CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125559Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number	125559
Priority or Standard	Priority (via priority review voucher)
Submit Date	24 November 2014
Received Date	24 November 2014
PDUFA Goal Date	24 July 2015
Division / Office	DMEP / ODE2
Reviewer Names	Julie Golden, M.D. (efficacy) Mary Roberts, M.D. (safety)
Review Completion Date	22 July 2015
Established Name	Alirocumab
Proposed Trade Name	Praluent
Therapeutic Class	PCSK9 inhibitor
Applicant	Sanofi-aventis U.S. LLC
Formulations	75 mg/mL and 150 mg/mL solutions for injection
Dosing Regimen	75 mg or 150 mg SC Q2wks
Indication	Hyperlipidemia
Intended Populations	HeFH, hyperlipidemia + high CV risk, statin intolerant

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The primary reviewers are in agreement that this application should be approved. This determination is informed by the robust LDL cholesterol (LDL-C)-lowering observed with alirocumab and a safety profile that to date appears acceptable. Nevertheless, there are limitations to the characterization of the benefit-risk assessment of alirocumab that are outlined in section 1.2, below. Given these limitations, we disagree with the sponsor's proposed indication, which describes use for a broad population of patients with cardiovascular (CV) risk factors as well as patients with "statin-intolerance". The reviewers' recommended indication targets patients in whom the benefit-risk is likely to be favorable in the absence of confirmatory CV outcomes data and a relatively limited pre-marketing safety database:

PRALUENT is 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.

1.2 Risk Benefit Assessment

Alirocumab, a monoclonal antibody, is a member of a new class of lipid-modifying therapies that inhibit the proprotein convertase subtilisin kexin type 9 (PCSK9), a serine protease that is secreted with the low density lipoprotein receptor (LDL-R) and promotes its degradation. By inhibiting PCSK9, alirocumab enhances recycling of LDL-R, which leads to clearance of LDL-C from the circulation and lower LDL-C concentrations.

Alirocumab was evaluated for efficacy in ten multicenter phase 3 trials that randomized 5296 patients: nine out of the 10 trials enrolled patients with heterozygous familial hypercholesterolemia (HeFH) and/or patients at high or very high cardiovascular (CV) risk. Five trials were placebo-controlled and five were active-controlled. Two dose regimens were evaluated: eight trials utilized a starting dose of 75 mg by subcutaneous injection every 2 weeks (Q2W) with up-titration at week 12 to 150 mg Q2W if LDL-C goals (consistent with ATP III) were not met, and two trials started all patients on 150 mg Q2W. Eight trials administered alirocumab in patients who were on background statin therapy (most trials enrolled patients who were taking the maximally tolerated dose of statin), and two trials administered alirocumab as monotherapy [one trial in patients with moderate CV risk (MONO), and one trial in patients identified with pre-specified criteria as "statin-intolerant" (ALTERNATIVE)]. The OPTIONS I and II trials were block-randomized based on background moderate doses of atorvastatin and rosuvastatin, respectively, and patients were randomized to addition of alirocumab or ezetimibe, statin dose up-titration, or in the case of the OPTIONS I atorvastatin 40 mg

regimen, a switch to rosuvastatin 40 mg. All ten phase 3 trials utilized the same primary endpoint: percent change in LDL-C from baseline at week 24. A summary of the phase 3 trials is shown below:

Table 1. Phase 3 Trials

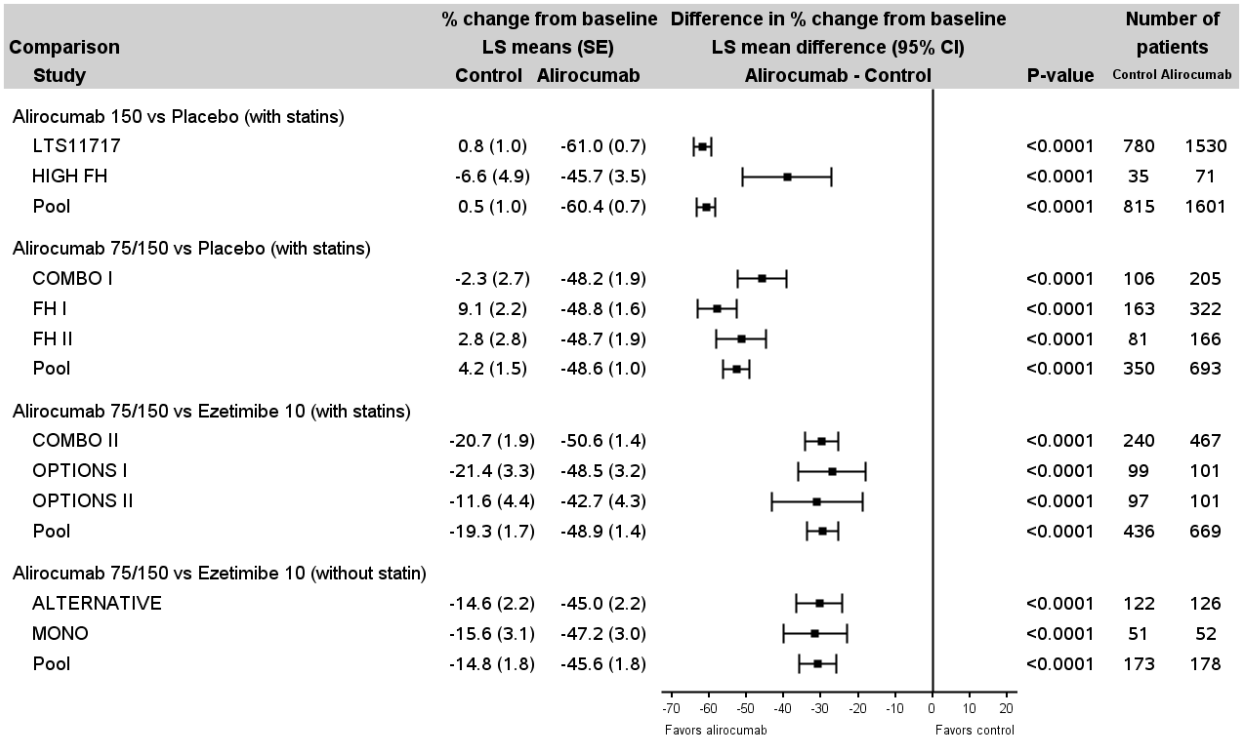
Trial	Primary endpoint	Population/design feature	Size	Control	Dose
FH I	% change in LDL-C at 24 wks	HeFH on maximally tolerated statin	486	placebo	75/150
FH II	% change in LDL-C at 24 wks	HeFH on maximally tolerated statin	249	placebo	75/150
HIGH FH	% change in LDL-C at 24 wks	HeFH with LDL-C > 160 mg/dL on maximally tolerated statin	107	placebo	150
LONG TERM (LTS11717)	% change in LDL-C at 24 wks	HeFH or high CV risk on maximally tolerated statin	2341	placebo	150
COMBO I	% change in LDL-C at 24 wks	High CV risk on maximally tolerated statin	316	placebo	75/150
COMBO II	% change in LDL-C at 24 wks	High CV risk on maximally tolerated statin	720	ezetimibe	75/150
OPTIONS I	% change in LDL-C at 24 wks	On 20 or 40 mg atorvastatin, randomized to alirocumab, ezetimibe, up-titration of statin, or higher potency statin	355	ezetimibe[a]	75/150
OPTIONS II	% change in LDL-C at 24 wks	On 10 mg or 20 mg rosuvastatin, randomized to alirocumab, ezetimibe, or up-titration of statin	305	ezetimibe[a]	75/150
ALTERNATIVE	% change in LDL-C at 24 wks	Statin-intolerant population (randomized after placebo run-in to alirocumab, ezetimibe, or atorvastatin)	314	ezetimibe[b]	75/150
MONO	% change in LDL-C at 24 wks	Moderate CV risk, on no background lipid modifying therapy	103	ezetimibe	75/150

[a] additional control: up-titration of current statin, or switch to higher potency statin (OPTIONS I)
[b] additional control: atorvastatin 20 mg QD
75/150 = starting dose of 75 mg Q2W with up-titration to 150 mg Q2W at week 12 if not meeting LDL-C goal

The sponsor's primary analysis, which utilized a mixed effect model with repeated measures on the intent-to-treat population in all trials, demonstrated that alirocumab was associated with decreases in calculated LDL-C of 36 to 61 percent from baseline, and statistically significant treatment differences of 39 to 62 percent as compared to placebo (all p-values <0.0001) and 24 to 36 percent as compared to ezetimibe (p-value <0.01 for all except the background rosuvastatin 20 mg regimen within the OPTIONS II

trial that did not reach statistical significance based on the pre-specified method for controlling type I error, p=0.014). Maximal LDL-C-lowering efficacy was observed at week 4 and persisted for the duration of the trials. A forest plot illustrating the primary endpoint results by trial is shown below (note that OPTIONS background statin regimens are pooled, demonstrating statistical significance):

Figure 1. Percent Change in LDL-C from Baseline at Week 24, Phase 3 Trials



Source: Clinical Overview, Figure 2

LDL-C efficacy was supported by other analyses, including absolute change in LDL-C at week 24, percent change in LDL-C at other time points, including weeks 12 and 52 (where applicable), percent change in directly measured LDL-C, and the proportions of patients meeting individual LDL-C treatment goals (defined as LDL-C less than 70 mg/dL in patients at very high CV risk, and less than 100 mg/dL for all others), as well as percent changes in week 24 in total cholesterol, apolipoprotein B, and non-high density lipoprotein cholesterol (non-HDL-C). By contrast, only three of the five placebo-controlled trials were statistically significant for percent changes in triglycerides at week 24 (treatment effect ranged from -0.6 to -17 percent), and four of the five for HDL-C (treatment effect ranged from +4 to +8 percent).

As alirocumab is a biologic therapy, anti-drug antibodies (ADA) can develop and could potentially impact efficacy (as well as safety). Treatment-emergent positive ADA responses were observed in 4.8% of patients in the alirocumab group and in 0.6% of

patients in the control group. Most of these responses were of low-titer, non-neutralizing, and/or transient. Upon review of patient-level data, there were several patients in whom neutralizing or high-titer antibodies appeared to be associated with loss of efficacy. There is not enough information at this time to fully characterize this effect.

The assessment of risk associated with alirocumab treatment is formed from an evaluation of four phase 2 trials and ten phase 3 studies encompassing a total of 3340 patients exposed to alirocumab as of the application cut-off date of August 31, 2014. The safety database is divided into two main safety pools based on the control employed – placebo or ezetimibe. The two alirocumab doses were combined as review of the data, albeit limited as no phase 3 trial employed parallel arms of the 75 mg and 150 mg Q2W doses, did not suggest dose-related safety signals. The placebo-controlled pool includes patients with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia on maximally tolerated background statin therapy. The ezetimibe-controlled pool consists of patients with non-familial hypercholesterolemia who may have not been receiving statin therapy or were at less than maximal doses of statin therapy. Within the placebo and ezetimibe-controlled pools, 1999 (81%) and 409 (47%) patients were exposed to alirocumab for at least 1 year, respectively.

Treatment groups within the placebo-controlled (alirocumab versus placebo) and ezetimibe-controlled pools (alirocumab versus ezetimibe) were well matched for demographics and baseline characteristics. The majority of patients in both the placebo-controlled and ezetimibe-controlled pools had a history of CHD (60 to 70%) – with almost half of patients in both the placebo-controlled pool and ezetimibe-controlled pool reporting a coronary revascularization procedure and approximately a third of patients reporting a history of a myocardial infarction. In both of the main safety pools, approximately 70% reported a history of hypertension and an estimated 30% reported a history of diabetes mellitus.

In the global pool of phase 3 studies combined (placebo and ezetimibe controlled), there were a total of 37 on-study deaths: 17 deaths (0.9%) in the control group and 20 deaths (0.6%) in the alirocumab group. The majority of these deaths were adjudicated as cardiovascular, which is not unexpected given the high cardiovascular risk profile of the population studied. Of import, the numbers are too small to draw any conclusions regarding the effect of alirocumab on reduction of risk of overall mortality.

In the pool of placebo-controlled studies, treatment-emergent serious adverse events (SAEs, fatal and non-fatal combined) were reported in 13.7% and 14.3% of patients in the alirocumab-treated and placebo-treated groups, respectively. Within the pool of ezetimibe-controlled studies, a slightly higher incidence of SAEs occurred in the alirocumab-treated (13.1%) versus the ezetimibe-treated (11.2%) groups. The highest percentage of patients reporting a SAE occurred in the “Cardiac disorders” system

organ class (SOC) in both the placebo-controlled pool (4.5% placebo, 4.4% alirocumab) and ezetimibe-controlled pool (4.0% ezetimibe, 5.6% alirocumab).

Within the placebo-controlled pool, a similar proportion of patients permanently discontinued treatment due to a treatment-emergent adverse event (TEAE): 5.1% patients in the placebo group and 5.3% patients in the alirocumab group. The greatest absolute difference between treatment groups in discontinuations was noted in the "Skin and subcutaneous disorders" SOC. Ten (0.4%) alirocumab-treated patients compared with zero placebo-treated patients discontinued treatment due to adverse events within this category, mostly associated with pruritus and rash-related events. In the ezetimibe-controlled pool, the overall incidence of discontinuation due to a TEAE was 9.7% in the ezetimibe and 8.8% in the alirocumab group. The TEAEs with the highest incidence leading to treatment discontinuation within this pool were muscle-related, with 3.6% and 5.5% of alirocumab and ezetimibe-treated patients, respectively, reporting an event within the "Musculoskeletal and connective disorders" SOC. This is primarily a reflection of the ALTERNATIVE study, which included a patient population considered statin intolerant because of a history of muscle-related symptoms. Alirocumab-treated patients had a higher incidence of TEAEs leading to discontinuation compared to ezetimibe-treated patients in the SOC "Investigations" (0.2% ezetimibe, 0.7% alirocumab) mostly related to abnormalities in liver enzymes.

Based on theoretical or identified concerns about PCSK9 inhibition or therapeutic protein products in general, or about alirocumab specifically, several adverse events of special interest (AESI) were prespecified for potential additional monitoring and reporting requirements. AESIs evaluated were local injection site reactions, general allergic events, neurologic events, neurocognitive events, diabetes mellitus, hepatic-related disorders, muscle-related disorders, and cardiovascular events.

In the global pool (phase 2/3 studies), higher incidences of local injection site reactions were reported in patients receiving alirocumab injection (6.1%) versus placebo injections (4.1%). Most injection site reactions were transient and of mild intensity and few patients discontinued treatment due to an injection site reaction (n=8, 0.2% alirocumab; n=6, 0.3% control). In alirocumab-treated patients, those with treatment-emergent anti-drug antibodies (ADA) reported a higher incidence of local injection site reactions (10.2%) compared to ADA-negative patients (5.9%).

General allergic events occurred with a higher incidence in alirocumab-treated patients in both the pool of placebo-controlled studies and pool of ezetimibe-controlled studies (7.8% placebo versus 8.6% alirocumab; 5.3% ezetimibe versus 6.8% alirocumab). The proportion of patients with treatment-emergent SAEs was low and similar across treatment groups within both the placebo-controlled and ezetimibe-controlled pools. The most commonly reported treatment-emergent adverse events were rash and pruritus. However, there were several allergic events of note, including cases of angioedema, leukocytoclastic vasculitis, and hypersensitivity. Patients with a medical

history of allergy were more likely to report an allergic event compared to patients without a history of allergy. However, a similar proportion of patients with or without treatment-emergent positive ADA reported a general allergic event (8.8% positive ADA, 8.2% negative ADA).

Neurologic events related to myelin-sheath disorders or neuropathies were collected based on theoretical concerns that low LDL-C levels may impair myelination. Within the pool of placebo-controlled studies, the incidence of patients with a neurologic event of special interest was similar. There were four alirocumab-treated patients that reported serious events that warrant mention – a case of Miller-Fisher syndrome (a variant of Guillain-Barre), optic neuritis, demyelination (multiple sclerosis), and transverse myelitis. With the exception of the Miller-Fisher syndrome case, none of the patients had two consecutive LDL-C levels less than 25 mg/dL or treatment-emergent anti-drug antibodies. After review of these cases a causal link with either alirocumab or low LDL-C levels cannot be confirmed, based on potential alternative etiologies and the very small number of cases.

The number of patients reporting a neurocognitive event was low, with similar frequencies between treatment groups in the pool of placebo-controlled studies (0.7% placebo, 0.8% alirocumab) and in the pool of ezetimibe-controlled studies (1.0% ezetimibe, 0.9% alirocumab). No alirocumab-treated patient discontinued due to an adverse neurocognitive event. Memory impairment was reported with greater incidence in alirocumab-treated patients compared to either placebo-treated or ezetimibe-treated patients. Memory impairment was not characterized as serious in the 8 alirocumab-treated patients reporting this event, no patient discontinued due to the event, and it did not appear to be coincident with persistent very low LDL-C levels (2 consecutive LDL-C<25 mg/dL). Serious neurocognitive events occurred in very few patients and were associated with pre-existing medical conditions and other confounders.

On background of maximally tolerated statin therapy in placebo-controlled studies, treatment with alirocumab was associated with a higher percentage of patients reporting hepatic-related events (1.8% placebo, 2.5% alirocumab). These events were primarily associated with abnormal hepatic laboratory values. Evaluation of pre-specified categorical changes in ALT defined as ≥3x ULN (if baseline ALT < ULN) or twice baseline (if baseline ALT ≥ULN) demonstrated a slightly higher percentage of alirocumab-treated patients with this shift in ALT versus either placebo or ezetimibe-treated patients, however larger increases in (ALT >5x ULN or >10x ULN) were similar between treatment groups. There were 3 events that met the biochemical criteria for Hy's Law (2 in placebo-treated patients and in 1 alirocumab-treated patient) – however all had alternative etiologies (hepatitis A, cholecystitis, and cholangitis, respectively), and therefore do not qualify as Hy's Law cases.

Based on non-clinical observations of optic nerve degeneration and chorioretinal lesions in rats and monkeys, respectively, eye disorders were assessed in the overall safety

population and with an ophthalmologic sub-study in a subset of patients in the placebo-controlled LONG TERM study. There were numerically higher incidences of ophthalmological TEAEs in alirocumab-treated (1.8%) versus placebo-treated patients (1.4%) and alirocumab-treated (0.8%) versus ezetimibe-treated patients (0.5%). However, the TEAEs reported were varied and did not demonstrate any specific pattern. An ophthalmological sub-study evaluated 139 patients (5.9% of LONG TERM study population) with additional ophthalmologic testing. Four (4.5%) patients in the alirocumab sub-study group had an event, however 1 case of "demyelination" was considered more consistent with a neurological event of interest. Two (3.9%) placebo-treated patients in this sub-study reported an event (diabetic neuropathy and macular degeneration).

In the placebo-controlled safety pool in which all patients were on statin therapy, 15.1% patients in the alirocumab group versus 15.4% patients in the placebo group experienced a musculoskeletal-related TEAE. Two cases of rhabdomyolysis in alirocumab-treated patients were reported; 1 occurring in a 81-year-old patient on atorvastatin 80 mg who experienced a fall and concurrent diagnosis of pneumonia; the other case was later downgraded to myositis. Muscle-related AEs were less common in patients considered statin intolerant treated with alirocumab compared to patients treated with atorvastatin or ezetimibe, however, within this patient population treated with alirocumab, muscle-related adverse events were still the most common reason for treatment discontinuation.

Approximately 31% of patients in the global safety pool (combined phase 2 and 3 studies) at baseline were normoglycemic, 37% had impaired fasting glucose, and 32% were diabetic. Distribution according to these glycemic categories was comparable between treatment groups in both the placebo-controlled and ezetimibe-controlled pools at baseline. Mean change in fasting glucose and HbA1c over time did not demonstrate meaningful differences between treatment groups by baseline glycemic status. However, in exploratory analyses of shifts in glycemic status during the TEAE period using adverse events, HbA1c, and fasting plasma glucose values, a higher proportion of normoglycemic alirocumab-treated patients versus placebo or ezetimibe-treated patients met the criteria for impaired fasting glucose at least once during the treatment period. However, it should be noted that there were also patients in both the alirocumab and comparator groups with impaired fasting glucose at baseline that shifted to the more favorable normal glucose control category. The proportion of patients meeting the criteria for the diabetes category diagnosed either by adverse event or laboratory value was 3.2% in the alirocumab group and 2.2% in the placebo group, with most diagnosed by laboratory data only. Overall, for the majority of patients, glucose control remained stable and serious diabetes-related adverse events were few. It is uncertain whether the observed shifts represent a true risk for worsening glycemic control with alirocumab treatment. Glycemic control is monitorable and treatable, factors which should be considered when evaluating the benefits and risks associated with alirocumab. The

incidence of new onset diabetes mellitus with alirocumab treatment will be further investigated as a post-marketing requirement.

Within the "Cardiac disorders" SOC, treatment-emergent cardiac disorders were reported in 8.0% of alirocumab-treated patients and 9.0% of placebo-treated patients. Serious TEAEs were similar in frequency between treatment groups (4.4% alirocumab, 4.5% placebo). In the global pool of phase 3 studies, adjudicated MACE events defined as CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization occurred in 52 (1.6%) patients in the alirocumab group and in 33 (1.8%) patients in the control group.

Approximately 20% and 40% of patients treated with alirocumab had at least one calculated LDL-C value less than 15 mg/dL and 25 mg/dL, respectively compared to less than 1% of control treated patients. The majority of patients were receiving 150 mg of alirocumab every two weeks at the time of these LDL-C values. As expected, significant prognostic factors for patients that achieved LDL-C less than 25 mg/dL include baseline LDL-C and dose of alirocumab. Conclusions generated from within group comparisons should be interpreted with caution as the two groups may not be representative of each other; there could be other factors that could possibly impact the results. In addition, the duration of exposure is on average 1 year and therefore, it is uncertain what, if any, adverse effects of prolonged exposure to very low levels of LDL-C will be. With these caveats in mind, at this time review of adverse events divided by levels of LDL-C achieved did not demonstrate a safety signal.

Because the potential for increased HCV infectivity in alirocumab-treated participants is a theoretical possibility, analyses were performed to assess potential cases of hepatitis C. Within the primary safety database at the application cut-off date there were no cases of RNA confirmed hepatitis C.

In summary, alirocumab demonstrates early and sustained LDL-C lowering from baseline across patient populations, regardless of background lipid-modifying therapies, and is generally well-tolerated. LDL-C has been considered a surrogate endpoint for cardiovascular (CV) risk for decades; however, in light of new data and other considerations, we sought the input from the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on whether the alirocumab-induced changes in LDL-C alone provide sufficient evidence that its benefit exceeds risk for one or more patient population(s). Approval on the basis of a reduction in LDL-C would indicate that, for the indicated population, the effect of alirocumab on LDL-C can "substitute" for an assessment of its effect on CV outcomes. The unexpected and disappointing results from CV outcomes trials for fenofibrate,[1,2] cholesteryl ester transfer protein (CETP)

1 Keech A, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. Lancet. 2005; 366(9500): 1849-61.
2 ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med,

inhibitors,[3,4] and niacin[5,6], although most involved drugs with modest effects on LDL-C, should at least give us pause as we consider the use of lipid biomarkers in the assessment of benefit/risk for various patient populations, especially in light of the strong evidence of CV benefit and excellent safety profile established for the statins. Indeed, new lipid-lowering guidelines issued by the American College of Cardiology (ACC) and the American Heart Association (AHA)[7] focus on statins as first-line cholesterol-lowering therapy for primary and secondary prevention of atherosclerotic cardiovascular disease. However, much discussion has been made of statin-intolerance in recent years, increasing the likelihood that alternative therapies for lowering LDL-C will be sought. We have concerns that many patients who have symptoms that may be entirely unrelated to statins could prematurely discontinue their statins and turn, instead, to a PCSK9 inhibitor, which will lack long-term safety data and CV outcomes. (One might consider the atorvastatin arm in the ALTERNATIVE trial to be informative in this context.[8])

Notably, the results from Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),[9] which were presented at the American Heart Association Scientific Sessions in November, 2014,[10] and published in the New England Journal of Medicine[11] have provided information regarding the association between non-statin LDL-C reduction (on a background of statin) and cardiovascular outcomes. The trial results, if confirmed following FDA review, suggest that ezetimibe/simvastatin was

2010; 362(17): 1563-74.
3 Barter PJ, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med, 2007; 357: 2109-22.
4 Schwartz GG, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med, 2012; 367: 2089-99.
5 Boden WE, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med, 2011; 365: 2255-67.
6 The HPS2-THRIVE Collaborative Group. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med, 2014; 371: 203-12.
7 Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014; 129(25 Suppl 2): S1-45.
8 ALTERNATIVE enrolled patients who could not tolerate, due to muscle symptoms, at least two statins, one at the lowest approved dose. Patients who did not experience a musculoskeletal adverse event during a 4-week placebo run-in were randomized to alirocumab, ezetimibe, or atorvastatin 20 mg. Approximately 70% of patients randomized to atorvastatin completed 24 weeks of the double-blind treatment period (i.e., exposed for at least 22 weeks and attended the week 24 visit).
9 Cannon CP, et al. IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008;156(5):826-32.
10 Cannon CP, et al. IMPROVE-IT Trial: A Comparison of Ezetimibe/Simvastatin versus Simvastatin Monotherapy on Cardiovascular Outcomes After Acute Coronary Syndromes. American Heart Association Scientific Sessions, Late Breaking Clinical Trials. Abstract presented 17 Nov 2014.
11 Cannon CP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. NEJM 2015; 327 (25):2387-97.

modestly more effective than simvastatin alone in reducing CV events in a very high-risk population, and would provide some reassurance that the LDL-C lowering observed with ezetimibe is associated with the expected effects on atherosclerotic CV events.

