucose. There was a higher percentage of patients in the alirocumab group who had a shift from normal to impaired glycemic category but there was conversely a higher percentage in the alirocumab group who had a shift from impaired to normal glycemic status. (b) (4)
(b) (4) diabetes and glycemic control will be monitored in the CVOT.

Drs. Roberts and McEvoy summarized CV findings in their reviews. No obvious signal of risk was identified but there are too few events to render any preliminary conclusion on the CV benefits or risks of alirocumab in advance of the ongoing CVOT.

Post-marketing Requirements

This application will be approved with 4 PMRs. Please see approval letter for terms and dates for each PMR:

- 2927-1 is for a dose-finding Phase 2 study and an efficacy and safety Phase 3 study in pediatric patients with HeFH ages 10 years to less than 18 years. This study is a required study under the Pediatrics Research and Equity Act (PREA)
- 2927-2 is a prospective observational study in pregnant women exposed to Praluent. The applicant is asked to evaluate fetal, infant and childhood outcomes of pregnant women exposed to Praluent. This requirement is based on findings in a monkey study where animals were dosed during organogenesis. Suppression of the humoral immune system was observed in the infant monkeys. The clinical significance of this one animal reproductive study is unknown.
- 2927-3 is for a large, randomized, controlled, long-term trial in which the incidence and severity of several AESI were identified during the BLA review. These include new-onset diabetes, injection site reactions, hypersensitivity, immunogenicity, and demyelination. These assessments are being evaluated in the ongoing CVOT
- 2927-4 is for a randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function

Labeling

See agreed-upon labeling contained in the action package for this approval.

As noted above, alirocumab will be indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C. The recommended starting dose will be 75 mg sc every 2 weeks and if upon LDL-C testing 4 to 8 weeks after initiation the clinician has determined the response is inadequate, the dosage may be increased to the maximal dose of 150 mg sc every 2 weeks. The Clinical Trials section of the label will include only the placebo-controlled trials and the patient population supporting the indicated population for use.

(b) (4)

Despite CV benefit having been established with statins, concern was expressed during the AC meeting that some physicians may reduce the dose of or eliminate statin therapy in the setting of very low LDL-C. (b) (4)

physicians should apply their knowledge of clinical evidence for CV risk reduction and make treatment decisions accordingly.

Overall Benefit-Risk Assessment

Elevated LDL-C levels are associated with excess cardiovascular morbidity and mortality and several trials, particularly statins, have shown a reduction in CV risk with the lowering of LDL-C. Despite the availability of several potent statins, there remains a population of patients who, despite maximally tolerated statin therapy, have not achieved an adequate cholesterol reduction based on baseline CV risks.

Alirocumab was clearly effective in lowering LDL-C across all Phase 2 and 3 trials enrolling patients with a wide range of baseline LDL-C. The magnitude of cholesterol reduction, especially in patients receiving maximally tolerated statin therapy who had not achieved adequate cholesterol lowering, holds promise that alirocumab might further lower residual CV risk in these patients. However, the definitive evidence for CV benefit with alirocumab when added to maximally tolerated statin awaits the completion of its ongoing CVOT. As such, a decision to approve this application will be based on the effect of alirocumab on a surrogate, which has been relied upon for approval of other cholesterol-lowering drugs for over 20 years because of an expected clinical benefit with LDL-C reduction. This expected benefit must also not be counterbalanced by a serious safety finding associated with alirocumab treatment.

The additional 38 to 56% mean reduction in LDL-C when alirocumab is added to a maximally tolerated statin (with or without other lipid-modifying therapies) in placebo-controlled trials is impressive and offers physicians and patients additional means to treat hypercholesterolemia when currently available therapies are insufficient. Limiting the indicated population further to patients on maximally tolerated statin with HeFH or patients with clinical atherosclerotic cardiovascular disease identifies those who are at greatest risk for a future CV event while we await the outcome of the CVOT.

Finally, the safety database for this program has not identified a serious safety signal that outweighs the expected benefits in this selected patient population. However, as we have learned from other drug development programs for chronic conditions, the size and duration of exposure in a pre-marketing application cannot fully characterize the safety of the product for its long-term use. Much about the safety of a chronically administered drug is discovered post-marketing in the prescribed setting or from ongoing investigations. For the latter, FDA has negotiated several PMRs and PMCs with the applicant to better understand the long-term risks of alirocumab. Until those investigations are complete, the benefit-risk calculus for alirocumab is best supported in patients on maximally tolerated statin with HeFH or with clinical atherosclerotic cardiovascular disease.

Recommendation

Approval

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARY H PARKS
07/24/2015