These considerations were presented at a meeting of EMDAC on 9 June 2015. The panel members provided the following general input:

- There was general consensus that there were no strong safety signals observed with alirocumab treatment at this time, however, several members expressed concern that the safety database was limited to a relatively short duration of exposure and therefore the indicated treatment population should be those at highest risk. Some adverse events may emerge or become more clearly defined only after many years of exposure to larger numbers of patients. It was stressed that the ongoing cardiovascular trial will provide information regarding cardiovascular risk reduction which will help inform the benefit/risk assessment especially if there are emerging safety concerns to consider.

- The panel acknowledged that there was little or no evidence that low LDL-C levels were harmful, however the consequences of long-term exposure to very low LDL-C levels was unknown and therefore it was difficult to advise healthcare providers on how to manage very low LDL-C levels (not yet defined) other than to avoid reducing the statin dose.

- There was some uncertainty (and therefore, discomfort) regarding the use of LDL-C as a surrogate endpoint for cardiovascular risk reduction in a broader patient population particularly with a new molecular entity, although for many panel members there was less uncertainty in the population of patients with genetic LDL receptor and LDL metabolism disorders.

- Some members appeared willing to accept some uncertainty about the clinical benefit in patients with a clear, serious unmet need, such as those with significant atherosclerotic CV disease with residually high LDL-C on maximally tolerated statin.

- Unanswered questions regarding the definition of “high” LDL-C remained (i.e., the available data do not define optimal LDL-C targets); however, some panel members seemed willing to allow some ambiguity and clinical practice flexibility until CV outcomes data are available.

- There was general agreement that “statin-intolerance” was not a well-defined entity, and many panel members did not support an indication for this condition. Panel members did seem concerned that this indication would divert use away from statins. As noted above, a related concern was that statin would be down-titrated in the event of (a yet undefined) “very low” LDL-C. Some panel members felt this should be explicitly recommended against.

- There appeared to be a unanimous call for completion of the ongoing CV outomes trial in an expeditious manner. However, the majority of panel members did not believe that this trial needed to be completed pre-approval.

After deliberating on the risks and benefits of alirocumab as well as the uncertainities inherent to development and study of a new molecular entity using a surrogate as the primary efficacy endpoint, the panel members voted 13 to 3 in favor of alirocumab approval in at least one dyslipidemic patient population. In clarifying comments of their vote, members cited that until additional efficacy and safety information is obtained from ongoing clinical trials, including the applicant's cardiovascular outcomes trial, the appropriate patient populations for treatment with alirocumab should be those at the very highest cardiovascular risk such as patients with heterozygous familial hypercholesterolemia and high risk patients on maximally tolerated statins who required additional LDL-C lowering.

The primary reviewers concur with the EMDAC on approval for alirocumab and echo their sentiments regarding the need to limit the indicated population to individuals considered high risk.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable. We are not recommending a Risk Evaluation and Mitigation Strategy (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

The sponsor should conduct as PMRs:

- A trial to evaluate PK/dose (part A) and safety and efficacy (part B) in patients ages 10 to < 18 years with HeFH on stable lipid modifying therapy and LDL-C ≥ 130 mg/dL.

- A prospective observational study to evaluate fetal, infant, and childhood outcomes of pregnant women exposed to Praluent and their live born offspring through the first 5 years of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant and childhood outcomes related to humoral immune suppression.

- A large, randomized, controlled, long-term trial in which the incidence and severity of new-onset diabetes mellitus, injection site reactions, hypersensitivity,

immunogenicity, and adverse events potentially related to demyelination with alirocumab treatment will be evaluated.

- A randomized, controlled, long-term trial that prospectively evaluates changes in neurocognitive function with alirocumab treatment. The trial must be adequately powered to exclude a clinically meaningful adverse effect.

The sponsor should conduct as PMCs:

- An evaluation of anti-drug antibodies in the event of loss of efficacy to inform clinical decision-making.

- Microbiology assessments, including:
  - A repeat of the microbial retention study (b) (4)
  - Providing additional bioburden and sterility test qualification data
  - (b) (4)

- An evaluation of container closure testing of the syringes and pens.

2 Introduction and Regulatory Background

2.1 Product Information

Alirocumab is a fully human monoclonal antibody (IgG1 isotype) that targets proprotein convertase subtilisin kexin type 9 (PCSK9). Alirocumab consists of two disulfide-linked human heavy chains, each covalently linked through a disulfide bond to a fully human kappa light chain. A single N-linked glycosylation site is located in each heavy chain within the CH2 domain of the Fc constant region of the molecule. Alirocumab has an approximate molecular weight of 146 kDa.

The drug product is presented as a subcutaneous injection at doses of 75 mg/mL or 150 mg/mL solution for injection in a single-use pre-filled pen or single-use pre-filled syringe.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 2. Drugs Currently Approved in the U.S. for the Treatment of Primary Hyperlipidemia and Mixed Dyslipidemia

Drug	Mechanism of Action	Relevant Indication	Other Indications
Colestipol hydrochloride (Colestid granule, Colestid tablet)	Bile acid sequestrant	adjunctive therapy to diet for the reduction of elevated serum total and low-density lipoprotein (LDL) cholesterol in	none

Drug	Mechanism of Action	Relevant Indication	Other Indications
		patients with primary hypercholesterolemia (elevated low density lipoproteins [LDL] cholesterol) who do not respond adequately to diet	
Lovastatin (Mevacor, Altoprev)	HMG-CoA reductase inhibitor	adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb)	primary prevention of coronary heart disease slow the progression of coronary atherosclerosis in patients with coronary heart disease adolescent patients with heterozygous familial hypercholesterolemia
Pravastatin (Pravachol)	HMG-CoA reductase inhibitor	adjunctive therapy to diet to reduce elevated Total-C, LDL-C, ApoB, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia	reduce the risk of MI, revascularization, and cardiovascular mortality in hypercholesterolemic patients without clinically evident CHD reduce the risk of total mortality by reducing coronary death, MI, revascularization, stroke/TIA, and the progression of coronary atherosclerosis in patients with clinically evident CHD reduce elevated serum TG levels in patients with hypertriglyceridemia treat patients with primary dysbetalipoproteinemia who are not responding to diet treat children and adolescent patients ages 8 years and older with HeFH after failing an adequate trial of diet therapy
Simvastatin (Zocor)	HMG-CoA reductase inhibitor	adjunctive therapy to diet to reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia	reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events reduce elevated TG in patients with hypertriglyceridemia and

Drug	Mechanism of Action	Relevant Indication	Other Indications
			reduce TG and VLDL-C in patients with primary dysbetalipoproteinemia reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with HeFH after failing an adequate trial of diet therapy
Fluvastatin (Lescol, Lescol XL)	HMG-CoA reductase inhibitor	adjunctive therapy to diet to reduce elevated TC, LDL-C, Apo B, and TG and increase HDL-C in adult patients with primary hyperlipidemia and mixed dyslipidemia	reduce elevated TC, LDL-C, and Apo B levels in boys and post-menarchal girls, 10 to 16 years of age, with HeFH after failing an adequate trial of diet therapy reduce the risk of undergoing revascularization procedures in patients with clinically evident CHD slow the progression of atherosclerosis in patients with CHD
Cholestyramine (Prevalite)	Bile acid sequestrant	adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia (elevated low-density lipoprotein [LDL] cholesterol) who do not respond adequately to diet	relief of pruritus associated with partial biliary obstruction
Atorvastatin (Lipitor)	HMG-CoA reductase inhibitor	adjunct therapy to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia	reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD

Drug	Mechanism of Action	Relevant Indication	Other Indications
			reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia reduce total-C and LDL-C in patients with HoFH reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH after failing an adequate trial of diet therapy
Extended release niacin (Niaspan)	Niacin	to reduce elevated TC, LDL-C, Apo B and TG, and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia	to reduce the risk of recurrent nonfatal myocardial infarction in patients with a history of myocardial infarction and hyperlipidemia in combination with a bile acid binding resin: • slows progression or promotes regression of atherosclerotic disease in patients with a history of coronary artery disease (CAD) and hyperlipidemia • as an adjunct to diet to reduce elevated TC and LDL-C in adult patients with primary hyperlipidemia to reduce TG in adult patients with severe hypertriglyceridemia
Colesevelam hydrochloride (Welchol tablet, Welchol for oral suspension)	Bile acid sequestrant	adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults with primary hyperlipidemia as monotherapy or in combination with a statin	reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with HeFH as monotherapy or in combination with a statin after failing an adequate trial of diet therapy improve glycemic control in adults with type 2 diabetes mellitus
Ezetimibe (Zetia)	Intestinal cholesterol and phytosterol absorption inhibitor	adjunct to diet to reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in	reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate

Drug	Mechanism of Action	Relevant Indication	Other Indications
		combination with a statin	reduce elevated total-C and LDL-C in patients with HoFH, in combination with atorvastatin or simvastatin reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)
Rosuvastatin (Crestor)	HMG-CoA reductase inhibitor	adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia	patients with hypertriglyceridemia patients with primary dysbetalipoproteinemia (Type III hyperlipoproteinemia) patients with HoFH to reduce LDL-C, total-C, and ApoB slowing the progression of atherosclerosis as part of a treatment strategy to lower total-C and LDL-C pediatric patients 10 to 17 years of age with HeFH to reduce elevated total-C, LDL-C and ApoB after failing an adequate trial of diet therapy risk reduction of MI, stroke, and arterial revascularization procedures in patients without clinically evident CHD, but with multiple risk factors
Ezetimibe, simvastatin (Vytorin)	Intestinal cholesterol absorption inhibitor and HMG-CoA reductase inhibitor	adjunctive therapy to diet to reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia	reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments
Fenofibrate (Tricor, Antara, Triglide, Lipofen, Fenoglide)	PPAR-α activator	adjunct to diet to reduce elevated LDL-C, Total-C, TG and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia	to reduce TG in adult patients with severe hypertriglyceridemia
Choline fenofibrate (Trilipix)	PPAR-α activator	adjunct to diet to reduce elevated LDL-C, Total-C, TG and Apo B, and to increase HDL-C in patients	to reduce TG in patients with severe hypertriglyceridemia

Drug	Mechanism of Action	Relevant Indication	Other Indications
		with primary hypercholesterolemia or mixed dyslipidemia	
Pitavastatin (Livalo)	HMG-CoA reductase inhibitor	adjunctive therapy to diet to reduce elevated TC, LDL-C, Apo B, TG, and to increase HDL-C in patients with primary hyperlipidemia or mixed dyslipidemia	none
Fenofibric acid (Fibricor)	PPAR-α activator	adjunct to diet to reduce elevated TC, LDL-C, TG and Apo B, and to increase HDL-C in adult patients with primary hypercholesterolemia or mixed dyslipidemia	to reduce TG in adult patients with severe hypertriglyceridemia
Atorvastatin calcium, ezetimibe (Liptruzet)	Intestinal cholesterol absorption inhibitor and HMG-CoA reductase inhibitor	adjunctive therapy to diet to reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia	reduce elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-lowering treatments

Source: Individual drug prescribing information (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm)

2.3 Availability of Proposed Active Ingredient in the United States

Alirocumab is not currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Alirocumab is first-in-class.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 3. Regulatory History

Date	Event
12 Nov 2009	US IND opened (105574) • IND placed on partial clinical hold for doses > 3 mg/kg due to insufficient information to assess risks to human subjects based on findings of liver sinusoidal cell hyperplasia and inflammation with sporadic hemorrhage, congestion, vacuolation, degeneration, and/or necrosis of adjacent hepatocytes that was only partially reversible after a 4-week recovery
5 Feb 2010	Submission of complete response to clinical hold
3 Mar 2010	Clinical hold removed
11 June 2010	Partial clinical hold for duration exceeding 92 days (inadequate duration of toxicological data in rats)

Date	Event
3 Dec 2010	Submission of complete response to clinical hold
23 Dec 2010	Clinical hold removed
12 Apr 2011	Correspondence re: LTS (long-term safety study) • Provide # of US sites and est. # of US subjects planned to enroll • Provide plans to ensure racial/ethnic diversity • Provide plans to ensure adequate representation of males and females as well as subjects > 65 yrs • Provide plan for completion of thorough QT study • Provide plan for addressing LDL < 25 mg/dL • Provide rationale for not maximizing statin dose • Provide assurance that 26 wk rat and monkey tox data will be provided prior to exceeding 13 wks in the clinic • Submit embryo-fetal data prior to enrolling WOCBP for greater than 12 wks • Submit study reports for completed 5 and 13 wk combination (+ Lipitor) tox studies in monkeys
6 Sep 2011, 27 Oct 2011, 17 Nov 2011	Correspondence re: LTS • Recommended changing open-label extension phase to a DB, PC extension (sponsor agreed) • Recommended using measured instead of calculated LDL-C (sponsor agreed for key time points) • Recommended monitoring adrenal function and neuro exams (sponsor made proposal that FDA agreed with) • Vit E testing at certain visits deemed acceptable • Recommended testing for hepatitis C at end of trial (sponsor agreed) • Recommended ophtho exams and preclinical eye findings be included in the ICF (sponsor proposed ophtho substudy; FDA agreed) • Recommended that all CV SAEs be adjudicated
9 Mar 2012	End-of-Phase 2 meeting minutes • FDA agreed with proposed phase 3 patient populations • Agreement on the 2 dosing regimens for the phase 3 program • Agreement on the design of ALTERNATIVE, including addition of a statin re-challenge arm • Agreement on assessment of LDL-C, including use of calculated and measured LDL-C • FDA informed the sponsor that alirocumab vs ezetimibe or vs statin up-titration would not be considered for the label before the CV outcomes trial was completed and provided a robust assessment of long-term safety and efficacy • Requirement for a minimum 25% of MACE from OUTCOMES be accrued prior to BLA submission (requirement was later removed; see below) • Planned safety database at the time of BLA submission acceptable • Agreement that the phase 3 program would provide adequate clinical data to support the S&E of the PFS and PFP • Planned pop PK/PD approach was reasonable • Approach to evaluating the effect of renal impairment and age in pop PK analysis was reasonable • Nonclinical and clinical programs appropriate to assess DDI potential • QT study considered unnecessary
27 Apr 2012	Agency Advice Letter • Agreement on definition of “statin intolerance”

Date	Event
	• The sponsor was informed that it would be a review issue whether FDA would include data from a statin intolerant trial in labeling before the CV outcomes trial was completed and provided a robust assessment of long-term safety and efficacy
5 Aug 2013	Type C meeting (written guidance) re: LTS interim analysis • FDA disagreed with proposal to unblind and analyze (and publically disclose) 6 mos of interim LTS data in order to inform dosing for the ongoing CVOT
9 Sep 2013, 3 Mar 2014, 19 May 2014, 15 Jul 2014	Statistical feedback on accounting for missing data, and SAPs, electronic data presentation, and ISS/ISE pooling
9 May 2014	Type C meeting (written responses) • If submitting prior to reaching the 25% of MACE in CVOT, include: o number (%) of primary endpoint events that have been accrued o number (%) that have been adjudicated o number accepted as endpoints vs. rejected o number (%) of subjects who have been randomized at time of BLA submission
4 Sep 2014	Pre-BLA meeting • Agreed with investigator financial disclosure information • Made recommendations regarding reviewer guides • Acknowledged planned use of priority voucher; in lieu of using the voucher, any decisions regarding priority review would be made after BLA submission • Recommended that different configurations (PFS, PFP) be submitted under a single application • Nonclinical program acceptable • Data presentation for 4-mo safety update agreed upon • Sponsor confirmed that CVOT would not be unblinded • Sponsor agreed to provide narratives for SAEs and deaths for ongoing OL studies • No determination was made on the need for a REMS • Agreed on approach for ISS/ISE • Conducting pediatric studies as described in the agreed iPSP should satisfy PREA, pending review of the full protocols • Formulation in phase 3 is identical to the to-be-marketed • Sponsor agreed to provide minutes of all DSMB and steering committee mtgs • Sponsor agreed to provide definitions for primary hypercholesterolemia and mixed dyslipidemia and justification for each lipid parameter proposed for labeling • The sponsor proposed to provide additional requested data related to the adjudication process within 30 days of the BLA submission; FDA agreed • Sponsor confirmed that lipid levels were never provided to adjudicators • The sponsor agreed to provide a study evaluating for needle stick prevention within the first 30 days of BLA submission
24 Nov 2014	BLA submitted

Source: Reviewer generated from information in Clinical Overview and meeting minutes

2.6 Other Relevant Background Information

PCSK9 Inhibition

The proprotein convertase subtilisin kexin type 9 (*PCSK9*) gene encodes a serine protease that binds to and down-regulates LDL receptors (LDL-R) in the liver. Overexpression of *PCSK9* (via "gain-of-function" mutations) leads to an autosomal dominant hypercholesterolemia phenotype[12] and increases risk for atherosclerotic CVD.[13] Conversely, single nucleotide polymorphisms encoding sequence variations that lead to missense or nonsense mutations of the *PCSK9* gene are associated with increases in LDL-R and decreased circulating LDL-C concentrations. A population study found that the moderate decrease in LDL-C in individuals with these DNA-sequence variations was associated with a substantial reduction in the incidence of coronary events, even in populations with a high prevalence of non-lipid-related cardiovascular risk factors.[14]

We are aware of three cases of individuals homozygous (or compound heterozygous) for loss-of-function *PCSK9* alleles with very low LDL-C concentrations that have been reported in the literature:

1. a 21-year-old African woman with an LDL-C of 15 mg/dL; no further information about this patient was provided, except that she was identified for genotyping at a postnatal clinic,[15]

2. a 32-year-old African American woman with an LDL-C of 14 mg/dL; she is an apparently healthy, normotensive, fertile, college-educated individual with normal liver and renal function tests,[16] and

3. a 49-year-old French white man who was found to have extremely low LDL-C (7 mg/dL) on admission for rapid-onset of an insulin-requiring diabetes mellitus of unknown etiology; LDL-C not during acute illness was reported to be 16 mg/dL. This patient was shown to have moderate liver steatosis on abdominal ultrasound with normal hepatic enzymes and liver function tests. He had no reported history of diarrhea, eye, or neurological abnormalities related to any vitamin deficiency. His

12 Abifadel M, et al. Mutations in *PCSK9* cause autosomal dominant hypercholesterolemia. Nat Genet. 2003; 34(2): 154-6.
13 Abifadel M, et al. Mutations and polymorphisms in the proprotein convertase subtilisin kexin 9 (PCSK9) gene in cholesterol metabolism and disease. Hum Mutat. 2009; 30(4): 520-9.
14 Cohen JC, et al. Sequence variations in *PCSK9*, low LDL, and protections against coronary heart disease. New Engl J Med. 2006; 354(12): 1264-72.
15 Hooper AJ, et al. The C679X mutation in *PCSK9* is present and lowers blood cholesterol in a southern African population. 2007; 193(2): 445-8.
16 Zhao Z, et al. Molecular characterization of loss-of-function mutations in *PCSK9* and identification of a compound heterozygote. Am J Hum Genet. 2006; 79: 514-23.

mother was deceased at age 66 from dementia, whereas his father was healthy at age 79. His grandparents died at the ages of 79, 87, 91, and 94 years.[17]

At this time there are too few cases to provide conclusive data about loss-of-function *PCSK9* polymorphisms and the risk of human disease, although given the association of statins with diabetes risk,[18] the development of diabetes in the 49-year-old man discussed above is of interest. (See Dr. Roberts' safety review for further discussion of alirocumab and glycemic parameters.)

Theoretical risks have been identified with the PCSK9 inhibitors as a class. The following issues of potential (theoretical) concern have been identified; please refer to Dr. Elmore's review for further information:

- *Immunosuppression, especially when co-administered with HMG Co-A reductase inhibitors (statins)*. Immune cells (especially lymphocytes) are critically dependent on adequate membrane cholesterol concentrations. Co-administration of statins, which inhibit intracellular synthesis of cholesterol and are themselves immunomodulatory,[19] could theoretically exacerbate the immunosuppressive potential of PCSK9 inhibitors.

- *Increased susceptibility to hepatitis C virus (HCV) infection*. CD81, a critical component of the HCV receptor, is under negative regulation by PCSK9. Therefore, inhibition of PCSK9, by upregulating CD81 expression, might increase the availability of the HCV receptor, thereby increasing susceptibility to HCV infection.

- *Increased risk of colorectal cancer via increased intestinal bile acid load.* Alirocumab, by increasing the expression of LDL-R, increases hepatic uptake of cholesterol. Given that the primary route of elimination of cholesterol by hepatocytes is conversion to bile acids, treatment with alirocumab may increase the load of bile acids delivered to the intestines, especially in hypercholesterolemic patients. Increased intestinal secondary bile acid load has been shown to increase intestinal cancer risk in rodents.

LDL Cholesterol as an Endpoint

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease. The link between LDL-C and cardiovascular disease is exemplified by the prototypical hypercholesterolemic condition, homozygous familial hypercholesterolemia (HoFH).

17 Cariou B, et al. PCSK9 dominant negative mutant results in increased LDL catabolic rate and familial hypobetalipoproteinemia. Arterioscler Thromb Vasc Biol (2009); 29: 2191-7.
18 Reviewed in: Robinson JG. Statins and diabetes risk: how real is it and what are the mechanisms? Curr Opin Lipidol (2015). Published online ahead of print.
19 Greenwood J, et al. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. Nat Rev Immunol, 2006; 6(5): 358-70.

These patients have a distinctive phenotype of extremely high LDL-C from birth, cutaneous or tendinous xanthomas, and the onset of CV disease in early childhood.[20] Untreated patients with HoFH often die by 20 years of age, although recent advances in LDL-C lowering therapy (e.g., statins and LDL apheresis) have delayed CV events and prolonged survival in these patients.[20]

Historically, the National Cholesterol Education Program Adult Treatment Panels (NCEP-ATP), appointed by the NHLBI, have recommended various LDL-C cut-offs to reduce cardiovascular risk. For example, the most recent ATPIII update recommended that in high-risk persons, the LDL-C goal is less than 100 mg/dL, but when CV risk is very high, an LDL-C goal of less than 70 mg/dL is "a reasonable clinical strategy."[21] Furthermore, for moderately high-risk persons, the recommended LDL-C goal is less than 130 mg/dL, with an LDL-C goal less than 100 mg/dL being a therapeutic option. However, in 2013, the NCEP-ATP cholesterol guidelines were updated by an expert panel from the American College of Cardiology (ACC) and the American Heart Association (AHA).[7] These guidelines have changed the paradigm of cholesterol treatment from LDL-C "goals" to the identification of patients most likely to benefit from cholesterol-lowering statin therapy. This is because the only strategy that has been utilized in cardiovascular outcomes trials conducted over the last 20 years has been the use of fixed doses of cholesterol-lowering drugs to reduce atherosclerotic CV risk, as opposed to treating to a specific LDL-C goal. Furthermore, because the overwhelming body of evidence for CV risk reduction has derived from statin trials, the guidelines, and standard-of-care medical practice focus on statins as first-line cholesterol-lowering therapy for primary and secondary prevention of atherosclerotic cardiovascular disease.

Two drugs that have been recently approved for HoFH (but notably have serious safety concerns that would preclude studying or approving for the general patient population) were evaluated based on changes in LDL-C. This is similar to the approval pathway for older LDL-C lowering drugs (e.g., ezetimibe); in the past, reduction of LDL-C alone has been viewed favorably as a surrogate outcome if the reduction was sufficiently robust and if the investigational product did not have safety signals raising concern that risk exceeded benefit. However, given new concerns about utilizing lipid biomarkers as a CVD surrogate with failed CV outcomes trials for fenofibrate,[1,2] cholesteryl ester transfer protein (CETP) inhibitors,[3,4] and niacin[5,6] as well as the strong evidence of CV benefit and excellent safety profile established for the statins, new lipid-altering drugs for broader patient populations face a high level of scrutiny prior to approval.

Notably, the results from Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT),[22] which were presented at the American Heart

20 Raal FJ, et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation, 2011; 124: 2202-7.
21 Grundy SM, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation, 2004; 110: 227-39.
22 Cannon CP, et al. IMPROVE-IT Investigators. Rationale and design of IMPROVE-IT (IMProved

Association Scientific Sessions in November, 2014,[23] have provided preliminary information regarding the association between non-statin LDL-C reduction (on a background of statin) and cardiovascular outcomes. (Note that the Division has not reviewed the results of the IMPROVE-IT trial; it is possible that the Division will reach different conclusions than the trial's investigators.) IMPROVE-IT evaluated ezetimibe/simvastatin 10/40 mg combination compared to simvastatin 40 mg monotherapy in over 18,000 patients with stabilized high-risk acute coronary syndrome with a composite primary outcome of cardiovascular death, myocardial infarction, nonfatal stroke, rehospitalization for acute coronary syndrome, or revascularization. According to the results that the investigators have presented, baseline mean LDL-C was 95 mg/dL in both groups and the mean LDL-C at one year was 53.2 mg/dL in the ezetimibe/simvastatin group and 69.9 mg/dL in the simvastatin group. The hazard ratio of the primary endpoint of first event has been reported to be 0.94 (95% CI 0.89, 0.99).[23] Thus, the preliminary IMPROVE-IT results, if confirmed, suggest that ezetimibe/simvastatin was modestly more effective than simvastatin alone in reducing CV events in a very high-risk population.

In the absence of CV outcomes data, FDA's considerations regarding the approval of novel LDL-lowering therapies such as alirocumab include the direction and magnitude of drug-induced changes in LDL-C, the effects of the drug on other markers of cardiometabolic risk, and characterization of the drug's safety profile.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was of high quality, well-organized, and reasonably complete. The sponsor has been responsive to information requests by providing additional information in a timely fashion during the review.

3.2 Compliance with Good Clinical Practices

The clinical trials described in this application were conducted as part of a global clinical program in compliance with Good Clinical Practice (GCP), and met the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the sponsor, all applicable international laws and regulations, and national laws and regulations of the countries in which the trials were conducted.

Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J. 2008;156(5):826-32.
23 Cannon CP, et al. IMPROVE-IT Trial: A Comparison of Ezetimibe/Simvastatin versus Simvastatin Monotherapy on Cardiovascular Outcomes After Acute Coronary Syndromes. American Heart Association Scientific Sessions, Late Breaking Clinical Trials. Abstract presented 17 Nov 2014.

Violations related to GCP non-compliance led to the closure of several clinical sites.

A Russian site that randomized 14 patients in FH I and 7 patients in HIGH FH was terminated. During a monitoring visit, the monitor discovered that several kits had been listed as being dispensed and recorded as having been injected (in either case report forms or patient diaries), but these were discovered to be at the site unopened, indicating that the injections had not actually been performed.

A U.S. site that randomized 1 patient in FH I, 6 patients in HIGH FH, 5 patients in OPTIONS I, 5 patients in OPTIONS II, and 6 patients in ALTERNATIVE was terminated. The Principal Investigator reportedly failed to maintain adequate records of the investigation and failed to ensure that the investigation was conducted in accordance with the investigational plan.

In trial COMBO I, one U.S. site was terminated due to violations related to GCP non-compliance due to protocol adherence and investigator oversight. A total of 5 patients were randomized at this site.

In trial LONG TERM, one U.S. site was terminated as the investigator failed to maintain adequate records of the investigation, including failure to ensure compliance with regard to the maintenance of medical records to confirm patient eligibility, inadequate documentation of informed consent, lack of maintenance of drug inventory logs, and lack of oversight by the investigator. One patient was randomized at this site.

Sensitivity analyses for efficacy were conducted by the sponsor excluding these sites; see section 6.1.4.

As described in Dr. Cynthia Kleppinger's inspection summary, clinical inspections by FDA consisted of seven domestic and seven foreign clinical sites representing 16 sites (four for each protocol), as well as the sponsor and CRO. For 10 clinical sites and the sponsor and CRO, a Form FDA 483 was not issued and the classifications are all NAI (No Action Indicated).

Four clinical sites were issued a Form FDA-483, citing inspectional observations. Preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). Although regulatory violations were noted, Dr. Kleppinger concluded that they are unlikely to significantly impact primary safety and efficacy analyses.

Dr. Kleppinger alerted the review team to several findings at the sponsor inspection that required further follow-up. A brief description of the issues and the sponsor's responses are provided below:

- A tool was provided to investigators to extrapolate off-treatment LDL-C values in order to confirm a clinical diagnosis of HeFH when no off-treatment LDL-C was available; however, this tool was not described in the protocol or CSR. The sponsor noted that this tool is published[24] and uses correction factors based on a large meta-analysis.[25] The sponsor states that the tool has been accepted and incorporated in the Dutch FH guidelines [article in Dutch].[26] The sponsor noted and confirmed at the late cycle meeting that this tool was used only to confirm the diagnosis in patients with a history of an HeFH diagnosis, as it was considered unethical to take off of lipid-lowering therapy for screening purposes. It was not used to screen for HeFH in the general population.

- The second issue was related to the identification of 108 patients who were re-screened for possible HeFH prior to enrollment in the HeFH-only open label extension portion of LONG TERM (in other words, these were patients who were identified as having established CHD/CHD risk equivalents and therefore were not screened for HeFH prior to enrollment in the double-blind portion of the trial). The sponsor stated that they received sporadic requests from investigators involved in the LONG TERM study to consider the eligibility of their patients for participation in the OLE study. (In patients eligible to participate in the LONG TERM study on the basis of CHD/CHD risk equivalents, the eCRF question "Does the subject have a diagnosis of HeFH (Yes/No)" could be answered based on known medical history. The diagnosis of HeFH supported by genotyping or calculation of a clinical score was only mandatory for patients eligible on the basis of heFH without CHD/CHD risk equivalent.) Rather than answering periodic requests from investigators for eligibility of their patients into the OLE study on a case-by-case basis, the sponsor decided to systematically review all patients without a diagnosis of HeFH at screening. The sponsor applied a set of clinical criteria to the available data in the eCRF for all of the 1924 patients who were identified as non-HeFH patients. This review of eCRF data included calculated LDL-C at the screening visit for which the LDL-C back-calculator was applied, the presence or history of arcus cornealis in patients < 45 years of age, the presence or history of tendon xanthomata, premature coronary artery disease, premature cerebral or vascular disease, and family history of premature CHD. This review resulted in an identification of 108 patients with a potential diagnosis of HeFH, with clinical criteria scores in the range identified as definite/certain cases of HeFH. Data queries were then sent for these 108 patients, asking sites to confirm whether or not their patient had HeFH. The final determination of HeFH status was made by the investigator based on the

24 Besseling J, et al. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disase: a study of a cohort of 14,000 mutation carriers. Atherosclerosis (2014); 233: 219-23.
25 Law MR, et al. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ (2003); 326: 1423-7.
26 Walma EP, et al. [The practice guideline 'Diagnosis and treatment of familial hypercholesterolaemia' of the Dutch ealth Care Insurance Board] [Article in Dutch]. Ned Tijdschr Geneeskd (2006); 150(1): 18-23.

consideration of all available information. The investigators confirmed HeFH in 51 of the 108 patients. All 51 patients had a clinical criteria score greater than 8 (as calculated by the sponsor), with 49 of 51 patients identified by the sponsor as having an estimated off-treatment LDL-C > 330 mg/dL using the LDL-C back-calculator. The 2 of 51 patients with off-treatment LDL-C < 330 mg/dL using the LDL-C back-calculator were identified by the sponsor based on the presence of xanthoma.

- The inspectors were made aware of 47 patients in LONG TERM with lipid testing done through local laboratories; this caused concern for unblinding. The sponsor responded that since the FDA inspection, a systematic approach for detecting cases of potential unblinding based on lipid testing done through local laboratories during the study and reported to the site and/or patient was undertaken. As a result of this more comprehensive investigation, the number of patients in LONG TERM with lipid testing done through local laboratories and reported to the site and/or patient was found to be 81. The sponsor conducted additional sensitivity analyses on the primary efficacy endpoint by excluding patients with lipid testing done through local laboratories regardless of whether the unblinded LDL-C value was obtained before or after the primary efficacy endpoint, and regardless of whether the patient had discontinued investigational medicinal product or not. The results of the two additional sensitivity analyses in the LONG TERM study, one for the 47 patients presented at the time of FDA inspection and another one for the 81 patients identified by the subsequent systematic approach, were conducted and were highly consistent with the primary efficacy analysis.

- FDA asked for clarification regarding inclusion of coronary artery calcium scoring as a non-invasive test for evidence of CHD to determine inclusion in the OPTIONS I and OPTIONS II trials. FDA noted that this test was not mentioned in any protocol or clinical study report, and was only identified during the sponsor inspection. This was not fully address via the response to the information request, so further clarification was provided at the late cycle meeting and post-late cycle meeting. The sponsor stated that, originally, this test was not used to determine eligibility. However, on review of the patients enrolled in OPTIONS I, OPTIONS II, and ALTERNATIVE, investigators for three patients requested calcium scores be considered (1 in OPTIONS I and 2 in ALTERNATIVE) as part of the entry criterion for “clinically significant CHD diagnosed by invasive or non-invasive test.” Notably, all three of the patients would have qualified for study entry without the calcium score, based on their calculated SCORE (> 1% for the ALTERNATIVE patients and > 5% for the OPTIONS I patient). Accordingly, no patients in the program were enrolled based solely on calcium scoring as an entry criterion.

Overall, the findings from the clinical inspections support the validity of data as reported by the sponsor under this BLA. See Dr. Kleppinger’s review for further details.

3.3 Financial Disclosures

The sponsor has adequately disclosed financial arrangements with clinical investigators. Disclosed interests or lack of disclosure despite due diligence do not raise significant questions about the integrity of the data. These were large, randomized controlled trials with objective endpoints and many investigators. It is unlikely the relatively small number of investigators with disclosed interests would impact the overall results. The total number of investigators with disclosed interests was 7, out of 3070 total investigators who screened at least one patient in the 12 covered phase 2 and 3 trials. The number of patients potentially impacted was small, 42 out of 5296 (0.8%) randomized in phase 3. For additional details, see section 9.6 in the appendix.

Table 4. Clinical Investigators with Disclosable Interests

Name	Role	Trial(s)	Details of Disclosed Financial Interests and Arrangements	Number of Patients Randomized
(b) (6)	Principal investigator	(b) (6)	Received $51,275.85 for attendance at advisory board meetings, WDC, and EASD from Sanofi from February 2012 until May 2014	(b) (4)
	Principal investigator		Received $44,789.00 as honoraria from Sanofi from January 2011 until May 2014	
	Principal investigator		Received $49,028.00 for consulting services and steering committee member participation from Sanofi from November 2011 until April 2014	
	Sub-investigator		Received $67,706.00 from Regeneron for a grant for a research study from September 2013 until April 2014	
	Principal investigator		Received $32,166.00 from Sanofi for attendance at conferences, advisory board meetings, and EASD from November 2013 until May 2014	
	Sub-investigator		Received $131,931.00 as honoraria from Sanofi from January 2011 until May 2014	
	Principal investigator		Received $148,272.00 from Sanofi for lectures from January 2012 until June 2014	

Source: Financial disclosure (eCTD 1.3.4), EFC12492 BIMO Part I, EFC12732 BIMO Part I, LTS11717 BIMO part I, R727-CL-1119 BIMO Part I, R727-CL-1110 BIMO Part I, R727-CL-1118 BIMO Part I

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Office of Biotechnology Products (OBP) recommends approval of alirocumab. The data submitted in this application are adequate to support the conclusion that the manufacture of Praluent (alirocumab) is well controlled and leads to a product that is pure and potent. OBP recommends that this product be approved for human use under conditions specified in the package insert.

OBP recommends approval of the proposed lot release/stability specifications and stability protocols for alirocumab drug substance and drug product.

OBP recommends an expiry period of (b) (4) months for alirocumab drug substance when stored at (b) (4) and an expiry period of 18 months for alirocumab drug product when stored at 2-8°C.

Please see the Office of Biotechnology Products's review for further details.

4.2 Clinical Microbiology

The BLA was reviewed for microbial control of the drug product manufacturing process and for drug product sterility assurance. The BLA is recommended for approval from a product quality microbiology perspective. For additional details please see Dr. Colleen Thomas's review. Product quality microbiology post-marketing commitments are listed in Section 1.4.

The manufacturing process of the alirocumab bulk drug substance from a microbiological quality perspective was reviewed and recommended for approval. For additional details please see Dr. Reyes Candau-Chacon's review.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology and toxicology team recommends approval. Dr. Lee Elmore is the primary reviewer. Toxicology studies of up to 6 months with weekly subcutaneous dosing that provide exposure multiples of up to 11-fold in rats and up to 103-fold in monkeys compared to the maximum recommended human dose of 150 mg Q2W, based on plasma exposure, were conducted. Dr. Elmore notes that overall, alirocumab was well-tolerated in rats and monkeys. In rats, exaggerated pharmacologic effects consisted of minimal to moderate liver sinusoidal cell hypertrophy (only observed early, not with chronic dosing) and reversible minimal to mild adrenal cortex hypertrophy. Both

tissues have been shown to be sensitive to low plasma HDL-C. Reproductive toxicity consisted of increased maternal deaths and decreased humoral immunity in infant monkeys. (b) (4)
Genetic toxicity and carcinogenicity studies were considered not applicable as alirocumab is a monoclonal antibody. Please see Dr. Elmore's review for further details.

4.4 Clinical Pharmacology

The pharmacokinetic (PK), and pharmacodynamic (PD) properties of alirocumab were assessed in ten clinical pharmacology phase 1 studies conducted in healthy individuals (including Japanese individuals), special populations (patients with hepatic impairment), and in patients with familial and non-familial hypercholesterolemia. The PK of alirocumab and its effects on PCSK9 were also assessed in five phase 2 and four phase 3 trials. Population pharmacokinetic (pop PK) studies were conducted using data from pre-specified phase 1, 2, and 3 trials. Clinical pharmacology assessments were evaluated in the trials outlined in Table 5:

Table 5. Pharmacokinetic and Pharmacodynamic Assessments in Clinical Trials

Study type	Study code	Alirocumab dose or dose range	Number enrolled
Biopharmaceutical studies (phase 1 studies)			
Single SC dose of 2 formulations	PKD12010	SC 200 mg as 175 mg/mL or 150 mg/mL solution	24
Single SC dose of 2 formulations	PKD12011	SC 200 mg as 175 mg/mL solution produced by cell line C1 or C2	24
Single SC dose of 2 formulations	PKD12275	SC 300 mg as 175 mg/mL solution (1 injection of 1.71 mL) or as 150 mg/mL solution (2 injections of 1 mL or 1 injection of 2 mL)	36
Single SC dose with 3 different injection sites	BDR13362	SC 75 mg as 75 mg/mL solution	60
Pharmacokinetics, pharmacodynamics, and initial tolerability in healthy subjects (phase 1 studies)			
Single ascending dose (healthy subjects)	CL-0902	IV 0.3, 1.0, 3.0, 6.0 or 12 mg/kg	40
Single ascending dose (healthy subjects)	CL-0904	SC 50, 100, 150 and 250 mg	32
Pharmacokinetics, pharmacodynamics, and initial tolerability in patients (phase 1 studies)			
Single to multiple ascending dose	CL-1001	SC 50, 100, and 150 mg, (Part A)	62
		200 mg (Part B)	10
Intrinsic factors (phase 1 studies)			
Race (Japanese), single dose (healthy subjects)	TDU12190 (Japan)	SC 100, 150, 250 and 300 mg,	32
Hepatic impairment (mild and moderate), single dose	POP12671	SC 75 mg	25 (17 with hepatic impairment)

Study type	Study code	Alirocumab dose or dose range	Number enrolled
Pharmacodynamics and pharmacokinetics/pharmacodynamics in healthy subjects (phase 1 studies)			
PD, PK, Safety Repeated doses	PKD12910	SC 150 mg Q4W (as add-on to ezetimibe, fenofibrate, or placebo)	72
Pharmacokinetics in patients (efficacy/safety studies) in phase 2 studies			
Dose finding study (non-FH) - Efficacy, Safety, PK	DFI11565	SC 50 mg, 100 mg and 150 mg Q2W, and 200 mg and 300 mg Q4W	183
Dose finding study (heFH) - Efficacy, Safety, PK	CL-1003	SC 150 mg Q2W, and 150 mg, 200 mg, and 300 mg Q4W	77
Dose finding study (non FH/Japan) Efficacy, Safety, PK	DFI12361	SC 50 mg, 75 mg and 150 mg Q2W	100
Efficacy, Safety, PK	DFI11566	SC 150 mg, Q2W	92
Patients with autosomal dominant hypercholesterolemia: GOFm in 1 or both alleles of the PCSK9 gene and in patients with either GOFm in 1 or both alleles of the PCSK9 gene or LOFm in 1 or more alleles of the Apo B gene	CL-1018	SC 150 mg Q2W	23
Pharmacokinetics in patients (efficacy/safety studies) in phase 3 studies			
Monotherapy study - Efficacy, Safety, PK	MONO (EFC11716)	SC 75 mg Q2W, (could be up-titrated to 150 mg Q2W at Week 12)	103
Long-term study - Safety, Efficacy, PK	LONG TERM (LTS11717)	SC 150 mg Q2W	2341
HeFH study Efficacy, Safety, PK	FH I (EFC12492)	SC 75 mg Q2W (could be up-titrated to 150 mg Q2W at Week 12)	486
High CV risk study Efficacy, Safety, PK	COMBO II (EFC11569)	SC 75 mg Q2W, (could be up-titrated to 150 mg Q2W at Week 12)	720
Population pharmacokinetics in efficacy/safety studies			
POP PK MM POP PK/PD	POH0377 POH0394	Pooled data from phase 1 (CL-0902, CL0904, CL-1001, TDU12190 and PKD12910), phase 2 (DFI11565, DFI11566, DFI12361 and CL-1003) and phase 3 (MONO, COMBO II, FH I, LONG TERM) clinical studies	Not applicable
TMDD	POH0400	Pooled data from phase 1, phase 2 (DFI11565, DFI11566, DFI12361 and CL-1003) and phase 3 (MONO) clinical studies	Not applicable

Apo B = apolipoprotein B; HeFH = heterozygous familial hypercholesterolemia; GOFm = gain of function mutation; IV = intravenous; LOFm = loss of function mutation; MM = Michaelis-Menten; PD = pharmacodynamics; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous; TMDD = target-mediated drug disposition

Source: Summary of Clinical Pharmacology, Table 1

Two devices were evaluated in phase 3, a pre-filled syringe (PFS) only used in the LONG TERM trial, and a pre-filled pen (PFP) used in all other phase 3 trials.

4.4.1 Mechanism of Action

Alirocumab is a fully humanized monoclonal antibody that binds to PCSK9 and inhibits its function. PCSK9 is a serine protease that is secreted from cells and internalized in the hepatic endosome with the LDL receptor (LDL-R), promoting the degradation of LDL-R.[27] As the LDL-R is the major pathway through which LDL-C is cleared from the circulation, PCSK9 increases circulating LDL-C. By inhibiting the binding of PCSK9 to the LDL-R, alirocumab increases available LDL-R to clear LDL particles, thereby lowering LDL-C.

4.4.2 Pharmacodynamics

Total (complexed and free) and free (not complexed) PCSK9 concentrations represent the molecular target of alirocumab.

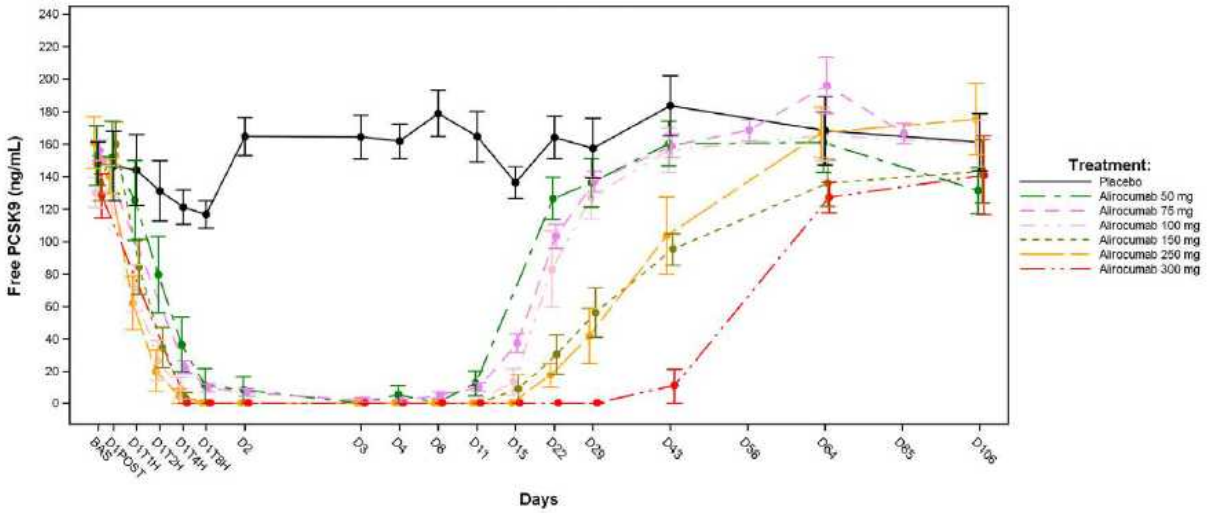
When alirocumab is in excess and free PCSK9 is depleted (target saturation), then any newly formed PCSK9 is immediately complexed. The elimination of the PCSK9-alirocumab complex is slow relative to formation, therefore over time, the concentration of total PCSK9 plateaus. Total PCSK9 is therefore a marker of target saturation. Once target binding is saturated, further increases in dose no longer result in further increases in total PCSK9 concentrations, but rather a prolongation of the plateau in total PCSK9 concentrations.

Once the concentrations of alirocumab are no longer sufficient to complex all newly synthesized free PCSK9, the concentrations of total PCSK9 decline along with the return of detectable concentrations of free PCSK9.

As Figure 2 demonstrates, alirocumab decreases free PCSK9 to zero in a non-dose-dependent manner. Different doses appear to affect duration of free PCSK9 suppression, with increasing doses prolonging the effect.

27 Lamber G, et al. Molecular basis of PCSK9 function. Atherosclerosis (2009). 203(1): 1-7.

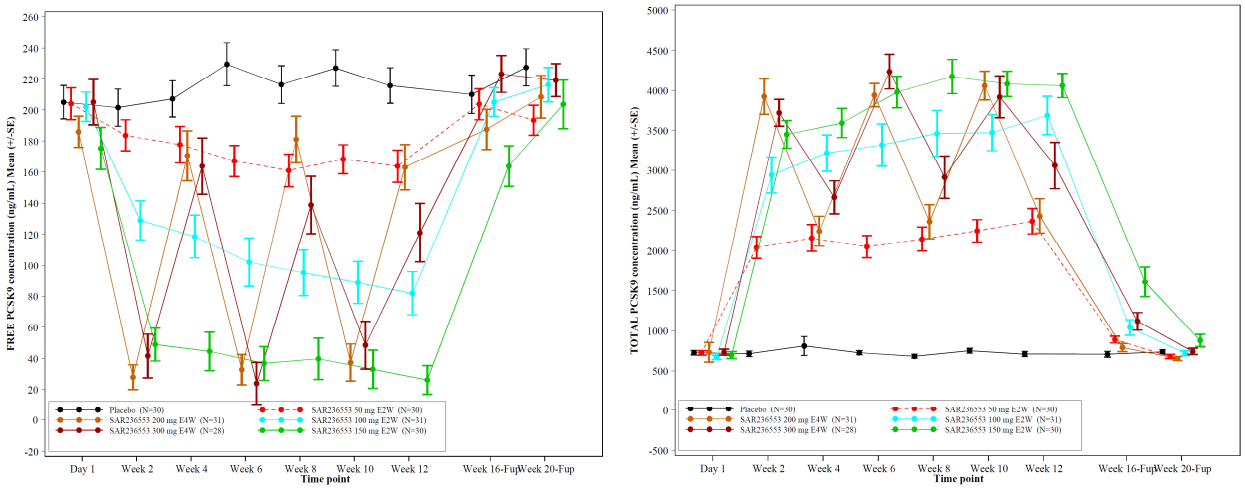
Figure 2. Free PCSK9 Concentrations by Alirocumab Dose, Pooled Phase 1 Studies



Source: Summary of Clinical Pharmacology, Figure 6

In the dose-ranging phase 2 trial, DFI11565, the largest decrease in free PCSK9 was seen in the 150 mg Q2W group. Doses higher than 150 mg did not result in higher total PCSK9 concentrations, indicating that saturation was achieved at 150 mg Q2W.

Figure 3. Free (Left) and Total (Right) PCSK9 by Alirocumab Dose, Trial DFI11565



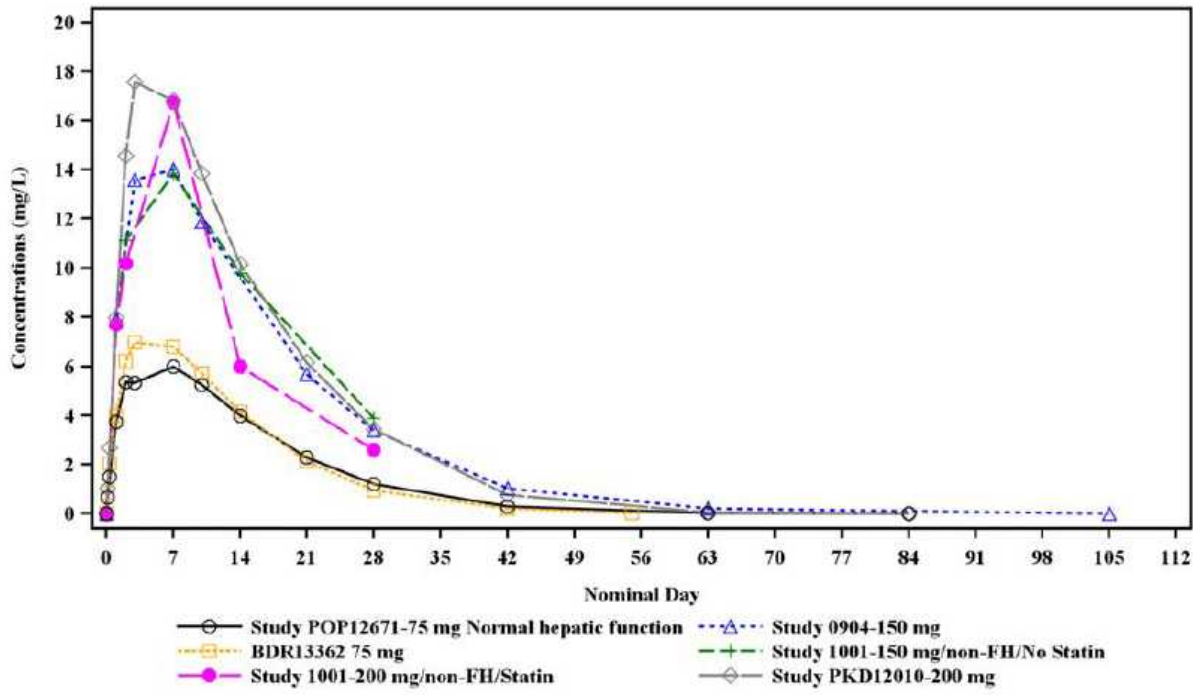
Source: Summary of Clinical Pharmacology, Figure 8

Dose response for efficacy is discussed further in section 6.1.8.

4.4.3 Pharmacokinetics

The pharmacokinetics of alirocumab were assessed after subcutaneous administration in healthy individuals, as demonstrated in Figure 4.

Figure 4. Mean Alirocumab Serum Concentrations in Healthy Subjects, Phase 1 Studies



Source: Summary of Clinical Pharmacology, Figure 2

Absorption

At steady state, median C_{max} was observed to be 3 days. The absolute bioavailability after SC administration is approximately 85%.

Injection in the thigh or arm resulted in a slightly lower mean C_{max} and AUC values compared to injection in the abdomen (Table 6); however population PK analysis did not find injection site to be a significant covariate.

Table 6. PK Ratio Estimates by Injection Site

Parameter	Comparison	Estimate	90% CI
C_{max}	Upper arm vs. abdomen	0.79	[0.66 – 0.93]
	Upper arm vs. thigh	0.90	[0.76 – 1.06]
	Thigh vs. abdomen	0.88	[0.74 – 1.04]
AUC	Upper arm vs. abdomen	0.92	[0.78 – 1.09]
	Upper arm vs. thigh	1.09	[0.93 – 1.28]
	Thigh vs. abdomen	0.84	[0.72 – 0.99]

Source: Summary of biopharmaceutic studies and associated analytic methods, Table 4

Based on pop PK, alirocumab exposure was similar when administered by PFS or PFP, see Table 7.

Table 7. Alirocumab Steady State Exposures at 150 mg Q2W by Drug Product Presentation, Phase 3 Trials

	Alirocumab 150 mg		
Drug product presentation	n	C_{max} (mg/L)	AUC_{0-336} (mg.h/L)
Prefilled syringe	1437	18.0 (46.6%) [16.5]	5030 (53.6%) [4470]
Prefilled pen	203	19.0 (46.7%) [18.3]	5390 (52.4%) [5030]

Note: Mean (CV) [Median]

Source: Summary of Clinical Pharmacology, Table 6

Distribution and Metabolism

Alirocumab has a small volume of distribution (0.04 to 0.05 L/kg). Specific metabolism studies were not conducted as alirocumab is a monoclonal antibody.

Excretion and Elimination

In monotherapy after 75 mg and 150 mg Q2W dosing regimens, the median apparent half-life of alirocumab over the dosing interval was 17 to 20 days.

Statin co-administration is thought to shorten alirocumab half-life by increasing production of PCSK9 and thus increasing the target-mediated clearance of alirocumab. In patients receiving statins co-administered with alirocumab at 75 mg and 150 mg Q2W, alirocumab median steady state apparent half-life over the dosing interval was 12

days. The effects of background statins (including on PK and LDL-C) are discussed further in section 6.1.10.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Phase 2 and 3 trials are summarized in section 6.1.1 (Table 9 and Table 10). Clinical Pharmacology trials are summarized in Table 5.

5.2 Review Strategy

Dr. Julie Golden reviewed alirocumab for efficacy, which included reviewing the lipid endpoints in the 10 pivotal phase 3 trials. Dr. Bradley McEvoy from the Office of Biostatistics provided statistical support. Dr. Mary Roberts reviewed alirocumab for safety, including adverse events, and laboratory, vital sign, and ECG parameters. Methods used in the safety review are detailed in section 7.1. The clinical reviewers collaborated on the preliminary assessment of adjudicated MACE and with Dr. Amy Rosenberg from the Office of Biotherapeutic Products on the review of alirocumab immunogenicity.

5.3 Discussion of Individual Studies/Clinical Trials

Information from individual trials is presented as appropriate in sections 6 (efficacy) and 7 (safety).

6 Review of Efficacy

Efficacy Summary

Alirocumab was evaluated for efficacy in ten multicenter phase 3 trials that randomized 5296 patients: 9 out of the 10 trials enrolled patients with heterozygous familial hypercholesterolemia (HeFH) and/or patients at high or very high cardiovascular (CV) risk. Five trials were placebo-controlled and five were active-controlled. Two dose regimens were evaluated: 8 trials utilized a starting dose of 75 mg by subcutaneous injection every 2 weeks (Q2W) with up-titration at week 12 to 150 mg Q2W if LDL-C goals (consistent with ATP III) were not met, and 2 trials started all patients on 150 mg Q2W. Eight trials administered alirocumab in patients who were on background statin therapy (most trials enrolled patients who were taking the maximally tolerated dose of statin), and two trials administered alirocumab as monotherapy [one trial in patients with moderate CV risk (MONO), and one trial in patients identified with pre-specified criteria as “statin-intolerant” (ALTERNATIVE)]. The OPTIONS I and II trials were block-randomized based on background moderate doses of atorvastatin and rosuvastatin,

respectively, and randomized to addition of alirocumab or ezetimibe, statin dose up-titration, or in the case of the OPTIONS I atorvastatin 40 mg regimen, switch to rosuvastatin 40 mg. All ten phase 3 trials utilized the same primary endpoint: percent change in LDL-C from baseline at week 24. A summary of the phase 3 trials is shown below:

Table 8. Phase 3 Trials

Trial	Primary endpoint	Population/design feature	Size	Control	Dose
FH I	% change in LDL-C at 24 wks	HeFH on maximally tolerated statin	486	placebo	75/150
FH II	% change in LDL-C at 24 wks	HeFH on maximally tolerated statin	249	placebo	75/150
HIGH FH	% change in LDL-C at 24 wks	HeFH with LDL-C > 160 mg/dL on maximally tolerated statin	107	placebo	150
LONG TERM (LTS11717)	% change in LDL-C at 24 wks	HeFH or high CV risk on maximally tolerated statin	2341	placebo	150
COMBO I	% change in LDL-C at 24 wks	High CV risk on maximally tolerated statin	316	placebo	75/150
COMBO II	% change in LDL-C at 24 wks	High CV risk on maximally tolerated statin	720	ezetimibe	75/150
OPTIONS I	% change in LDL-C at 24 wks	On 20 or 40 mg atorvastatin, randomized to alirocumab, ezetimibe, up-titration of statin, or higher potency statin	355	ezetimibe[a]	75/150
OPTIONS II	% change in LDL-C at 24 wks	On 10 mg or 20 mg rosuvastatin, randomized to alirocumab, ezetimibe, or up-titration of statin	305	ezetimibe[a]	75/150
ALTERNATIVE	% change in LDL-C at 24 wks	Statin-intolerant population (randomized after placebo run-in to alirocumab, ezetimibe, or atorvastatin)	314	ezetimibe[b]	75/150
MONO	% change in LDL-C at 24 wks	Moderate CV risk, on no background lipid modifying therapy	103	ezetimibe	75/150

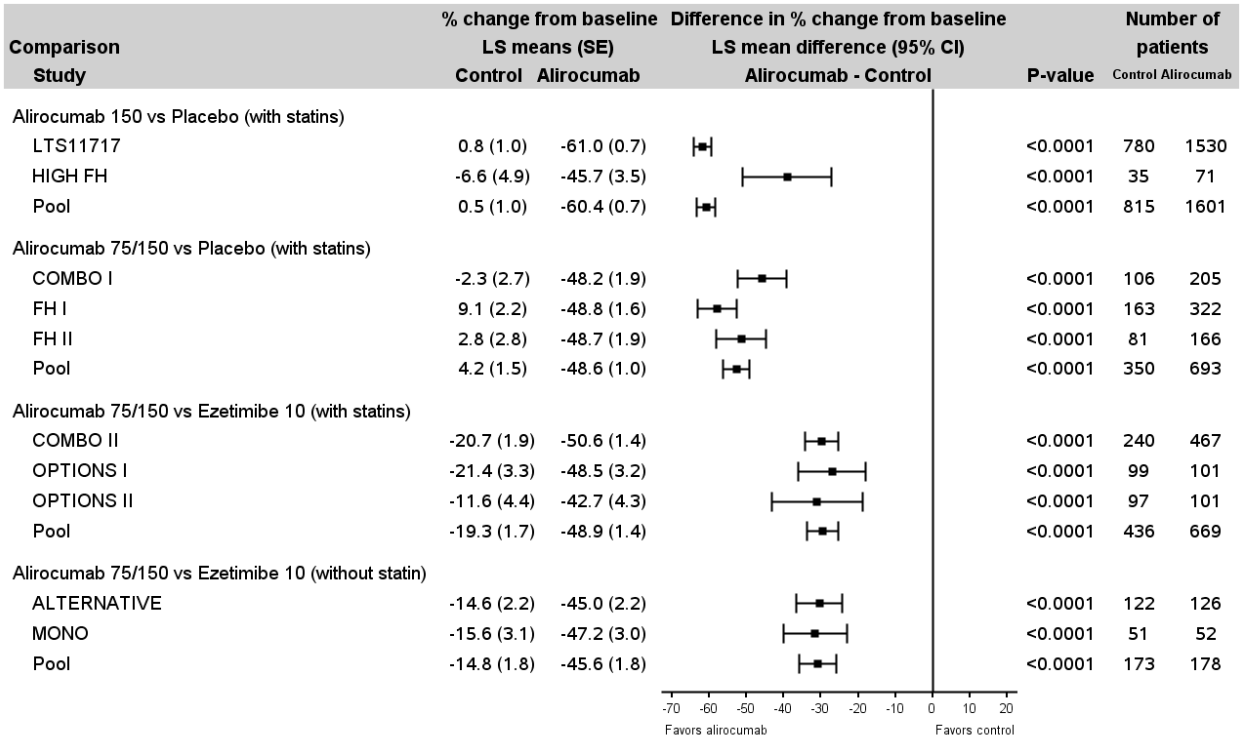
[a] additional control: up-titration of current statin, or switch to higher potency statin (OPTIONS I)
[b] additional control: atorvastatin 20 mg QD
75/150 = starting dose of 75 mg Q2W with up-titration to 150 mg Q2W at week 12 if not meeting LDL-C goal

Source: Efficacy reviewer's summary

The sponsor's primary analysis, which utilized a mixed effect model with repeated measures on the intent-to-treat population, demonstrated that, in all trials, alirocumab was associated with decreases in calculated LDL-C of 36 to 61 percent from baseline, and statistically significant treatment differences of 39 to 62 percent as compared to placebo (all p-values <0.0001) and 24 to 36 percent as compared to ezetimibe (p-value <0.01 for all except the background rosuvastatin 20 mg regimen within the OPTIONS II trial that did not reach statistical significance based on the pre-specified method for controlling type I error, p=0.014). Maximal LDL-C-lowering efficacy was observed at

week 4 and persisted for the duration of the trials. A forest plot illustrating the primary endpoint results by trial is shown below (note that OPTIONS background statin regimens are pooled, demonstrating statistical significance):

Figure 5. Percent Change in LDL-C from Baseline at Week 24, Phase 3 Trials



Source: Clinical Overview, Figure 2

LDL-C efficacy was supported by other analyses, including absolute change in LDL-C at week 24, percent change in LDL-C at other time points, including weeks 12 and 52 (where applicable), percent change in directly measured LDL-C, and the proportions of patients meeting individual LDL-C treatment goals (defined as LDL-C less than 70 mg/dL in patients at very high CV risk, and less than 100 mg/dL for all others), as well as percent changes in week 24 in total cholesterol, apolipoprotein B, and non-high density lipoprotein cholesterol (non-HDL-C). By contrast, only three of the five placebo-controlled trials were statistically significant for percent changes in triglycerides at week 24 (treatment effect ranged from -0.6 to -17 percent), and four of the five for HDL-C (treatment effect ranged from +4 to +8 percent).

As alirocumab is a biologic therapy, anti-drug antibodies (ADA) can develop and could potentially impact efficacy (as well as safety). Treatment-emergent positive ADA responses were observed in 4.8% of patients in the alirocumab group and in 0.6% of patients in the control group. Most of these responses were of low-titer, non-neutralizing, and/or transient. Upon review of patient-level data (which were somewhat

limited), there were several patients in whom neutralizing or high-titer antibodies appeared to be associated with loss of efficacy. There is not enough information at this time to fully characterize this effect.

6.1 Indication

The applicant has proposed the following indications:

PRALUENT is indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (Apo A-1).

PRALUENT is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT).

PRALUENT is indicated as monotherapy, or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.

The sponsor has also proposed a Limitation of Use:

The effect of PRALUENT on cardiovascular morbidity and mortality has not been determined.

The sponsor considers the targeted patient populations to be as follows:

- Patients with heterozygous familial hypercholesterolemia (HeFH)
- Patients without familial hypercholesterolemia, but with elevated LDL-C and high or very high cardiovascular (CV) risk on statin therapy
- Patients who are “intolerant” of statins due to muscle-related adverse effects

The alirocumab development program assessed these patient populations in a variety of trials, as discussed further.

6.1.1 Methods

Table 9 describes two dose-ranging phase 2 trials. The results of these trials are discussed further in the discussion of data supporting dosing recommendations (section

6.1.8). The efficacy review focused on the 10 safety and efficacy phase 3 trials (Table 10) that have either:

- been completed (COMBO I, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO), or

- are ongoing and have completed the "first-step analysis"; i.e., analysis of the primary endpoint at week 24 and all key secondary endpoints up to week 52 (FH I, FH II, HIGH FH, COMBO II, and LONG TERM).

Table 9. Phase 2 Trials

Trial	Design	Patient Population	Randomization
DFI11565	Randomized, double-blind, placebo-controlled, dose-ranging	LDL-C ≥ 100 mg/dL on stable atorvastatin	Alirocumab: 50 mg SQ Q2W for 12 wks, 30 randomized patients Alirocumab: 100 mg SC Q2W for 12 wks, 31 randomized pts Alirocumab: 150 mg SC Q2W for 12 wks, 31 randomized patients Alirocumab: 200 mg SC Q4W for 12 wks, alternating with placebo SC Q4W (1 injection Q2W), 30 randomized pts Alirocumab: 300 mg Q4W for 12 wks, alternating with placebo Q4W (1 injection Q2W), 30 randomized patients Placebo: SC Q2W for 12 wks, 31 randomized pts
CL-1003	Randomized, double-blind, placebo-controlled, dose-ranging	HeFH with LDL-C ≥ 100 mg/dL on a stable statin dose ± ezetimibe	Alirocumab: 150 mg SC Q4W for 12 wks, alternating with placebo SC Q4W (1 injection Q2W), 15 randomized pts Alirocumab: 200 mg SC Q4W for 12 wks, alternating with placebo SC Q4W (1 injection Q2W), 16 randomized pts Alirocumab: 300 mg SC Q4W for 12 wks, alternating with placebo SC Q4W (1 injection Q2W), 15 randomized pts Alirocumab: 150 mg SC Q2W for 12 wks, 16 randomized patients Placebo: SC Q2W for 12 wks, 15 randomized pts

Source: SCE Tables 61 and 62

Table 10. Phase 3 Trials

Trial	Design	Patient Population	Randomization
FH I (EFC12492)	Randomized, double-blind, placebo-controlled	HeFH not adequately controlled on stable maximally tolerated statin ± other LMT (LDL-C ≥ 70 mg/dL with documented CVD or ≥ 100 mg/dL w/o documented CVD)	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 78 wks[a], 323 randomized patients Placebo:SC Q2W for 78 wks[a], 163 randomized patients
FH II (CL-1112)	Randomized, double-blind, placebo-controlled	HeFH not adequately controlled on stable maximally tolerated statin ± other LMT (LDL-C ≥ 70 mg/dL with documented CVD or ≥ 100 mg/dL w/o documented CVD)	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 78 wks[a], 167 randomized patients Placebo:SC Q2W for 78 wks[a], 82 randomized patients
HIGH FH (EFC12732)	Randomized, double-blind, placebo-controlled	HeFH and LDL-C ≥ 160 mg/dL despite stable maximally tolerated daily statin therapy ± other LMT	Alirocumab:150 mg SC Q2W for 78 wks[a], 72 randomized patients Placebo:SC Q2W for 78 wks[a], 35 randomized patients
LONG TERM (LTS11717)	Randomized, double-blind, placebo-controlled	High CV risk with hypercholesterolemia not adequately controlled with a statin at a maximally tolerated daily dose ± other LMT	Alirocumab:150 mg SC Q2W for 18 mos[b], 1553 randomized patients Placebo:SC Q2W for 18 mos[b], 788 randomized patients
COMBO I (EFC11568)	Randomized, double-blind, placebo-controlled	History of CVD and LDL-C ≥ 70 mg/dL, or moderate CKD or diabetes with additional risk factors and LDL-C ≥ 100 mg/dL on stable maximally tolerated daily statin therapy ± other LMT	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 52 wks, 209 randomized patients Placebo:SC Q2W for 52 wks, 107 randomized patients
COMBO II (EFC11569)	Randomized, double-blind, ezetimibe-controlled, double-dummy	History of CVD and LDL-C ≥ 70 mg/dL or moderate CKD or diabetes with additional risk factors and LDL-C ≥ 100 mg/dL with statin therapy	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 104 wks[a], 479 randomized patients Ezetimibe:10 mg PO QD for 104 wks[a], 241 randomized patients
OPTIONS I (CL-1110)	Randomized, double-blind, active-controlled	High or very high CV risk with non-FH or heFH not adequately controlled with atorvastatin (20 mg or 40 mg) ± other LMT (excluding ezetimibe)	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 24 wks, 104 randomized patients Ezetimibe:10 mg PO QD for 24 wks, 102 randomized patients Atorvastatin: 40 mg or 80 mg PO QD for 24 wks, 102 randomized patients Rosuvastatin: 40 mg PO QD

Trial	Design	Patient Population	Randomization
			for 24 wks, 45 randomized patients
OPTIONS II (CL-1118)	Randomized, double-blind, active-controlled	High or very high CV risk with non-FH or heFH not adequately controlled with rosuvastatin (10 mg or 20 mg) ± other LMT (excluding ezetimibe)	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 24 wks, 103 randomized patients Ezetimibe:10 mg PO QD for 24 wks, 101 randomized patients Rosuvastatin: 10 mg or 20 mg PO QD for 24 wks, 101 randomized patients
ALTERNATIVE (CL-1119)	Randomized, double-blind, double-dummy, active-controlled	Primary hypercholesterolemia and moderate, high, or very high CV risk intolerant to statins	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 24 wks[c], 126 randomized patients Ezetimibe:10 mg PO QD for 24 wks[c], 125 randomized patients Atorvastatin: 20 mg PO QD for 24 wks[c], 63 randomized patients
MONO (EFC11716)	Randomized, double-blind, ezetimibe-controlled, double-dummy	LDL-C between 100 mg/dL and 190 mg/dL with moderate CV risk (10-yr risk of fatal CVD of ≥ 1% and < 5% using a Systematic Coronary Risk Estimation (SCORE))	Alirocumab:75 mg SC Q2W with possible up-titration at wk 12 to 150 mg SC Q2W for 24 wks, 52 randomized patients Ezetimibe:10 mg PO QD for 24 wks, 51 randomized patients

[a] First-step analysis: Study ongoing, with all patients having completed the first 52 weeks (12 months)
[b] First-step analysis: Study ongoing, with all patients having completed the first 52 weeks (12 months), and approx. 600 pts having completed the 18 mo double-blind treatment period
[c] Patients completing the 24-wk treatment period entered into an ongoing 3-yr OL extension
Note: HeFH patients from FH I, FH II, HIGH FH, and LONG TERM could enter into an OL trial

Source: SCE Tables 63-72

Among the phase 3 trials, the essential parameters of the trial designs were similar. All trials included a screening and injection training period of 2 to 6 weeks duration (the OPTIONS trials and ALTERNATIVE also employed a separate 4-week run-in period; specific design issues for those trials are described further below), a double-blind treatment period of 6, 12, 18, or 24 months, and an 8-week follow-up period for those patients not entering into an open-label extension period. The efficacy period was defined as the time from the first injection up to 21 days after the last injection.

All phase 3 trials had the same primary efficacy endpoint: percent mean calculated LDL-C change from baseline at week 24. Other variables are summarized below:

Table 11. Summary of Efficacy Variables in Phase 3 Trials

Endpoints	Analysis	W12	W24	W52*
Continuous endpoints				
Calculated LDL-C (% change)	ITT [a]	**Key**	**Primary**	**Key**
	On-treatment [b]	**Key**	**Key**	SENS
Calculated LDL-C (absolute change)	**ITT**	Other	Other	Other
	On-treatment			
Measured LDL-C (% change)	**ITT**		Key for LONG TERM only**	
	On-treatment		SENS**	
Apo B (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	Other	**Key**	
Non-HDL-C (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	Other	**Key**	
Total-C (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	Other	Other	
Lp(a) (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	Other	Other	
Fasting TGs (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	SENS	SENS	
HDL-C (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	SENS	SENS	
Apo A-1 (% change)	**ITT**	**Key**	**Key**	Other
	On-treatment	SENS	SENS	
Binary endpoints: Proportion of patient reaching predefined targets				
Calculated LDL-C <70 mg/dL (1.81 mmol/L) for very high CV risk patients or LDL-C <100 mg/dL (2.59 mmol/L) for moderate to high CV risk patients*	**ITT**	Other	**Key**	Other
	On-treatment		**Key**	
Calculated LDL-C <100 mg/dL (2.59 mmol/L)*	**ITT**	Other	Other	Other
	On-treatment		Other	
Calculated LDL-C <70 mg/dL (1.81 mmol/L)*	**ITT**	Other	**Key**	Other
	On-treatment		**Key**	
Calculated LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction in LDL-C (if calculated LDL-C ≥70 mg/dL [1.81 mmol/L]), in very high CV risk patients*	**ITT**	Other	Other	Other
	On-treatment			

Endpoints	Analysis	W12	W24	W52*
≥50% reduction from baseline in calculated LDL-C	**ITT**	Other	Other	Other
	On-treatment			
Apo B <80 mg/dL (0.8 g/L)	**ITT**	Other	Other	Other
	On-treatment			
Non-HDL-C <100 mg/dL (2.59 mmol/L)	**ITT**	Other	Other	Other
	On-treatment			
Non-HDL-C <130 mg/dL (3.37 mmol/L)	**ITT**	Other	Other	Other
	On-treatment			
Ratios				
Apo B/Apo A-1 (absolute change)	**ITT**	Other	Other	Other
	On-treatment			
Total-C/HDL-C (absolute change)	**ITT**	Other	Other	Other
	On-treatment			

ITT = Intent-to-treat; Key = Key secondary efficacy endpoint; Other = Other secondary efficacy endpoint; Primary = Primary efficacy endpoint; SENS = Sensitivity analysis to the key secondary efficacy endpoint; W12 = Week 12.

* When applicable. The asterisks indicate parameters or time-points that are specific to some studies. Details are provided for each study in Table 6 for key secondary endpoints (presented in the order of the hierarchical procedure).

** Measured LDL-C (ultracentrifugation) when performed was analyzed at Week 24 as a sensitivity analysis in other studies than LONG TERM. It was analyzed at Week 24 as a sensitivity analysis using on-treatment analysis in LONG TERM.

a Also referred to as ITT estimand analysis performed in the ITT population.

b Also referred to as on-treatment estimand analysis performed in the mITT population.

Note: A blank cell indicates that the analysis was not planned.

Source: SCE, Table 5

Eight of the 10 trials utilized a dose up-titration scheme during the double-blind treatment period: FH I, FH II, COMBO I, COMBO II, OPTIONS II, ALTERNATIVE, and MONO (see Figure 6, below, for a schematic of the up-titration study design). In these trials, all patients were initiated at an alirocumab dose of 75 mg SC Q2W, and were up-titrated to 150 mg at week 12 if they did not meet the following LDL-C targets at week 8 (this design feature is discussed further in section 6.1.8):

- LDL-C ≥ 70 mg/dL for patients at very high CV risk as defined as a history of CHD or CHD risk equivalent:

- LDL-C ≥ 100 mg/dL for patients at high and moderate CV risk

The definitions for the CV risk categories in the trials are presented below:

Table 12. Definitions of CV Risk Categories

	LONGTERM	COMBO I COMBO II	FH I FH II HIGH FH	OPTIONS I OPTIONS II	ALTERNATIVE	MONO
Very high CV risk						
Documented history of CHD[1]	X	X	X	X	X	
CHD risk equivalent						
PAD[2], ischemic stroke[3]	X	X	X	X	X	
Other vascular diseases[4]				X	X	
Diabetes mellitus A[5] or B[6]	A	A	A	B	B	
Moderate CKD[7]	X	X	X			
SCORE ≥10%[8]				X	X	
High CV risk						
heFH with no history of CHD or CHD risk equivalent	X		X	X	X	
Diabetes mellitus (if not fulfilling criteria for very high CV risk)				X	X	
Moderate CKD[7]				X	X	
SCORE ≥5%[8]				X	X	

	LONGTERM	COMBO I COMBO II	FH I FH II HIGH FH	OPTIONS I OPTIONS II	ALTERNATIVE	MONO
Moderate CV risk						
SCORE ≥1 and <5%[8]					X	X

[1] Documented history of Coronary Heart Disease (CHD), including ≥1 of the following: acute myocardial (MI), silent MI, unstable angina, coronary revascularization procedure, clinically significant CHD diagnosed by invasive or non-invasive testing ((such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging).

[2] Documented peripheral artery disease (PAD) with ≥ 1 of: a) current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin and ankle-brachial index (ABI) in either leg at rest ≤ 0.90, or b) history of intermittent claudication and endovascular procedure or surgical intervention because of atherosclerotic disease, or c) history of critical limb ischemia and thrombolysis, endovascular procedure or surgical intervention because of atherosclerotic disease. Please note: The OPTIONS I, OPTIONS II and ALTERNATIVE studies did not have specific requirements for the diagnosis of PAD.

[3] Documented ischemic stroke considered as being of atherothrombotic origin, with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. CT or MRI must have been performed to rule out hemorrhage and non-ischemic neurological disease.

[4] Other vascular diseases: abdominal aortic aneurysm, atherosclerotic renal artery stenosis, carotid artery disease (transient ischemic attack [TIA] or >50% obstruction of a carotid artery).

[5] Known history of type 1 or type 2 diabetes mellitus (DM) and 2 or more additional risk factors, among: a) History of hypertension (established on antihypertensive medication); b) Documented history of ankle-brachial index ≤0.90; c) Documented history of microalbuminuria or macroalbuminuria (30) OR dipstick urinalysis at screening visit (Week-3) with >2+ protein; d) Documented history of pre–proliferative or proliferative retinopathy or laser treatment for retinopathy; e) Known family history of premature CHD (CHD in father or brother before 55 years of age; CHD in mother or sister before 65 years of age).
Patients with DM were classified in the very high CV risk category in the 2011 ESC/EAS guidelines for the management of dyslipidaemias, regardless of additional risk factors. More stringent criteria were applied in the protocols, in anticipation of possible future adjustments in the guidelines, as literature did not fully support DM with no history of CVD and no additional risk factor being a CHD risk equivalent.

[6] Type 1 or type 2 diabetes mellitus with target organ damage (ie, retinopathy, nephropathy, microalbuminuria).
In the 2012 update of the European guidelines, only patients with DM and target organ damage were classified in the very high CV risk category. The other patients with DM were classified in the high CV risk category.

[7] Documented moderate chronic kidney disease (CKD) as defined by 30 ≤eGFR <60 mL/min/1.73 m² for 3 months or more, including the screening visit.
Patients with severe and moderate CKD were classified in the very high CV risk category in 2011 ESC/EAS Guidelines for the management of dyslipidemias. In the 2012 update of these guidelines, only patients with severe CKD were classified in the very high CV risk category, and patients with moderate CKD were classified in the high CV risk category.

[8] Calculated 10-year fatal CVD risk assessed with SCORE (Systemic Coronary Risk Estimation) (2011 ESC/EAS Guidelines for the management of dyslipidemias) .

Source: Information of Topics Requested on 19 Feb 2015, Agency Request Item No. 2, Table 2

A summary of lipid criteria utilized for up-titration, including a comparison with criteria used for trial eligibility, is presented in the following table:

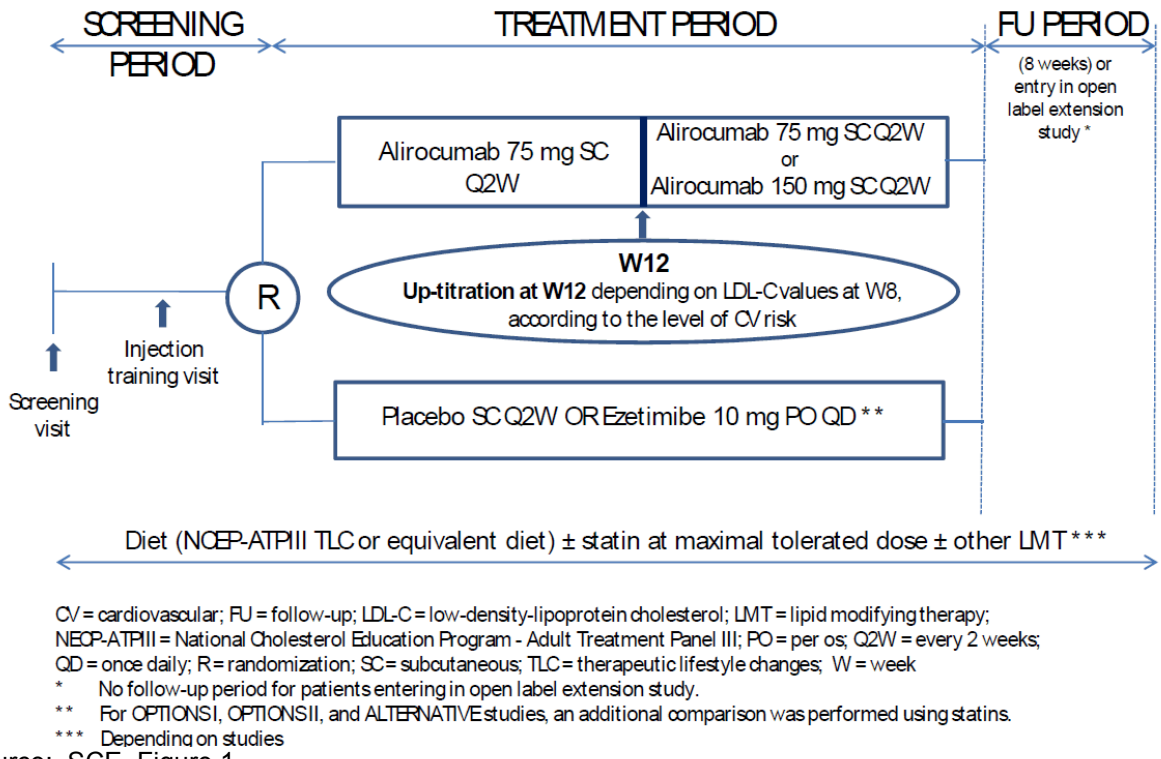
Table 13. LDL-C Threshold for Baseline Inclusion and Up-Titration, Phase 3 Trials

Studies	Baseline CV risk	LDL-C threshold in inclusion criteria	LDL-C threshold for up-titration
FH I/FH II	Prior CVD No prior CVD	≥70 mg/dL (1.81 mmol/L) ≥100 mg/dL (2.59 mmol/L)	≥70 mg/dL (1.81 mmol/L)
COMBO I/COMBO II	Prior CVD No prior CVD	≥70 mg/dL (1.81 mmol/L) ≥100 mg/dL (2.59 mmol/L)	≥70 mg/dL (1.81 mmol/L)
OPTIONS I/OPTIONS II	VH H	≥70 mg/dL (1.81 mmol/L) ≥100 mg/dL (2.59 mmol/L)	≥70 mg/dL (1.81 mmol/L) ≥100 mg/dL (2.59 mmol/L)
ALTERNATIVE	VH H and M	≥70 mg/dL (1.81 mmol/L) ≥100 mg/dL (2.59 mmol/L)	≥70 mg/dL (1.81 mmol/L) ≥100 mg/dL (2.59 mmol/L)
MONO	M	≥100 mg/dL (2.59 mmol/L)	≥100 mg/dL (planned) ≥70 mg/dL (actual*)

CVD = cardiovascular disease; VH = very high CV risk patients; H = high CV risk patients; M = moderate CV risk patients
* discussed in section 6.1.4
Source: SCE, Table 4

The study design for the trials that utilized the up-titration scheme (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO) is illustrated in the schematic below:

Figure 6. Study Design, Trials FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO



CV = cardiovascular; FU = follow-up; LDL-C = low-density-lipoprotein cholesterol; LMT = lipid modifying therapy; NECP-ATPIII = National Cholesterol Education Program - Adult Treatment Panel III; PO = per os; Q2W = every 2 weeks; QD = once daily; R = randomization; SC = subcutaneous; TLC = therapeutic lifestyle changes; W = week

* No follow-up period for patients entering in open label extension study.

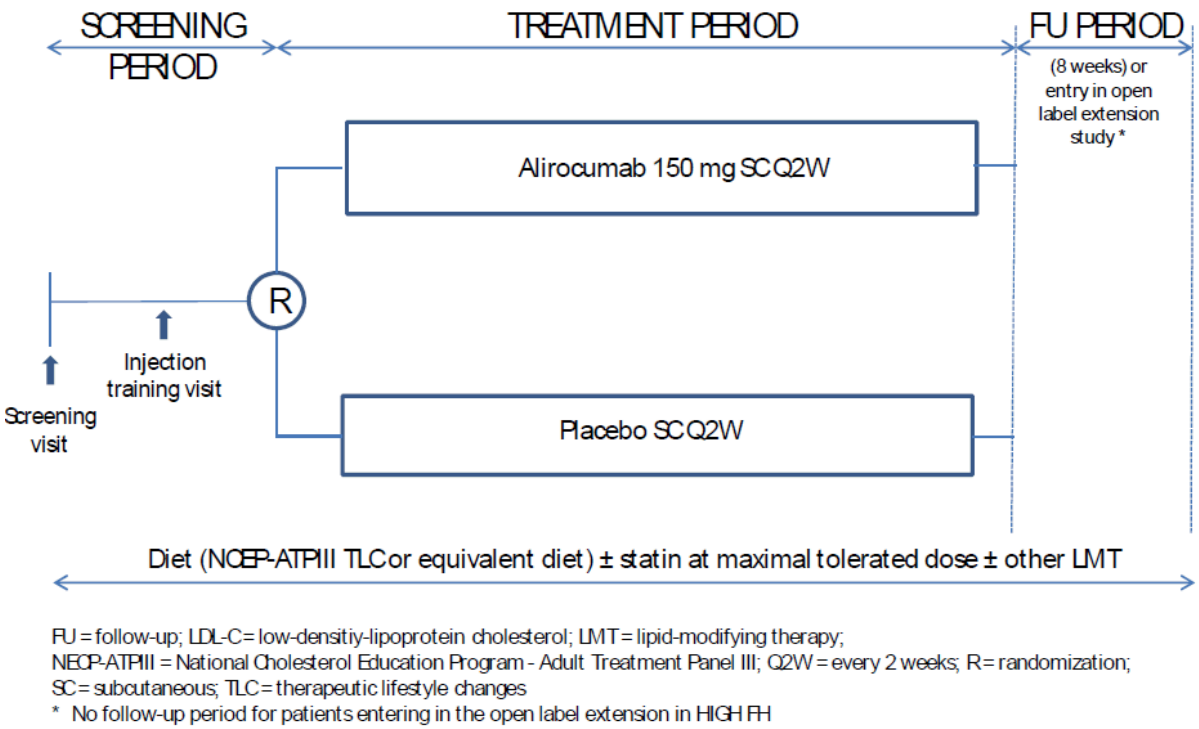
** For OPTIONS I, OPTIONS II, and ALTERNATIVE studies, an additional comparison was performed using statins.

*** Depending on studies

Source: SCE, Figure 1

Two trials (HIGH FH and LONG TERM) started patients on 150 mg SC Q2W and continued them on this dose for the duration of the trial. The study design for those two trials is outlined in Figure 7.

Figure 7. Study Design, HIGH FH and LONG TERM



FU = follow-up; LDL-C = low-densitiy-lipoprotein cholesterol; LMT = lipid-modifying therapy;
NECP-ATPIII = National Cholesterol Education Program - Adult Treatment Panel III; Q2W = every 2 weeks; R = randomization;
SC = subcutaneous; TLC = therapeutic lifestyle changes
* No follow-up period for patients entering in the open label extension in HIGH FH

Source: SCE, Figure 2

Placebo for alirocumab was used as comparator in the five trials where patients were receiving background statin at the maximally tolerated dose (FH I, FH II, HIGH FH, COMBO I, and LONG TERM). Patients in these studies could also concomitantly receive almost any other LMT, if previously received. Patients must have been on stable maximally tolerated daily registered doses of statins with or without other LMT for at least 4 weeks (6 weeks for fenofibrate) before the screening visit. From the screening visit until week 24 of the double-blind treatment period, the background LMT was not to be changed, with the exception of circumstances discussed in section 6.1.6.

Ezetimibe 10 mg PO QD was the active comparator in the other five trials, with a background of statin therapy (COMBO II, OPTIONS I and OPTIONS II), or no statin (ALTERNATIVE and MONO). In COMBO II, alirocumab was compared to ezetimibe (EZE) in patients who were receiving background statin at the maximally tolerated dose, without any other LMT. ALTERNATIVE included an atorvastatin rechallenge arm – as described below – to validate the definition of statin intolerance used for patients' eligibility. In OPTIONS I and OPTIONS II, an additional comparison consisted of intensifying the pre-randomization statin therapy, as described below.

Because of the differences in study designs for the ALTERNATIVE and OPTIONS trials, these design features are highlighted below.

ALTERNATIVE

Primary Objective: To demonstrate the reduction of LDL-C by alirocumab in comparison to ezetimibe (EZE) after 24 weeks in patients with primary hypercholesterolemia who are intolerant to statins.

Note: Statin intolerance was defined as the inability to tolerate at least two statins: one statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily regimen of a statin (e.g., one to three times weekly) were also considered as not able to tolerate a daily dose and were eligible to enroll in the study if they could not tolerate a cumulative weekly statin dose of seven times the lowest approved tablet size, and the criteria outlined above were also met.

Study Population: Patients with moderate, high, or very high CV risk who were intolerant to statins and met lipid inclusion criteria as outlined in Table 13 were eligible. Patients who reported a skeletal muscle-related AE other than those due to strain or trauma during the 4-week single-blind placebo (alirocumab placebo plus ezetimibe / atorvastatin placebo) run-in were excluded.

Treatments: Patients were randomized in a 2:2:1 scheme to the following:

- Alirocumab 75 mg Q2W + placebo atorvastatin/EZE (N=126)
- (Over-encapsulated) EZE 10 mg PO QD + placebo alirocumab (N=125)
- (Over-encapsulated) atorvastatin 20 mg PO QD + placebo alirocumab (N=63)

Alirocumab dose titration at week 12 was conducted as described above.

Reviewer comment: This study design was agreed upon with FDA during alirocumab development.

OPTIONS I

Primary Objective: To evaluate the reduction of LDL-C after 24 weeks of treatment with alirocumab plus atorvastatin vs. EZE plus atorvastatin vs. doubling the atorvastatin dose vs. switch from atorvastatin to rosuvastatin, in patients with hypercholesterolemia at high CV risk.

Study Population: Patients at high and very high CV risk with non-FH or HeFH who were not adequately controlled with atorvastatin 20 mg or 40 mg with or without other LMT (excluding EZE).

Patients who had been on a stable atorvastatin 20 mg or 40 mg QD dose for at least 4 weeks were screened for study eligibility, which included an injection training visit. Patients who had not been on a stable dose of atorvastatin 20 mg or 40 mg QD for 4 weeks, were being switched from another statin to atorvastatin, or were not on a statin but should have been according to local guidance, were treated with atorvastatin 20 mg or 40 mg QD based on the medical judgment of the study physician during a 4-week open label run-in period prior to the screening period.

Treatments: Patients were block-randomized to one of the seven study treatment arms as follows:

Patients on a 20 mg atorvastatin regimen at baseline (randomized in a 1:1:1 ratio):
- Alirocumab + atorvastatin 20 mg + placebo-EZE
- Placebo-alirocumab + atorvastatin 40 mg + placebo-EZE
- Placebo-alirocumab + atorvastatin 20 mg + EZE 10 mg

Patients on a 40 mg atorvastatin regimen at baseline (randomized in a 1:1:1:1 ratio):
- Alirocumab + atorvastatin 40 mg + placebo-EZE
- Placebo-alirocumab + atorvastatin 80 mg + placebo-EZE
- Placebo-alirocumab + rosuvastatin 40 mg + placebo-EZE
- Placebo-alirocumab + atorvastatin 40 mg + EZE 10 mg

Within each atorvastatin regimen (20 mg or 40 mg), randomization was stratified according to whether the patient had a prior history of MI or ischemic stroke (Yes/No).

Alirocumab dose titration at week 12 was conducted as described above.

OPTIONS II

Primary Objective: To evaluate the reduction of LDL-C after 24 weeks of treatment with alirocumab plus rosuvastatin vs. EZE plus rosuvastatin vs. doubling the rosuvastatin dose, in patients with hypercholesterolemia at high CV risk.

Study Population: Patients at high and very high CV risk with non-FH or HeFH who were not adequately controlled with rosuvastatin 10 mg or 20 mg with or without other LMT (excluding EZE).

Patients who had been on a stable rosuvastatin 10 mg or 20 mg QD dose for at least 4 weeks were screened for study eligibility, which included an injection training visit. Patients who had not been on a stable dose of rosuvastatin 10 mg or 20 mg QD for 4

weeks, were being switched from another statin to rosuvastatin, or were not on a statin but should have been according to local guidance, were treated with rosuvastatin 10 mg or 20 mg QD based on the medical judgment of the study physician during a 4-week open label run-in period prior to the screening period.

Treatments: Patients were block randomized to one of the six study treatment arms as follows:

Patients on a 10 mg rosuvastatin regimen at baseline (randomized in a 1:1:1 ratio):
- Alirocumab + rosuvastatin 10 mg + placebo-EZE
- Placebo-alirocumab + rosuvastatin 20 mg + placebo-EZE
- Placebo-alirocumab + rosuvastatin 10 mg + EZE 10 mg

Patients on a 20 mg atorvastatin regimen at baseline (randomized in a 1:1:1 ratio):
- Alirocumab + rosuvastatin 20 mg + placebo-EZE
- Placebo-alirocumab + rosuvastatin 40 mg + placebo-EZE
- Placebo-alirocumab + rosuvastatin 20 mg + EZE 10 mg

Within each rosuvastatin regimen (10 mg or 20 mg), randomization was stratified according to whether the patient had a prior history of MI or ischemic stroke (Yes/No).

Alirocumab dose titration at week 12 was conducted as described above.

6.1.2 Demographics

Among the 10 trials, demographic and other baseline characteristics varied depending on the trial population (e.g., HeFH, a spectrum of CV risk, “statin intolerant”) and the country or countries that the respective trial was conducted in.

As expected, patients enrolled in trials devoted to the HeFH population (FH I, FH II, and HIGH FH) were younger than those patients enrolled in the trials that predominantly enrolled a high CV risk patient population (COMBO I, COMBO II, LONG TERM, OPTIONS I, OPTIONS II, and ALTERNATIVE). In general, the trials with patients with high CV risk had a higher representation of males than females. Baseline body weight and BMI were similar among these patient populations. (The MONO trial enrolled patients with moderate CV risk and is presented in the following table separately.)

Table 14. Demographic and Selected Baseline Characteristics among Phase 3 Trials

	HeFH Only	High/Very High CV Risk (± HeFH)	Moderate CV Risk
	FH I FH II HIGH FH	COMBO I COMBO II LONG TERM OPTIONS I OPTIONS II ALTERNATIVE	MONO
	N=842	N=4351	N=103
Age (years)			
Mean (SD)	52.1 (12.8)	61.3 (10.1)	60.2 (5.0)
Min, Max	18, 87	18, 89	45, 72
Age Group (years [n (%)]			
<45	232 (27.6%)	236 (5.4%)	0
≥45 to <65	464 (55.1%)	2407 (55.3%)	84 (81.6%)
≥65 to <75	128 (15.2%)	1324 (30.4%)	19 (18.4%)
≥75	18 (2.1%)	84 (8.8%)	0
Sex [n (%)]			
Male	462 (54.9%)	2785 (64.0%)	55 (53.4%)
Female	380 (45.1%)	1566 (36.0%)	48 (46.6%)
Weight (kg)			
Mean (SD)	84.3 (16.6)	87.9 (19.2)	85.5 (17.6)
Min, Max	43, 151	38, 192	50, 131
Weight Group (kg [n (%)]			
<50	7 (0.8%)	26 (0.6%)	0
≥50 to <70	154 (18.3%)	663 (15.2%)	18 (17.5%)
≥70 to <100	534 (63.4%)	2686 (61.7%)	63 (61.2%)
≥100	147 (17.5%)	976 (22.4%)	22 (21.4%)
BMI (kg/m^2)			
Mean	29.0 (4.9)	30.5 (5.8)	29.3 (6.3)
Min, Max	18, 50	16, 61	17, 50
BMI Group (kg/m^2 [n (%)]			
<25	165 (19.6%)	673 (15.5%)	30 (29.1%)
≥25 to <30	380 (45.1%)	1654 (38.0%)	35 (34.0%)
≥30	297 (35.3%)	2016 (46.3%)	38 (36.9%)
Missing	0	8 (0.2%)	0

Source: Reviewer created from sponsor datasets

Demographics were fairly well matched between the groups. Of note, in the HIGH FH trial, males represented 62.9% of the placebo-treated patients, but only 48.6% of the

alirocumab-treated patients (see section 6.1.4 for a discussion of efficacy in trial HIGH FH, and section 6.1.7 for a discussion of subgroups).

There was considerable variability between the trials regarding regions represented, and this impacted racial and ethnic diversity among the trials. Specifically, the trial conducted solely in the United States, COMBO I, demonstrated racial and ethnic diversity more representative of the U.S. population than the other trials. Overall, most of the patients were white (90.1%), followed by black (4.8%) and Asian (2.1%) backgrounds. A total of 6.1% of patients were of Hispanic ethnicity.

Overall, 38.1% of patients were from North America, 32.9% of patients were from Western Europe, 15.6% of patients were from Eastern Europe, and 13.5% of patients were from the rest of the world.

Table 15. Regional, Racial, and Ethnic Diversity, Phase 3 Trials

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720	ALT N=314	MONO N=103	OI N=355	OII N=305
Region (%)										
N. America	29.0%	0	30.8%	23.4%	100%	32.5%	73.6%	47.6%	74.4%	65.9%
W. Europe	32.3%	69.9%	10.3%	45.1%	0	15.1%	15.9%	52.4%	16.6%	23.3%
E. Europe	14.0%	30.1%	27.1%	18.5%	0	30.6%	0	0	0	0
Rest of World	24.7%	0	31.8%	13.0%	0	21.8%	10.5%	0	9.0%	10.8%
Race (%)										
White	91.4%	98.0%	87.9%	92.7%	81.6%	84.7%	93.9%	90.3%	86.2%	83.9%
Black	1.0%	0.8%	1.9%	3.3%	16.1%	3.9%	3.8%	9.7%	10.7%	8.9%
Asian	1.2%	1.2%	5.6%	0.8%	0.9%	7.4%	1.3%	0	1.7%	3.6%
Other	6.4%	0	4.7%	3.2%	1.3%	4.0%	1.0%	0	1.4%	3.6%
Ethnicity (%)										
Hispanic	5.0%	0.4%	5.6%	5.2%	10.8%	2.8%	1.9%	1.0%	18.9%	13.4%

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II

Source: ISE, Tables 2.1.1, 2.1.2, and 2.1.3

A listing of the countries represented in the phase 3 trials is presented below:

Table 16. Countries Represented by Region, Phase 3 Trials

Region	Country	N
North America	United States	1855
North America	Canada	162
Western Europe	United Kingdom	572
Western Europe	Netherlands	225
Western Europe	Spain	191
Western Europe	Germany	159
Western Europe	Denmark	143
Western Europe	France	133
Western Europe	Norway	107
Western Europe	Italy	79
Western Europe	Belgium	40
Western Europe	Sweden	40
Western Europe	Finland	31
Western Europe	Austria	13
Western Europe	Portugal	8
Eastern Europe	Russian Federation	249
Eastern Europe	Poland	146
Eastern Europe	Hungary	143
Eastern Europe	Czech Republic	120
Eastern Europe	Bulgaria	78
Eastern Europe	Romania	44
Eastern Europe	Ukraine	44
Rest of World	South Africa	432
Rest of World	Israel	93
Rest of World	Mexico	81
Rest of World	Republic of Korea	42
Rest of World	Australia	34
Rest of World	Argentina	28
Rest of World	Chile	2
Rest of World	Colombia	2

Source: Reviewer created from sponsor's datasets

Medical History

The majority of the phase 3 trials focused on patient populations with HeFH and/or high CV risk (one trial, MONO, evaluated alirocumab as monotherapy in patients with moderate CV risk). Overall, 64% of patients had history of any coronary heart disease (CHD), 34% of patients had a prior myocardial infarction (MI), 45% of patients had prior revascularization procedures, and 8% of patients had prior ischemic stroke.

Other diseases and risk factors reported overall in the phase 3 trials included diabetes mellitus (31%), hypertension (70%), and current tobacco smoking (19%).

Table 17 and Table 18 summarize CV history and risk among the phase 3 trials.

Table 17. Cardiovascular Risk Factors, Phase 3 Trials with HeFH and/or High CV Risk Populations

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720
Any CV history/risk factors	51.2%	38.6%	57.0%	90.6%	98.7%	99.7%
Coronary heart disease[a]	46.3%	35.3%	49.5%	68.6%	78.2%	90.1%
Acute MI	23.5%	16.5%	22.4%	37.2%	41.1%	57.8%
Silent MI	2.1%	1.2%	0.9%	2.9%	4.4%	2.1%
Unstable angina	12.6%	9.2%	12.1%	12.4%	17.1%	21.1%
Coronary revascularization	32.5%	28.1%	23.4%	46.2%	61.1%	68.8%
Other[b]	27.8%	17.7%	28.0%	29.0%	16.5%	36.9%
CHD risk equivalents[a]	16.3%	7.6%	16.8%	41.1%	43.0%	31.0%
Ischemic stroke	3.3%	2.4%	3.7%	9.9%	8.5%	8.3%
Peripheral arterial disease	2.7%	2.4%	0.9%	5.2%	3.5%	4.9%
Moderate chronic kidney disease	6.0%	1.2%	4.7%	13.9%	19.3%	11.7%
DM + 2 or more risk factors[c]	6.0%	2.8%	8.4%	20.6%	21.2%	12.5%
CV risk per protocol definition						
Very high	51.2%	38.6%	57.0%	91.5%	100%	100%
High	48.8%	61.4%	43.0%	8.5%	0	0
Moderate	0	0	0	0	0	0
HeFH	100%	100%	100%	17.7%	0	0

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
Note: A patient can be counted in several categories.
[a] according to the items pre-listed in the e-crf
[b] diagnosed by invasive or non-invasive testing
[c] including ankle-brachial index ≤ 90, hypertension, nephropathy, retinopathy or family history of premature CHD

Source: SCE, Tables 29 and 43

Table 18. Cardiovascular Risk Factors, Phase 3 Monotherapy and Options Trials

	ALT N=314	MONO N=103	OI N=355	OII N=305
Any CV history/risk factors	100%	99%	100%	100%
Coronary heart disease[a]	46.5%	0	56.3%	58.0%
Acute MI	13.7%	0	25.9%	27.5%
Silent MI	3.5%	0	4.5%	3.6%
Unstable angina	8.6%	0	9.0%	13.1%
Coronary revascularization	32.5%	0	38.3%	42.6%
Other[b]	28.3%	0	40.3%	45.6%
CHD risk equivalents[a]	23.2%	0	28.2%	25.9%
Ischemic stroke	9.2%	0	7.3%	5.2%
Peripheral arterial disease	1.9%	0	3.1%	3.9%
Abdominal aortic aneurysm	2.5%	0	2.3%	3.3%
Asymptomatic carotid artery occlusion > 50%	7.0%	0	0	0
Carotid endarterectomy or stent	3.5%	0	0.3%	0.7%
Renal artery stenosis	0.3%	0	0	0
Renal artery stent	0.3%	0	0	0
DM with target organ damage	3.5%	0	12.1%	10.5%
Other risk factors				
DM without target organ damage	20.4%	0	38.0%	31.5%
Moderate chronic kidney disease	5.1%	0	10.4%	7.2%
CV risk per protocol definition				
Very high	54.1%	0	60.3%	63.0%
High	28.3%	0	39.7%	37.0%
Moderate	13.7%	100%	0	0
HeFH	15.0%	0	9.0%	13.4%

ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II
Note: A patient can be counted in several categories.
Note: the MONO study excluded high-risk patients, CHD and CHD risk-equivalent items were not collected in this study. In this table, 0 cases were assumed for this study
[a] according to the items pre-listed in the CRF
[b] diagnosed by invasive or non-invasive testing

Source: SCE, Tables 30, 31, 44, and 45

In the phase 3 trials that enrolled patients with HeFH (FH I, FH II, HIGH FH, and LONG TERM), the diagnosis of HeFH was made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis was based on either the Simon Broome criteria[28] with the criteria for 'definite FH' or the WHO/Dutch Lipid Network criteria[28] with a score more than 8 points (diagnosis 'certain'). The following table summarizes HeFH diagnoses in the four trials that enrolled these patients:

28 Described in: Marks D, et al. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis (2003); 168(1): 1-14.

Table 19. Summary of HeFH Diagnoses, Trials FH I, FH II, HIGH FH, and LONG TERM

	FH I N=486	FH II N=249	HIGH FH N=107	LONG TERM N=2341
HeFH	100%	100%	100%	17.7%
Time from HeFH diagnosis (yrs), median	9.0	11.5	11.7	7.2
Confirmation of HeFH diagnosis				
Genotyping	39.3%	73.9%	17.8%	40.2%
Clinical criteria only	60.5%	26.1%	82.2%	59.8%

Source: CSR EFC12492, Table 13; R727-CL-1112, Table 12; EFC12732, Table 15; LTS11717, Table 13

Baseline Lipid Parameters

Table 20 presents the baseline mean/median LDL-C, HDL-C, and TG among the 10 phase 3 trials (mean values by group are described with the relevant efficacy analyses in sections 6.1.4 and 6.1.5). In most trials, the entry criterion for LDL-C was either ≥ 70 mg/dL and/or ≥ 100 mg/dL depending on the individual patient's CV risk at entry, with the exception of HIGH FH, which focused on an HeFH population with LDL-C ≥ 160 mg/dL on maximally tolerated LMT. Mean baseline LDL-C was higher in the HeFH trials (particularly HIGH FH) as well as in ALTERNATIVE, which was conducted in patients considered to be statin intolerant.

Table 20. Baseline Lipid Parameters, Phase 3 Trials

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720	ALT N=314	MONO N=103	OI N=355	OII N=305
Calculated LDL-C (mg/dL)										
Number	486	249	106	2341	316	720	313	103	355	305
Mean (SD)	144.6 (49.7)	134.4 (41.1)	197.8 (53.4)	122.4 (42.2)	102.2 (31.6)	107.3 (35.7)	191.3 (69.3)	139.7 (25.8)	105.1 (34.1)	111.3 (39.0)
Measured LDL-C (mg/dL)[a]										
Number	412	219	NA	1999	208	642	265	NA	323	278
Mean (SD)	140.1 (47.6)	131.8 (39.3)		116.7 (38.7)	96.6 (31.2)	102.9 (34.9)	183.2 (69.8)		101.4 (32.7)	106.9 (38.1)
HDL-C (mg/dL)										
Number	486	249	107	2341	316	720	314	103	355	305
Mean (SD)	49.8 (15.3)	53.1 (15.7)	48.1 (13.3)	49.9 (12.3)	48.5 (13.8)	47.3 (13.4)	50.0 (14.3)	57.1 (17.8)	48.7 (13.4)	50.0 (13.1)
Fasting TG (mg/dL)										
Number	486	249	107	2340	315	720	314	103	355	305
Median	112.0	104.0	129.0	132.7	127.0	137.0	155.5	117.0	122.0	128.0
Q1, Q3	83.0, 152.0	81.0, 141.0	94.0, 171.0	94.0, 185.0	92.0, 186.0	100.0, 195.0	108.0, 229.0	87.0, 153.0	89.0, 175.0	92.0, 185.0

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II
[a] LDL-C by ultracentrifugation not conducted in HIGH FH or MONO

Source: SCE, Tables 47, 49, and 51

Baseline Statin Use

In the FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM trials, patients were on maximally tolerated doses of atorvastatin, rosuvastatin, or simvastatin as background therapy by protocol. Patients were to be on the high doses of these statins (atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg) unless issues such as tolerability or local labeling prohibited use of these doses. Of the 4219 patients enrolled in these six trials, 2497 (59.2%) entered the study on high doses of these statins, as defined above. Reasons for patients not receiving high doses are presented in Table 21.

Table 21. Baseline Statin Use, Phase 3 Trials in HeFH or High CV Risk Populations

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720
Taking atorva 40 to 80 mg, rosuva 20 to 40 mg, or simva 80 mg daily at screening	83.3%	88.0%	79.4%	46.8%	62.7%	68.6%
Reasons for not taking high dose of statin[a]						
Muscle symptoms and/or increase CPK	8.0%	8.8%	7.5%	17.2%	10.1%	8.2%
Liver disease or elevated LFTs	0.6%	2.8%	0	1.7%	0.9%	1.8%
Concomitant medications	0.2%	0.4%	0	2.1%	0.6%	1.0%
Advanced age	0	0.4%	0	1.9%	2.8%	1.5%
Low body mass index	0	0	0	0.4%	0.3%	0.1%
IGT/IFG	0	0	0.9%	1.8%	4.7%	1.7%
Regional practice / local labeling	7.2%	0.8%	12.1%	28.0%	17.4%	16.5%
Anxious about potential cognitive impairment or AE	0.4%	0	0	0.5%	0	1.3%
Other	1.4%	1.6%	0	3.3%	3.8%	1.8%
Atorvastatin	36.4%	39.0%	29.9%	38.7%	32.9%	49.3%
10 mg QD	0.8%	1.6%	0	4.3%	0.6%	1.5%
20 mg QD	1.9%	3.2%	0	8.5%	2.8%	5.1%
40 mg QD	9.5%	16.1%	12.1%	15.0%	18.0%	23.6%
80 mg QD	23.7%	17.7%	16.8%	10.6%	11.4%	18.9%
Other	0.6%	0.4%	0.9%	0.3%	0	0.1%
Rosuvastatin	52.1%	56.2%	45.8%	24.0%	31.6%	29.4%
5 mg QD	2.3%	0.8%	2.8%	1.2%	1.3%	1.5%
10 mg QD	1.4%	2.4%	0	4.3%	1.9%	3.6%
20 mg QD	13.0%	15.3%	10.3%	8.9%	15.5%	16.8%
40 mg QD	35.2%	36.9%	32.7%	9.4%	12.7%	7.1%
Other	0.2%	0.8%	0	0.2%	0.3%	0.4%
Simvastatin	11.5%	4.8%	27.1%	37.3%	34.8%	21.4%
10 mg QD	0.8%	0.4%	4.7%	2.7%	0.3%	1.3%
20 mg QD	1.2%	1.6%	2.8%	10.0%	7.9%	6.1%
40 mg QD	7.2%	1.2%	13.1%	20.9%	20.9%	11.5%
80 mg QD	1.9%	1.6%	6.5%	2.9%	5.4%	2.1%
Other	0.4%	0	0	0.7%	0.3%	0.4%

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
[a] A patient can be counted in several categories.
IGT: impaired glucose tolerance; IFG: impaired fasting glucose

Source: SCE, Tables 52 and 53

MONO and ALTERNATIVE evaluated patients not on background statin, and the two OPTIONS trials evaluated patients on a less-than-maximal dose of statin (OPTIONS I: atorvastatin 20 mg 47.6%, 40 mg 52.4%; OPTIONS II: rosuvastatin 10 mg 47.5%, 20 mg 52.5%).

Other LMTs were used to varying degrees in the phase 3 trials as well, and these are presented in the table below.

Table 22. LMT Other Than Statins, Phase 3 Trials

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720	ALT N=314	MONO N=103	OI N=355	OII N=305
LMT other than statins[a]	62.8%	69.9%	27.1%	28.1%	42.1%	5.7%	47.8%	3.9%	22.2%	21.3%
LMT other than dietary supplements[b]	61.1%	67.9%	26.2%	22.8%	36.1%	2.4%	38.2%	1.9%	18.0%	18.0%
BA sequestrants	5.6%	12.0%	2.8%	1.4%	3.2%	0%	ND	ND	ND	ND
Ezetimibe	57.0%	66.3%	24.3%	14.3%	8.2%	NA	ND	ND	ND	ND
Fibrates	4.7%	1.6%	0%	6.1%	11.1%	1.1%	ND	ND	ND	ND
Fish oil	2.1%	0.4%	2.8%	1.1%	7.0%	0.3%	ND	ND	ND	ND
Dietary supplements[c]	5.8%	6.0%	0.9%	7.5%	7.6%	3.3%	9.6%	1.9%	4.2%	3.3%

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II
BA = bile acid
[a] in combination with statins or not
[b] not described further for ALT, MONO, OI, or OII
[c] included omega-3 fatty acids at daily doses < 1000 mg, plant stanols, flax seed oil, and psyllium
NA=not applicable
ND=not described

Source: ISE, Tables 2.4.2, 2.4.3, and 2.4.4

Proportions of patients on statins, high-potency statins, and other LMTs were fairly well-balanced between groups in the individual trials.

6.1.3 Subject Disposition

Screening Period

Table 23 enumerates the proportion of patients screened for the individual phase 3 trials and selected reasons for screening failure. For example, the most common reason for screen failure in the LONG TERM trial was LDL-C value at screening that was lower than the minimum required for study entry.

Table 23. Disposition of Screened Patients, Phase 3 Trials

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720	ALT N=314	MONO N=103	OI N=355	OII N=305
Number screened	597	322	206	5142	640	1112	519	204	859	672
% screen failures	18.6%	22.7%	48.1%	54.4%	50.6%	35.3%	30.4%	49.5%	58.7%	54.6%
Reason for screening failure[a]										
LDL-C exclusion	5.9%	8.7%	38.8%	39.4%	24.7%	14.5%	2.3%	10.3%	38.0%	30.4%
Safety laboratory exclusion or pregnancy	4.7%	3.7%	6.8%	5.4%	9.1%	7.5%	17.9%	14.7%	9.5%	7.6%
Newly dx or poorly controlled DM	1.7%	0.3%	3.4%	NA[b]	11.1%	5.6%	2.3%	0%	7.6%	8.5%

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II
NA = not applicable
[a] Proportion of total screened; patients may have more than one reason
[b] Not a separate exclusion criterion – HbA1c > 10% was excluded under the safety laboratory exclusion criterion

Source: CSRs for individual trials and Inclusion/Exclusion datasets (SDTM)

ALTERNATIVE

In addition to a screening period, the ALTERNATIVE trial included a single-blind placebo run-in period. Of 361 patients who completed the screening period, 314 patients (87.0%) completed the single-blind placebo (placebo for alirocumab Q2W plus placebo for EZE/atorvastatin capsules PO QD) run-in period and were randomized into three treatment groups:

- Alirocumab 75 mg Q2W + placebo atorvastatin/EZE (N=126)
- (Over-encapsulated) EZE 10 mg PO QD + placebo alirocumab (N=125)
- (Over-encapsulated) atorvastatin 20 mg PO QD + placebo alirocumab (N=63)

Of the 47 placebo run-in failures, 23 (48.9%) reported at least one skeletal muscle-related AE:

Table 24. Number (%) of Patients with Skeletal Muscle-related TEAEs During the Single-blind Placebo Run-in Period

	Run-in failures N=47	Randomized patients N=314
At least one run-in period skeletal muscle AE	23 (48.9%)	7 (2.2%)
Myalgia	9 (19.1%)	1 (0.3%)
Muscle spasms	7 (14.9%)	0
Pain in extremity	3 (6.4%)	4 (1.3%)
Musculoskeletal stiffness	2 (4.3%)	0
Musculoskeletal pain	1 (2.1%)	2 (0.6%)
Back pain	1 (2.1%)	0
Muscular weakness	1 (2.1%)	0

Source: ALTERNATIVE CSR, Table 8

Randomized Period

In the 10 phase 3 trials, 5296 patients were randomized: 3188 to alirocumab, 1175 to placebo, 620 to ezetimibe, and 313 to statin. Of these 5296 patients, nine patients (0.2%) were randomized but not treated, 5222 patients (98.6%) were included in the intent-to-treat (ITT, primary analysis) population, and 5180 patients (97.8%) were included in the modified ITT (mITT) population, defined below.

In the phase 3 trials, the ITT population was defined as all randomized patients who had an evaluable primary efficacy endpoint. The primary efficacy endpoint was considered evaluable when the following conditions were met:

- Availability of a baseline calculated LDL-C value, and
- Availability of at least one calculated LDL-C value within one of the analysis windows up to week 24

The mITT population was defined as all randomized patients who took at least one dose or part of a dose of the study drug and had an evaluable primary efficacy endpoint (defined above) during the efficacy treatment period, defined as:

- For trials versus placebo: the time period from the first double-blind injection up to the day of last injection +21 days
- For trials versus active control: the time period from the first double-blind treatment (capsule or injection, whichever comes first) up to the day of last injection +21 days or the day of last capsule intake +3 days, whichever comes first

Table 25. ITT and mITT Populations, Phase 3 Trials

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720	ALT N=314	MONO N=103	OI N=355	OII N=305
ITT	99.8%	99.2%	99.1%	98.7%	98.4%	98.2%	98.7%	100%	97.2%	97.7%
mITT	99.6%	99.2%	99.1%	98.2%	97.8%	97.1%	95.9%	98.1%	95.8%	96.1%

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II

Source: SCE Tables 37, 38, and 39

Disposition for the phase 3 trials are presented in Table 26. Note that five trials are ongoing. In the five trials that have completed, between 15 and 30% of patients have prematurely discontinued according to a strict definition for 'completers' that requires that that the interval between the last injection and last visit (i.e., either week 24, week 52, week 78, or week 104, depending on the trial) was no more than 21 days. Patients outside of this window are captured in the 'other' category, below.

Table 26. Disposition, Phase 3 Trials

	FH I N=486	FH II N=249	HFH N=107	LT N=2341	CI N=316	CII N=720	ALT N=314	MONO N=103	OI N=355	OII N=305
Ongoing	87%	94%	71%	58%	NA	85%	NA	NA	NA	NA
Completed	1%	0%	9%	22%	73%	0%	70%	85%	81%	80%
Prematurely D/C	11%	6%	20%	20%	27%	15%	30%	15%	19%	20%
AE	4%	2%	4%	6%	7%	7%	22%	9%	5%	6%
Other[a]	3%	2%	9%	8%	11%	3%	7%	3%	11%	11%
Phys. Decision	<1%	0%	0%	<1%	1%	<1%	0%	0%	1%	<1%
Rel. to IMP Administration	<1%	<1%	0%	1%	1%	1%	0%	0%	<1%	0%
Subj. Moved	1%	0%	2%	1%	1%	1%	0%	1%	1%	<1%
W/D Consent	<1	<1%	0%	0%	0%	<1%	0%	1%	0%	0%
Poor Compliance - Other	1%	<1%	3%	1%	1%	1%	0%	0%	1%	1%
Poor Compliance - Life Events	<1%	1%	2%	2%	4%	1%	0%	1%	1%	1%
Poor Compliance - Inconvenient	1%	0%	0%	1%	1%	1%	1%	0%	1%	1%

HFH = HIGH FH
LT = LONG TERM
CI = COMBO I
CII = COMBO II
ALT = ALTERNATIVE
OI = OPTIONS I
OII = OPTIONS II
IMP = investigational medicinal product
NA = not applicable
[a] patients who completed the study but whose Week 24/Week52/Week 78/Week 104 visit (visit depending on trial treatment duration) was outside the prespecified window were considered not to have completed the trial per eCRF and are accounted for in the "Other" category
A patient was considered as having completed the planned treatment duration if he/she was exposed to treatment for at least 102 weeks in study COMBO II, at least 76 weeks in studies FH I, FH II, HIGH FH, LTS17117, at least 50 weeks in study COMBO I, or at least 22 weeks in studies OPTIONS I, OPTIONS II, ALTERNATIVE and MONO with associated visit performed

Source: Reviewer derived from BLA datasets

A separate assessment of disposition in the ALTERNATIVE trial was undertaken, given the interest in the statin-intolerant population, particularly since these patients could have been randomized to receive a statin (in this case, atorvastatin 20 mg). Among the 314 randomized patients, one patient randomized to the ezetimibe treatment group did not receive study treatment. The sponsor utilized the strict definition of treatment completer, described above, as well as a more inclusive definition that considered patients to be completers as long as treatment duration was at least 22 weeks and they attended a week 24 visit, regardless of the time window of the visit. Completers categorized by both definitions are as follows for the treatment groups:

Table 27. Patient Disposition, ALTERNATIVE Trial

	Atorvastatin (N=63)	Ezetimibe (N=125)	Alirocumab 75 Q2W/Up150 Q2W (N=126)	All (N=314)
Randomized but not treated	0	1 (0.8%)	0	1 (0.3%)
Patient's decision for not being treated[a]	0	0	0	0
Reason for not treated				
Visit Window Issue - Instructed By Sponsor To Screen Fail.	0	1 (0.8%)	0	1 (0.3%)
Randomized and treated	63 (100%)	124 (99.2%)	126 (100%)	313 (99.7%)
Completed 24 weeks of double-blind treatment period (at least 22 weeks of exposure and visit W24 performed)	44 (69.8%)	88 (70.4%)	102 (81.0%)	234 (74.5%)
Complete the study treatment period (as per CRF)	42 (66.7%)	82 (65.6%)	96 (76.2%)	220 (70.1%)
Did not complete the study treatment period (as per CRF)	21 (33.3%)	42 (33.6%)	30 (23.8%)	93 (29.6%)
Patient's decision for treatment discontinuation[a]	15 (23.8%)	33 (26.4%)	26 (20.6%)	74 (23.6%)
Reason for not completing study treatment period (as per CRF)				
Discontinued due to adverse event	16 (25.4%)	31 (24.8%)	23 (18.3%)	70 (22.3%)
Discontinued due to poor compliance to protocol	2 (3.2%)	0	0	2 (0.6%)
Protocol became inconvenient to participate	2 (3.2%)	0	0	2 (0.6%)
Life events made continuing too difficult	0	0	0	0
Poor compliance to protocol - Other reasons	0	0	0	0
Other reasons[b]	3 (4.8%)	11 (8.8%)	7 (5.6%)	21 (6.7%)

Source: Post-text Table 11.1.2A
Note: Percentages are calculated using the number of patients randomized as denominator.
Only the main reason for stopping treatment was entered in e-CRF. For detailed reasons related to IMP auto-injector administration, several reasons may be provided.
[a] Additional information as regard study treatment discontinuation.
[b] Includes patients who completed the 24-week double-blind treatment period (at least 22 weeks of exposure and week 24 visit performed) but did not meet the definition of "treatment completer" as per the CRF.

Source: CSR R727-CL-1119, Table 9

Reviewer comment: Note that 69.8% of purportedly "statin-intolerant" patients who were treated with atorvastatin 20 mg in this trial completed the double blind 24-week portion of the trial (at least 22 weeks of exposure and a visit at week 24 performed). This is numerically similar to, or only slightly less than, the other groups' proportions of completers in this trial as seen in Table 27. Although this is a select statin-intolerant population (i.e., these are patients who agreed to be randomized to a statin), it is instructive that a majority of these patients were able to tolerate statin therapy, at least for the duration of this trial.

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint in all 10 phase 3 trials is the percent change in mean LDL-C at week 24 in the ITT patient population. In the eight trials that included an up-titration design feature, this endpoint includes the LDL-C results of patients who remained on 75 mg Q2W (63.4% to 85.4% of patients) as well as those who were up-titrated to 150 mg Q2W at week 12 and thereafter. See section 6.1.8 for more details on LDL-C changes based on up-titration status.

Primary analyses of efficacy endpoints included all lipid data collected within the pre-specified window, regardless of whether the patient was continuing therapy or not. The mixed effect model with repeated measures (MMRM) was used for the primary efficacy analysis. Missing data were not explicitly imputed; the MMRM model relied on the "missing-at-random" assumption. See Dr. McEvoy's review for FDA analyses that specifically address missing data utilizing other assumptions. (Note that during pre-submission discussions, FDA requested a pattern mixture model to account for possible non-random missingness in the data; the sponsor implemented this as a sensitivity analysis.)

In all phase 3 trials, the MMRM included the fixed categorical effects of treatment group, randomization strata (see table below), time point, treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction.

Table 28. Definition of Treatment Groups, Time Point, and Randomization Strata Used in the MMRM, Phase 3 Trials

Study	Treatment group	Time point	Randomization strata
FH I	Alirocumab, Placebo	Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52	Prior history of MI or ischemic stroke: Yes, No Statin treatment: High dose, Low/moderate dose [a] Geographic region: North America, Western Europe, Eastern Europe, Rest of World
FH II	Alirocumab, Placebo	Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52	Prior history of MI or ischemic stroke: Yes, No Statin treatment: High dose, Low/moderate dose [a]
HIGH FH	Alirocumab, Placebo	Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52	Prior history of MI or ischemic stroke: Yes, No Statin treatment: High dose, Low/moderate dose [a]
COMBO I	Alirocumab, Placebo	Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52	Prior history of MI or ischemic stroke: Yes, No Statin treatment: High dose, Low/moderate dose [a]
COMBO II	Alirocumab, Ezetimibe	Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52	Prior history of MI or ischemic stroke: Yes, No Statin treatment: High dose, Low/moderate dose [a] Geographic region: North America, Western Europe, Eastern Europe, Rest of World
LONG TERM)	Alirocumab, Placebo	Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52	Heterozygous familial hypercholesterolemia population (heFH): Yes, No Prior history of MI or ischemic stroke: Yes, No Statin treatment: High dose, Low/moderate dose [a] Geographic region: North America, Western Europe, Eastern Europe, Rest of World
OPTIONS I	Patients on atorvastatin 20 mg before randomization: Alirocumab+ Atorvastatin 20 mg, Atorvastatin 40mg, Ezetimibe+ Atorvastatin 20 mg Patients on atorvastatin 40 mg before randomization: Alirocumab+ Atorvastatin 40 mg, Atorvastatin 80mg, Rosuvastatin 40mg, Ezetimibe + Atorvastatin 40 mg	Week 4, Week 8, Week 12, Week 16, Week 24	Prior history of MI or ischemic stroke: Yes, No

Study	Treatment group	Time point	Randomization strata
OPTIONS II	Patients on rosuvastatin 10 mg before randomization: Alirocumab + Rosuvastatin 10 mg, Rosuvastatin 20 mg, Ezetimibe + Rosuvastatin 10 mg Patients on rosuvastatin 20 mg before randomization: Alirocumab + Rosuvastatin 20 mg, Rosuvastatin 40 mg, Ezetimibe + Rosuvastatin 20 mg	Week 4, Week 8, Week 12, Week 16, Week 24	Prior history of MI or ischemic stroke: Yes, No
ALTERNATIVE	Alirocumab, Ezetimibe [b]	Week 4, Week 8, Week 12, Week 16, Week 24	Prior history of MI or ischemic stroke: Yes, No
MONO	Alirocumab, Ezetimibe	Week 4, Week 8, Week 12, Week 16, Week 24	No randomization strata [c]

a High dose: Atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily. Low/moderate dose: Simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily
b Patients randomized in the Atorvastatin arm were not included in the efficacy analyses
c For MONO study, stratum (diabetes) was not included in the model since less than 5% of the patients randomized in the study reported diabetes mellitus in the medical history

Source: SCE, Table 11

HeFH Trials

FH I, FH II, and HIGH FH evaluated the effect of alirocumab in the HeFH-only population.

FH I is a placebo-controlled 18-month trial to assess the effect of alirocumab (starting dose 75 mg Q2W with potential up-titration to 150 mg Q2W) in patients with HeFH not adequately controlled on LMT (stable, maximally tolerated statin ± other LMT). The trial is ongoing, with a first-step analysis at the last patient's week 52 visit conducted for the BLA. The week 24 primary analysis is shown in Table 29:

Table 29. Percent Mean Change from Baseline in LDL-C at Week 24, Trial FH I

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a]	322	144.7 (51.2)	-48.8 (1.6)	
Pbo	163	144.4 (46.8)	9.1 (2.2)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. Pbo			-57.9 (-63.3, -52.6)	<0.0001

[a] 135 (43.4%) of the 311 alirocumab on-treatment patients were up-titrated at week 12

Source: CSR EFC12492, Table 21

A sensitivity analysis that excluded the sites with serious GCP non-compliance resulted in a difference in LS means of -58.6 (95% CI -63.7, -53.5).

FH II has the same HeFH population and study design as FH I. This trial was conducted 100% ex-U.S. The results of the week 24 primary analysis – reflected in both the percent change from baseline in the alirocumab group and the between-treatment difference – are similar to FH I as shown in Table 30:

Table 30. Percent Mean Change from Baseline in LDL-C at Week 24, Trial FH II

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a]	166	134.6 (41.3)	-48.7 (1.9)	
Pbo	81	134.0 (41.6)	2.8 (2.8)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. Pbo			-51.4 (-58.1, -44.8)	<0.0001

[a] 61 (38.6%) of the 158 alirocumab on-treatment patients were up-titrated at week 12

Source: CSR R727-CL-1112, Table 20

Trial HIGH FH has a similar design to FH I and FH II, with the exception that it enrolled patients whose LDL-C was poorly controlled (LDL-C ≥ 160 mg/dL at screening) while on maximally tolerated statin therapy ± other LMT. [Of note, there were 18 patients who had LDL-C < 160 mg/dL at baseline, despite having LDL-C ≥ 160 mg/dL at screening. Two of these patients, both treated with alirocumab, had LDL-C < 100 mg/dL (89 and 99 mg/dL) at baseline. The reason for the large discrepancy between screening and baseline is unclear.] All patients were treated with alirocumab at a dose of 150 mg Q2W throughout the treatment period (i.e., there was no dosing with 75 mg Q2W and therefore no up-titration). Note that the percent LDL-C change from baseline was similar in this trial as compared to FH I and FH II, despite initiating therapy with a higher dose.

Table 31. Percent Mean Change from Baseline at Week 24, Trial HIGH FH

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 150	71	196.3 (57.9)	-45.7 (3.5)	
Pbo	35	201.0 (43.4)	-6.6 (4.9)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. Pbo			-39.1 (-51.1, -27.1)	<0.0001

Source: CSR EFC12732, Table 23

Potential contributors to the apparent attenuated effect compared with other trials could include: (1) the trial's small size (although the upper bound of the 95% CI does not overlap with the lower bound of the 95% CI of the LONG TERM treatment effect), (2) the "difficult-to-treat" patient population (notably, the subset of patients with baseline LDL-C ≥ 160 mg/dL and HeFH in LONG TERM more closely approximated the HIGH FH result in week 24 percent change in LDL-C; see section 6.1.7), (3) there were proportionally more females in this trial than in other trials, (4) a difference in device

used (LONG TERM = pre-filled syringe, HIGH FH = pre-filled pen), and/or (5) the activities of two clinical sites that were later detected to have significant GCP compliance issues. A sensitivity analysis that excluded the sites with serious GCP non-compliance – site 643-710 (7 patients evaluable for LDL-C in the ITT population, of whom 5 were in the alirocumab group) and site 840-743 (6 patients evaluable for LDL-C of whom 4 were in the alirocumab group) – resulted in a difference in LS means of -48.0 (95% CI -59.4, -36.6).

Trials in Patients at High CV Risk (LONG TERM and COMBO Trials)

The LONG TERM trial is a placebo-controlled 18-month trial that is evaluating the effect of alirocumab in patients with high and very high CV risk (as defined above in section 6.1.1), with either HeFH or non-familial forms of hypercholesterolemia not adequately controlled (LDL-C ≥ 70 mg/dL) on maximally tolerated statin ± other LMT. LONG TERM is one of two trials (HIGH FH being the other) that is treating patients with alirocumab 150 mg Q2W throughout the treatment period. The difference in the LDL-C percent change from baseline was greater (greater reduction) with alirocumab versus placebo in LONG TERM than in other placebo-controlled trials (Table 32 and Figure 8), even including HIGH FH, which also utilized only the 150 mg Q2W dose.

Table 32. Percent Mean Change from Baseline at Week 24, Trial LONG TERM

Treatment	**N**	**Baseline Mean, mg/dL (SD)**	**LS Mean % Change from Baseline (SE)**	
Aliro 150	1530	122.8 (42.7)	-61.0 (0.7)	
Pbo	780	122.0 (41.6)	0.8 (1.0)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. Pbo			-61.9 (-64.3, -59.4)	<0.0001

Source: CSR LTS11717, Table 21

No sensitivity analysis excluding the site with serious GCP non-compliance was conducted as the site only contributed one patient.

COMBO I is a 12-month, placebo-controlled trial conducted solely in the U.S. in patients at very high CV risk (see section 6.1.1) with hypercholesterolemia not adequately controlled on stable maximally tolerated statin therapy ± other LMT. Alirocumab was initiated at 75 mg Q2W with potential up-titration to 150 mg Q2W at week 12. The 24-week primary analysis is demonstrated in Table 33:

Table 33. Percent Mean Change from Baseline at Week 24, Trial COMBO I

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a]	205	100.3 (29.7)	-48.2 (1.9)	
Pbo	106	104.6 (32.3)	-2.3 (2.7)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. Pbo			-45.9 (-52.5, -39.3)	<0.0001
[a] 32 (16.8%) of the 191 alirocumab on-treatment patients were up-titrated at week 12				

Source: CSR EFC11568, Table 22

A sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference in LS means of -45.8 (95% CI -52.4, -39.2).

COMBO II is a 24-month, active (ezetimibe)-controlled trial in patients at very high CV risk with hypercholesterolemia not adequately controlled on stable maximally tolerated statin therapy. Alirocumab was initiated at 75 mg Q2W with potential up-titration to 150 mg Q2W at week 12. A first-step analysis was conducted for the BLA at 52 weeks; the primary analysis (as with the other trials) is at 24 weeks. The results are presented in Table 34:

Table 34. Percent Mean Change from Baseline at Week 24, Trial COMBO II

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a]	467	108.3 (36.5)	-50.6 (1.4)	
EZE	240	104.5 (34.1)	-20.7 (1.9)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. EZE			-29.8 (-34.4, -25.3)	<0.0001
[a] 82 (18.4%) of the 446 alirocumab on-treatment patients were up-titrated at week 12				

Source: CSR EFC11569, Table 24

Non-Statin Trials

ALTERNATIVE is a 24-week, active (ezetimibe)-controlled trial in patients at moderate, high, or very high CV risk with hypercholesterolemia who are “statin intolerant” (see section 6.1.1 for the definition of statin intolerance and other key design features). The primary efficacy analysis evaluated the LDL-C-lowering effect with alirocumab (75 mg Q2W with potential up-titration to 150 mg Q2W at week 12) as compared to ezetimibe, as seen in Table 35. Note that there was also an atorvastatin “challenge” arm; however, formal statistical analyses evaluating the effect of atorvastatin versus the other comparators were not conducted. For completeness, the unadjusted mean percent LDL-C change from baseline at 24 weeks among the three different treatment arms is presented below (Table 35).

Table 35. Percent Mean Change from Baseline at Week 24, Trial ALTERNATIVE

Treatment	N	Baseline Mean, mg/dL (SD)	Mean (95% CI) % Change from Baseline [LS Mean (SE)]	
Aliro 75/150[a]	126	191.1 (72.7)	-47.3 (-61.5, -37.9) [-45.0 (2.2)]	
EZE	122	194.2 (71.2)	-15.2 (-27.1, -9.5) [-14.6 (2.2)]	
Atorva	62	188.4 (59.3)	-31.9 (-50.5, -19.7)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. EZE			-30.4 (-36.6, -24.2)	<0.0001
[a] 54 (49.5%) of the 109 alirocumab on-treatment patients were up-titrated at week 12				

Source: CSR R727-CL-1119, Table 26 and Table 11.6.1.7.3A

A sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference in LS means between alirocumab and ezetimibe of -30.7 (95% CI -36.9, -24.6).

Reviewer comment: The clinical significance of any difference in LDL-lowering between the alirocumab and atorvastatin group, if one indeed exists (the 95% CIs overlap), is unknown.

MONO is a 24-week, active (ezetimibe)-controlled trial in patients with moderate CV risk and LDL-C between 100 and 190 mg/dL not on background LMT. All patients randomized to alirocumab were initially treated with 75 mg Q2W. Those patients whose LDL-C remained ≥ 100 mg/dL after 8 weeks were to be up-titrated to 150 mg Q2W at week 12 (see discussion of the study design in section 6.1.1); however, there was an administrative error in the automated and blinded process (which was detected only after database lock) and all patients with LDL-C ≥ 70 mg/dL were up-titrated to 150 mg Q2W at week 12. Of the 14 patients up-titrated, 13 had an LDL-C between 70 mg/dL and 100 mg/dL at week 8. The results of the primary analysis are shown in Table 36:

Table 36. Percent Mean Change from Baseline at Week 24, Trial MONO

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a]	52	141.1 (27.1)	-47.2 (3.0)	
EZE	51	138.3 (24.5)	-15.6 (3.1)	
Between-treatment difference			**Difference in LS means (95% CI)**	**p value**
Aliro vs. EZE			-31.6 (-40.2, -23.0)	<0.0001
[a] 14 (30.4%) of the 46 alirocumab on-treatment patients were up-titrated at week 12				

Source: CSR EFC11716, Table 22

Reviewer comments: Given that almost all patients who were up-titrated should not have been as per protocol, the week 12 data (i.e., prior to up-titration) could be considered more relevant to the efficacy in this population. The week 12

results are presented in section 6.1.5; note that the percent change from baseline and treatment difference between groups is similar to week 24.

Although this trial is supportive of the LDL-C-lowering effect observed in other phase 3 trials, the efficacy reviewer believes it is premature to conclude that monotherapy with alirocumab (i.e., first-line therapy in a moderate-risk population) is appropriate in the absence of CV outcomes data. Note that the mean percent change in LDL-C from baseline for rosuvastatin in a hyperlipidemia patient population ranges from 45% (5 mg) to 63% (40 mg), as compared to 7% for placebo.[29]

OPTIONS Trials

OPTIONS I is a 24-week, active-comparator trial to assess alirocumab versus ezetimibe, atorvastatin up-titration, or switching atorvastatin to rosuvastatin, in high and very high CV risk patients with hypercholesterolemia not adequately controlled (LDL-C ≥ 70 mg/dL or ≥ 100 mg/dL in patients with very high or high CV risk, respectively) on a less-than-maximal dose of atorvastatin (20 mg or 40 mg) ± other LMT excluding ezetimibe. See section 6.1.1 for details of the treatment arms. The efficacy of add-on alirocumab was evaluated in five primary efficacy pairwise comparisons, two within the atorvastatin 20 mg regimen and three within the atorvastatin 40 mg regimen:

Table 37. Primary Pairwise Comparisons, Trial OPTIONS I

Atorvastatin dose regimen	Pairwise comparison
Atorvastatin 20 mg	Comparison 1: alirocumab + atorvastatin 20 mg arm versus atorvastatin 40 mg arm
	Comparison 2: alirocumab + atorvastatin 20 mg arm versus ezetimibe + atorvastatin 20 mg arm
Atorvastatin 40 mg	Comparison 3: alirocumab + atorvastatin 40 mg arm versus atorvastatin 80 mg arm
	Comparison 4: alirocumab + atorvastatin 40 mg arm versus rosuvastatin 40 mg arm
	Comparison 5: alirocumab + atorvastatin 40 mg arm versus ezetimibe + atorvastatin 40 mg arm

Source: SCE, Table 20

The Bonferroni method was used to control multiplicity due to the multiple treatment groups. The statistical testing of the five primary pairwise comparisons was evaluated at the 2-sided significance level of 0.01 per comparison. In addition, a hierarchy was assigned to the endpoints to control multiplicity within the treatment groups.

The primary results are shown for patients on the atorvastatin 20 mg and 40 mg regimens in Table 38 and Table 39, respectively:

29 Crestor (rosuvastatin) prescribing information.

Table 38. Percent Mean Change from Baseline at Week 24, Trial OPTIONS I, Atorvastatin 20 mg Regimen

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a] + atorva 20	55	103.4 (34.9)	-44.1 (4.5)	
EZE + atorva 20	53	101.4 (29.3)	-20.5 (4.7)	
Atorva 40	53	100.5 (30.9)	-5.0 (4.6)	
Between-treatment difference			**Difference in LS means (99% CI)**	**p value**
Aliro vs. EZE			-23.6 (-40.7, -6.5)	<0.0004
Aliro vs. atorva			-39.1 (-55.9, -22.2)	<0.0001
[a] 4 (8.0%) of the 50 alirocumab on-treatment patients were up-titrated at week 12				

Source: CSR R727-CL-1110, Table 30

A sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference in LS means of -23.6 (95% CI -36.6, -10.6) versus ezetimibe and -39.1 (95% CI -51.8, -26.3) versus atorvastatin up-titration.

Table 39. Percent Mean Change from Baseline at Week 24, Trial OPTIONS I, Atorvastatin 40 mg Regimen

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)	
Aliro 75/150[a] + atorva 40	46	117.2 (37.4)	-54.0 (4.3)	
EZE + atorva 40	46	99.2 (29.4)	-22.6 (4.3)	
Rosuva 40	45	109.8 (39.0)	-21.4 (4.2)	
Atorva 80	47	108.6 (37.5)	-4.8 (4.2)	
Between-treatment difference			**Difference in LS means (99% CI)**	**p value**
Aliro vs. EZE			-31.4 (-47.4, -15.4)	<0.0001
Aliro vs. rosuva			-32.6 (-48.4, -16.9)	<0.0001
Aliro vs. atorva			-49.2 (-65.0, -33.5)	<0.0001
[a] 9 (20.9%) of the 43 alirocumab on-treatment patients were up-titrated at week 12				

Source: CSR R727-CL-1110, Table 31

A sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference in LS means of -33.7 (95% CI -45.9, -21.5) versus ezetimibe, -33.7 (95% CI -45.8, -21.6) versus rosuvastatin 40 mg, and -51.3 (95% CI -63.4, -39.1) versus atorvastatin up-titration.

OPTIONS II is a 24-week, active-comparator trial to assess alirocumab versus ezetimibe or rosuvastatin up-titration, in high and very high CV risk patients with hypercholesterolemia not adequately controlled (LDL-C ≥ 70 mg/dL or ≥ 100 mg/dL in patients with very high or high CV risk, respectively) on a less-than-maximal dose of rosuvastatin (10 mg or 20 mg) ± other LMT excluding ezetimibe. See section 6.1.1 for details of the treatment arms. The efficacy of add-on alirocumab was evaluated in four

primary efficacy pairwise comparisons, two within the rosuvastatin 10 mg regimen and two within the rosuvastatin 20 mg regimen:

Table 40. Primary Pairwise Comparisons, Trial OPTIONS II

Rosuvastatin dose regimen	Pairwise comparison
Rosuvastatin 10 mg	Comparison 1: alirocumab + rosuvastatin 10 mg arm versus rosuvastatin 20 mg arm
	Comparison 2: alirocumab + rosuvastatin 10 mg arm versus ezetimibe + rosuvastatin 10 mg arm
Rosuvastatin 20 mg	Comparison 3: alirocumab + rosuvastatin 20 mg arm versus rosuvastatin 40 mg arm
	Comparison 4: alirocumab + rosuvastatin 20 mg arm versus ezetimibe + rosuvastatin 20 mg arm

Source: SCE, Table 23

The Bonferroni method was used to control multiplicity due to the multiple treatment groups. The statistical testing of the four primary pairwise comparisons was evaluated at the 2-sided significance level of 0.0125 per comparison. In addition, a hierarchy was assigned to the endpoints to control multiplicity within the treatment groups.

The primary results are shown for patients on the atorvastatin 20 mg and 40 mg regimens in Table 41 and Table 42, respectively.

Table 41. Mean Percent Change from Baseline at Week 24, Trial OPTIONS II, Rosuvastatin 10 mg Regimen

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)
Aliro 75/150[a] + rosuva 10	48	107.8 (26.5)	-50.6 (4.2)
EZE + rosuva 10	47	102.0 (42.3)	-14.4 (4.4)
Rosuva 20	48	105.9 (36.0)	-16.3 (4.1)

Between-treatment difference	Difference in LS means (98.75% CI)	p value
Aliro vs. EZE	-36.1 (-51.5, -20.7)	<0.0001
Aliro vs. rosuva	-34.2 (-49.2, -19.3)	<0.0001

[a] 7 (15.9%) of the 44 alirocumab on-treatment patients were up-titrated at week 12

Source: CSR R727-CL-1118, Table 30

A sensitivity analysis that excluded the site with serious GCP non-compliance did not have an impact on LS means differences (-36.1 (95% CI -48.1, -24.1) versus ezetimibe, and -34.2 (95% CI -45.9, -22.5) versus rosuvastatin up-titration).

As seen in Table 42, the addition of alirocumab to rosuvastatin 20 mg did not result in statistically significant LDL-C lowering compared with either the addition of ezetimibe to rosuvastatin 20 mg or the up-titration of rosuvastatin 20 mg to 40 mg, although there was a numerical 20 to 25 percentage point difference in LS means.

Table 42. Mean Percent Change from Baseline at Week 24, Trial OPTIONS II, Rosuvastatin 20 mg Regimen

Treatment	N	Baseline Mean, mg/dL (SD)	LS Mean % Change from Baseline (SE)
Aliro 75/150[a] + rosuva 20	53	118.1 (32.5)	-36.3 (7.1)
EZE + rosuva 20	50	119.4 (48.5)	-11.0 (7.2)
Rosuva 40	52	113.7 (43.3)	-15.9 (7.1)

Between treatment difference	Difference in LS means (98.75% CI)	p value
Aliro vs. EZE	-25.3 (-50.9, 0.3)	0.0136[b]
Aliro vs. rosuva	-20.3 (-45.8, 5.1)	0.0453[b]

[a] 10 (20.8%) of the 48 alirocumab on-treatment patients were up-titrated at week 12
[b] did not reach statistical significance at the 0.0125 level

Source: CSR R727-CL-1118, Table 31

A sensitivity analysis that excluded the site with serious GCP non-compliance resulted in a difference in LS means of -27.6 (95% CI -48.2, -7.0) versus ezetimibe and -23.4 (95% CI -43.9, -3.0) versus rosuvastatin up-titration.

Reviewer comment (applicable to the results of OPTIONS I and OPTIONS II): Although alirocumab demonstrates numeric ± statistical improvement in LDL-C as compared to the other regimens tested, the clinical significance (in terms of CV benefit) has yet to be settled. Higher doses of statins and higher potency statins have demonstrated CV benefit[30,31] or a trend toward benefit[32,33,34] as compared to lower doses of or lower potency statin. Furthermore, as described in section 2.6, preliminary data suggest there may be benefit to the addition of ezetimibe to statin in patients with acute coronary syndromes (ACS).[23] Therefore, in the efficacy reviewer's opinion, superiority claims to these alternative regimens in the absence of CV outcomes data would be inappropriate.

Integrated Summary of Primary Efficacy

Figure 8 summarizes the primary efficacy results (versus placebo or ezetimibe comparator) for the 10 phase 3 trials. The sponsor has provided comparisons between

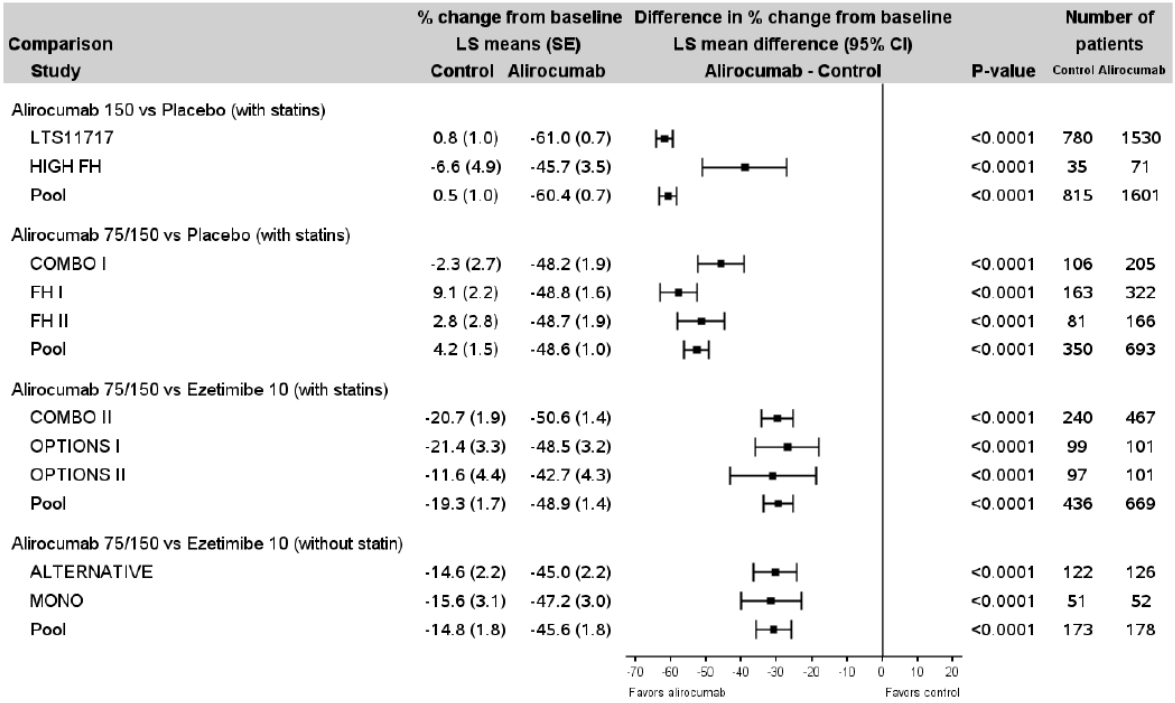
30 Cannon CP, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med (2004); 250: 1495-504.
31 LaRosa JC, et al. Intensive lipid lowering with atorvastatin in patients with coronary artery disease. N Engl J Med (2005); 352: 1425-35.
32 de Lemos JA, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA (2004); 292: 1307–16.
33 Pedersen TR, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA (2005); 294**:** 2437–45.
34 Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12 064 survivors of myocardial infarction: a double-blind randomised trial. Lancet (2010); 376: 1658-69.

trials that include similar comparator, populations of similar CV risk, similar background therapy, and similar dose used as initiation dose (75 mg or 150 mg Q2W). The OPTIONS trials are shown by pooled background statin therapy.

Although there are differences in treatment effect among the individual trials, pools of the placebo-controlled and ezetimibe-controlled trials demonstrate point estimates in the range of 30 to 60 percentage point lowering with overlapping 95% confidence intervals.

As noted above, LONG TERM and HIGH FH were the only two trials that initiated with alirocumab 150 mg Q2W and continued that dose throughout the treatment period. The LDL-C percent reduction from baseline (alirocumab versus placebo) was greater in LONG TERM than in HIGH FH; this finding is discussed elsewhere in this review.

Figure 8. Percent Change from Baseline in LDL-C at Week 24, Phase 3 Trials (ITT Analysis)



Source: SCE, Figure 17

The sponsor conducted a number of sensitivity analyses to address missing data. These analyses were consistent with the primary analysis. Please see Dr. McEvoy's review for a comprehensive statistical evaluation of missing data, utilizing current best practices.[35]

35 See: National Research Council Panel on Missing Data in Clinical Trials (2010)

6.1.5 Analyses of Secondary Endpoints

A hierarchical testing procedure was defined to test the primary and the key secondary endpoints while controlling for multiplicity. For the majority of the trials, the first key secondary endpoint was the percent change in calculated LDL-C from baseline to week 24 using an on-treatment approach. After this key secondary endpoint, the week 12 percent change in LDL-C was assessed, followed by other lipid endpoints utilizing the LDL-C analyses, response rates using pre-defined LDL-C thresholds, and then other lipid parameters. See Table 43 for the testing approach used in the different phase 3 trials.

Table 43. Key Secondary Efficacy Endpoints, Phase 3 Trials

Key secondary endpoint	FH I, FH II, HIGH FH	LONG TERM	COMBO I, COMBO II	OPTIONS I, OPTIONS II, ALTERNATIVE	MONO
Percent change in calculated LDL-C from baseline to Week 24 (on-treatment estimand).	1st key	1st key	1st key	1st key	-
Percent change in calculated LDL-C from baseline to Week 12 (ITT estimand).	2nd key	2nd key	2nd key	2nd key	1st key
Percent change in calculated LDL-C from baseline to Week 12 (on-treatment estimand).	3rd key	3rd key	3rd key	3rd key	-
Percent change in measured LDL-C from baseline to Week 24 (ITT estimand).	-	4th key	-	-	-
Percent change in Apo B from baseline to Week 24 (ITT estimand).	4th key	5th key	4th key	4th key	2nd key
Percent change in Apo B from baseline to Week 24 (on-treatment estimand).	5th key	6th key	5th key	5th key	-
Percent change in non-HDL-C from baseline to Week 24 (ITT estimand).	6th key	7th key	6th key	6th key	3rd key
Percent change in non-HDL-C from baseline to Week 24 (on-treatment estimand).	7th key	8th key	7th key	7th key	-
Percent change in Total-C from baseline to Week 24 (ITT estimand).	8th key	9th key	8th key	8th key	4th key
Percent change in Apo B from baseline to Week 12 (ITT estimand).	9th key	10th key	9th key	9th key	5th key

Key secondary endpoint	FH I, FH II, HIGH FH	LONG TERM	COMBO I, COMBO II	OPTIONS I, OPTIONS II, ALTERNATIVE	MONO
Percent change in non-HDL-C from baseline to Week 12 (ITT estimand).	10th key	11th key	10th key	10th key	6th key
Percent change in Total-C from baseline to Week 12 (ITT estimand).	11th key	12th key	11th key	11th key	7th key
Percent change in calculated LDL-C from baseline to Week 52 (ITT estimand).	12th key	13th key	12th key	-	-
Proportion of very high CV risk patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) or moderate [a] to high CV risk patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 (ITT estimand).	13th key	14th key	-	12th key	-
Proportion of very high CV risk patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) or moderate to high CV risk patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 (on-treatment estimand).	14th key	15th key	-	13th key	-
Proportion of patients reaching calculated LDL-C <100 mg/dL (2.59 mmol/L) at Week 24 (ITT estimand).	-	-	-	-	8th key
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 (ITT estimand).	15th key	16th key	13th key	14th key	9th key
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 (on-treatment estimand).	16th key	17th key	14th key	15th key	-
Percent change in Lp(a) from baseline to Week 24 (ITT estimand).	17th key	18th key	15th key	16th key	10th key
Percent change in HDL-C from baseline to Week 24 (ITT estimand).	18th key	19th key	16th key	17th key	11th key
Percent change in fasting TGs from baseline to Week 24 (ITT estimand).	19th key	20th key	17th key	18th key	14th key
Percent change in Apo A-1 from baseline to Week 24 (ITT estimand).	20th key	21st key	18th key	19th key	16th key
Percent change in Lp(a) from baseline to Week 12 (ITT estimand).	21st key	22nd key	19th key	20th key	13th key
Percent change in HDL-C from baseline to Week 12 (ITT estimand).	22nd key	23rd key	20th key	21st key	12th key
Percent change in fasting TGs from baseline to Week 12 (ITT estimand).	23rd key	24th key	21st key	22nd key	15th key
Percent change in Apo A-1 from baseline to Week 12 (ITT estimand).	24th key	25th key	22nd key	23rd key	17th key

a Moderate CV risk only applicable to ALTERNATIVE study

Source: SCE, Table 6

The sponsor's testing hierarchy is acknowledged; however, the secondary results presented here are focused primarily on various LDL-C analyses, since this variable is of greatest interest and clinical relevance. The other lipid variables will then be described as supportive information.

LDL-C Analyses

On-treatment, Percent Change at Week 24

Percent change from baseline in LDL-C was analyzed using the mITT population (as defined in section 6.1.3), utilizing LDL-C collected during the efficacy treatment period (the first double-blind injection up to the day of the last injection +21 days).

As part of the discussion of calculated versus measured LDL-C, below, on-treatment LDL-C results are shown for the LONG TERM trial in Figure 10. Because the on-treatment analyses gave very similar results to the primary efficacy ITT analyses for all phase 3 trials, these results will not be discussed further.

Absolute Change at Week 24

Percent change is generally used to describe LDL-C lowering effects (with statins) across a wide range of populations. This is because percent LDL-C lowering is generally consistent across baseline LDL-C, suggesting that absolute change in LDL-C varies across baseline LDL-C categories. (Subgroup analysis evaluating change in percent LDL-C across baseline LDL-C categories is discussed and shown in section 6.1.7, specifically Figure 16.) Decreasing absolute LDL-C has been shown to correlate with lowering the risk of CV events. For example, a meta-analysis of statin trials estimated that for each 1.0 mmol/L (~39 mg/dL) the rate of major vascular events – defined in the referenced publication as the first occurrence of any major coronary event, coronary revascularization, or ischemic stroke – was reduced by ~22%.[36] However, whether this relationship applies to PCSK9 inhibitors is unknown.

In the alirocumab phase 3 trials, the following analyses of absolute LDL-C lowering demonstrate some variability between trials in absolute decreases from baseline. Baseline LDL-C is included in this table as well; some of the variability could be related to differences in baseline LDL-C among trials. (For example, the two trials with the highest mean baseline LDL-C, HIGH FH and ALTERNATIVE, were associated with the greatest absolute LDL-C change from baseline in the alirocumab group, as expected from the similar mean percent reduction in LDL-C observed among alirocumab-treated patients in these trials).

36 Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet (2010); 376:1670-81.

Table 44. Absolute Change in LDL-C at Week 24, Phase 3 Trials

	Baseline LDL-C (mg/dL)	Control (abs change, mg/dL)	Alirocumab (abs change, mg/dL)	LS Means Difference (95% CI)	p-value
FH I[a]	144.6	11.0	-73.3	-84.3 (-92.1, -76.5)	<0.0001
FH II[a]	134.4	2.2	-66.7	-68.9 (-78.4, -59.3)	<0.0001
HIGH FH[a]	197.8	-15.5	-90.8	-75.3 (-98.4, -52.2)	<0.0001
LONG TERM[a]	122.4	-3.6	-74.2	-70.6 (-73.5, -67.7)	<0.0001
COMBO I[a]	102.2	-3.9	-50.3	-46.4 (-53.2, -39.5)	<0.0001
COMBO II[b]	107.3	-24.5	-55.4	-30.9 (-35.7, -26.2)	<0.0001
OPTIONS I (atorva 20)[b]	103.9[c]	-20.8	-47.5	-26.7 (-40.0, -13.4)	<0.0001[d]
OPTIONS I (atorva 40)[b]	116.4[c]	-23.6	-62.3	-38.6 (-51.6, -25.6)	<0.0001[d]
OPTIONS II (rosuva 10)[b]	107.3[c]	-17.4	-52.2	-34.9 (-47.3, -22.4)	<0.0001[d]
OPTIONS II (rosuva 20)[b]	118.3[c]	-25.4	-43.5	-18.1 (-34.2, -2.1)	0.0273[d]
ALTERNATIVE[b]	191.1[c]	-32.8	-84.2	-51.4 (-63.0, -39.8)	<0.0001
MONO[b]	139.7	-23.0	-66.9	-43.9 (-56.3, -31.5)	<0.0001

a placebo-controlled
b ezetimibe-controlled
c alirocumab group only
d p-value not adjusted for multiplicity

Source: CSR EFC12492-15-2-eff-data, table 7; CSR R727-CL-1112, table 31; LTS11717-15-2-eff-data, table 7; EFC11568-eff-data, table 8; EFC11569-15-2-eff-data, table 8; CSR R727-CL-1110, tables 43 and 57; CSR R727-CL-1118, tables 44 and 58; CSR R727-CL-1119, table 36; CSR EFC11716, table 42

Week 12 Percent Change in LDL-C

Week 12 LDL-C changes are often used to assess efficacy of lipid-lowering drugs. Because alirocumab demonstrates its effect by the first LDL-C measurement (week 4), week 12 should provide a reasonable assessment of the 75 mg dose in the FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO trials, since the 12-week time point is prior to alirocumab up-titration and also any alteration of background LMTs, per protocol.

Percent LDL-C changes at week 12 are consistently greater than control, and despite the up-titration protocol, the magnitude is similar to week 24. (The percent LDL-C change in the subsets of patients who underwent dose up-titration are presented in section 6.1.8)

Table 45. Percent Change from Baseline in LDL-C at Week 12, Phase 3 Trials

	Baseline LDL-C (mg/dL)	Control (% change)	Alirocumab (% change)	LS Means Difference (95% CI)	p-value
Alirocumab 75 mg					
FH I[a]	144.6	5.7	-43.5	-49.2 (-53.9, -44.5)	<0.0001
FH II[a]	134.4	4.6	-43.5	-48.4 (-54.7, -42.2)	<0.0001
COMBO I[a]	102.2	1.1	-46.3	-47.4 (-53.6, -41.3)	<0.0001
COMBO II[b]	107.3	-21.8	-51.2	-29.4 (-33.7, -25.1)	<0.0001
OPTIONS I[b]	109.7[c]	-25.9	-49.3	-23.4 (-30.5, -16.3)	<0.0001[d]
OPTIONS II[b]	113.2[c]	-18.4	-40.7	-22.3 (-31.9, -12.6)	<0.0001[d]
ALTERNATIVE[b]	191.1[c]	-15.6	-47.0	-31.5 (-36.9, -26.1)	<0.0001
MONO[b]	139.7	-19.6	-48.1	-28.5 (-35.7, -21.2	<0.0001
Alirocumab 150 mg					
HIGH FH[a]	197.8	-6.6	-46.9	-40.3 (-51.4, -29.3)	<0.0001
LONG TERM[a]	122.4	1.5	-63.3	-64.8 (-67.2, -62.4)	<0.0001

a placebo-controlled
b ezetimibe-controlled
c alirocumab group only
d p-value not adjusted for multiplicity

Source: SCE, Figure 20, individual CSRs

Proportions of Patients Achieving LDL-C Targets

As discussed in section 2.6, the previous NCEP-ATP cholesterol guidelines recommended that in patients at high risk for CV events, the LDL-C goal should be < 100 mg/dL, and in those at very high risk, an LDL-C goal of < 70 mg/dL is "a reasonable clinical strategy,"[21] although recent guideline updates in the U.S. focus less on goals and more on the patient populations likely to achieve benefit from statin-based lipid therapy.[7] Nevertheless, it is useful to consider analyses of proportions of patients achieving various LDL-C goals, since in practice many physicians are likely to continue to follow this strategy, particularly in the highest risk patients. Prespecified LDL-C targets (for up-titration) were defined as described in section 6.1.1, Table 13; for "very high" CV risk patients, the target was defined as < 70 mg/dL, and for "high" CV risk patients, the target was < 100 mg/dL.

Table 46 and Table 47 demonstrate that a statistically significantly greater proportion of patients in the alirocumab groups, compared with control, met their individual goals as would be expected based on the mean LDL-C reduction observed and the baseline LDL-C values of the population. The trials with lower proportions of patients reaching individual LDL-C targets (HIGH FH and ALTERNATIVE, 41 and 42%, respectively) had higher mean LDL-C at baseline. In the MONO trial, due to an administrative error, patients were up-titrated at week 12 if LDL-C was greater than 70 mg/dL (rather than 100 mg/dL as specified in the protocol); therefore, in theory, the efficacy in this trial could be overestimated since the goal for these patients with moderate CV risk is less than 100 mg/dL. Nevertheless, the week 12 results in the MONO trial (proportion of patients achieving LDL-C < 100 mg/dL) were very similar to the week 24 results.

Table 46. Proportion of Patients Meeting LDL-C Targets at Week 24, Placebo-Controlled Phase 3 Trials

Trial	Placebo	Alirocumab	p-value
FH I[a]	2.4%	72.2%	<0.0001*
FH II[a]	11.3%	81.4%	<0.0001*
HIGH FH[a]	5.7%	41.0%	0.0016*
LONG TERM[a]	8.5%	80.7%	<0.0001*
COMBO I[b]	9.0%	75.0%	<0.0001*

a LDL-C < 70 mg/dL among very high risk patients or LDL-C < 100 mg/dL among moderate to high CV risk patients
b LDL-C < 70 mg/dL (very high risk patients only)
* P-values with an asterisk were formally tested based on the study-wise predefined hierarchical sequence and achieved statistical significance

Source: CSR EFC12492, Table 28; R727-CL-1112, Table 26; EFC12732, Table 30; LTS11717, Table 27; EFC11568, Table 29

Table 47. Proportion of Patients Meeting LDL-C Targets at Week 24, Ezetimibe-Controlled Phase 3 Trials

Trial	Statin (Atorva 20)	Ezetimibe	Alirocumab	p-value
COMBO II[b]	N/A	45.6%	77.0%	<0.0001*
ALTERNATIVE[a]	19.2%[d]	4.4%	41.9%	<0.0001*
MONO[c]	N/A	32.2%	88.1%	<0.0001*

a LDL-C < 70 mg/dL among very high risk patients or LDL-C < 100 mg/dL among moderate to high CV risk patients
b LDL-C < 70 mg/dL (very high risk patients only)
c LDL < 100 mg/dL (moderate risk patients only)
d methodology different for statin arm; no imputation of missing data
* P-values with an asterisk were formally tested based on the study-wise predefined hierarchical sequence and achieved statistical significance (vs. ezetimibe)
N/A=not applicable

Source: CSR EFC11569, Table 31; R727-CL-1119, Table 32; Appendix Clinical Response, 23 Jan 2015, Table 61; EFC11716, Table 29

In the OPTIONS trials, alirocumab was associated with numerically, but not necessarily statistically significant, greater proportions of patients achieving LDL-C goals versus comparators.

Table 48. Proportion of Patients Meeting LDL-C Targets at Week 24, OPTIONS Trials

Trial	Statin Up-Titration	More Potent Statin (Rosuva 40)	Eze + Statin	Aliro + Statin	p-value
OPTIONS I (atorva 20)[a]	34.5%	N/A	68.4%	87.2%	<0.0001* (vs. statin up-titration)
					0.0284[b] (vs. ezetimibe)
OPTIONS I (atorva 40)[a]	18.5%	62.2%	65.1%	84.6%	<0.0001* (vs. statin up-titration)
					0.0025* (vs. more potent statin)
					0.0011* (vs. ezetimibe)
OPTIONS II (rosuva 10)[a]	45.0%	N/A	57.2%	84.9%	<0.0001* (vs. statin up-titration)
					0.0007* (vs. ezetimibe)
OPTIONS II (rosuva 20)[a]	40.1%	N/A	52.2%	66.7%	0.0022 (vs. statin up-titration)
					0.1177 (vs. ezetimibe)

a LDL-C < 70 mg/dL among very high risk patients or LDL-C < 100 mg/dL among moderate to high CV risk patients
* P-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance
b The endpoint was formally tested based on the predefined hierarchical sequence, but did not achieve statistical significance at the 0.01 level

Source: R727-CL-1110, Tables 39 and 53; R727-CL-1118, Tables 40 and 54

In the most recent U.S. cholesterol guidelines, the use of high intensity statins is recommended in all high CV risk patients rather than specific LDL-C targets, to achieve at least a 50% LDL-C reduction, regardless of the LDL-C concentration.[7] Therefore, the 50% target is considered clinically relevant (although, notably, it is unknown whether achieving an additional 50% lowering *on top of a statin* provides a similar degree of CV protection). In the alirocumab program, the proportion of patients achieving a 50% greater reduction in LDL-C was evaluated in all trials, although it was not analyzed as part of the testing algorithm that controlled for type I error. Results are presented below, by trial.

Table 49. Proportion of Patients Achieving at Least 50 Percent Reduction in Baseline LDL-C, Phase 3 Trials

	Control	Alirocumab
FH I[a]	0%	56.8%
FH II[a]	0%	60.2%
HIGH FH[a]	8.7%	55.3%
LONG TERM[a]	1.9%	75.7%
COMBO I[a]	3.3%	54.6%
COMBO II[b]	8.9%	62.2%
OPTIONS I[b]	9.1%	64.4%
OPTIONS II[b]	9.7%	56.2%
ALTERNATIVE[b]	2.5%	57.9%
MONO[b]	0%	61.5%

a placebo-controlled
b ezetimibe-controlled
Note: This endpoint was not formally tested based on a predefined hierarchical sequence

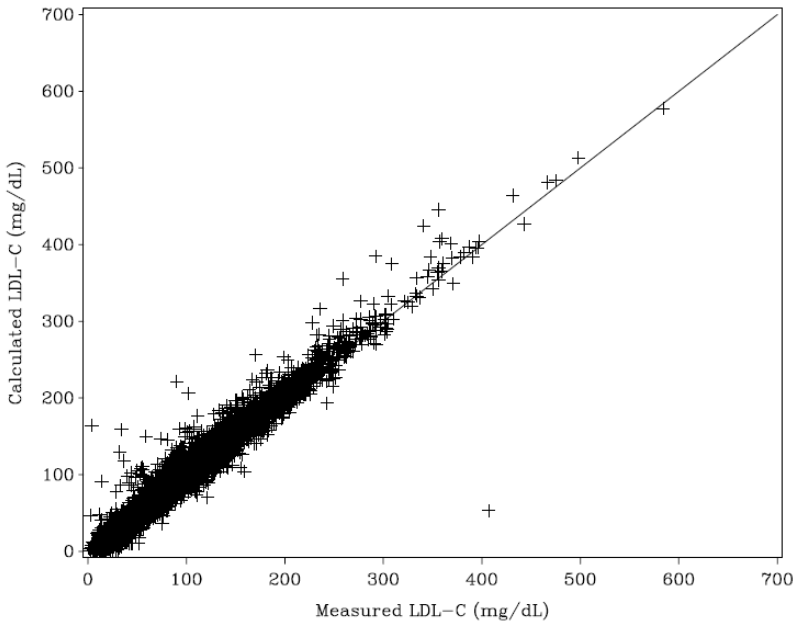
Source: ISE, Table 4.8.1.35

Measured LDL-C

Calculated LDL-C was selected as primary endpoint for the BLA, as the Friedewald equation (LDL-C = TC – HDL-C – TG/5)[37] is typically used in clinical practice. Measured and calculated LDL-C tend to be highly correlated; this is supported by the following figure from the phase 3 trial data:

37 Friedewald WT, et al. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. Clin Chem, 1972. 18(6): 499-502.

Figure 9. Calculated LDL-C versus Measured LDL-C, Pool of Phase 3 Trials, All Treatment Groups Combined



Source: ISE, Figure 4.10.1.1

However, the Friedewald equation tends to underestimate LDL-C in the setting of high TG (historically ≥ 400 mg/dL, but perhaps as low as ≥ 150 mg/dL as suggested in a recent publication), and at low LDL-C (e.g., < 70 mg/dL).[38] Because of the potential for overestimating the treatment effect with calculated LDL-C, directly measured LDL-C[39] was utilized at certain time points to support the calculated results.

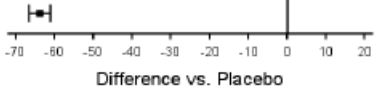
Measurement of LDL-C by ultracentrifugation was performed in LONG TERM at baseline and at key efficacy time points, after 12 weeks, 24 weeks, 12 months, and 18 months of therapy. Directly measured LDL-C was added by protocol amendment at baseline and at Week 24 to most other phase 3 studies (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, and ALTERNATIVE), to support the data obtained with the Friedewald equation. However, in some trials there was a considerable amount of missing data: the proportions of randomized patients with available measured LDL-C values at baseline and during the week 24 analysis window were, for LONG TERM 84%, FH I 72%, FH II 75%, COMBO I 61%, COMBO II 77%, OPTIONS I 91%, OPTIONS II 80%, and ALTERNATIVE 73%.

38 Martin SS, et al. Friedewald-estimated versus directly measured low-density lipoprotein cholesterol and treatment implications. J Am Coll Cardiol (2013). 62(8): 732-9.
39 Quantitative LDL cholesterol by ultracentrifugation; LONG TERM: Covance Central Laboratory, all other phase 3 trials: Medpace Reference Laboratories

The LONG TERM trial had the highest proportion of patients who achieved very low LDL-C in the alirocumab program (< 25 mg/dL, 37.4% and <15 mg/dL, 14.8%), and therefore would presumably be most likely to overestimate the treatment effect with utilizing the calculated LDL-C values (indeed, a review of measured LDL-C results from the other seven trials supports this conclusion). As shown in Figure 10, placebo-subtracted percent change in calculated LDL-C in LONG TERM is about 3 to 4 percentage points greater than that of measured LDL-C at each time point, for both ITT and on-treatment analyses.

Figure 10. Summary of Percent Change in Calculated and Measured LDL-C, LONG TERM Trial

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	1.5 (1.0)	-63.3 (0.7)		<0.0001* K
		Week 24	0.8 (1.0)	-61.0 (0.7)		<0.0001* P
		Week 52	4.4 (1.2)	-56.8 (0.8)		<0.0001
	On-treatment	Week 12	1.4 (1.0)	-64.2 (0.7)		<0.0001* K
		Week 24	0.7 (1.0)	-62.8 (0.7)		<0.0001* K
		Week 52	4.6 (1.1)	-59.9 (0.8)		<0.0001
Measured LDL-C	ITT	Week 12	2.8 (1.1)	-60.6 (0.8)		<0.0001
		Week 24	3.5 (1.1)	-57.8 (0.8)		<0.0001* K
		Week 52	6.5 (1.2)	-54.4 (0.9)		<0.0001
	On-treatment	Week 12	2.8 (1.1)	-61.2 (0.8)		<0.0001
		Week 24	3.4 (1.1)	-59.6 (0.8)		<0.0001
		Week 52	6.5 (1.1)	-57.4 (0.8)		<0.0001



P: Primary efficacy endpoint
K: Key secondary efficacy endpoint
For primary and key secondary efficacy endpoints, the p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.
Source: SCE, Figure 25

Other Lipid Parameters

Apolipoprotein B, non-HDL-C, and Total Cholesterol

Apo B and non-HDL-C are considered biomarkers of CV risk that incorporate information not only about LDL particles (or LDL-C) but also other putatively atherogenic lipoproteins (or their cholesterol content), such as VLDL-C. These biomarkers are thought to enhance prediction of CV risk, particularly when triglycerides are elevated.

ATP III considered non-HDL-C as a secondary target of lipid-lowering drug therapy;[40] however, the most recent guidelines do not.[7,41] The following tables demonstrate that, consistent with the LDL-C lowering, there is a robust and consistent effect on apo B, non-HDL-C, and total cholesterol as compared with either placebo or ezetimibe.

Table 50. Summary of Apo B Changes at Week 24, Phase 3 Trials

	Baseline Apo B (mg/dL)	Control (% change)	Alirocumab (% change)	LS Means Difference (95% CI)	p-value
FH I[a]	114.1	4.7	-41.1	-45.8 (-49.8, -41.8)	<0.0001
FH II[a]	107.9	-3.5	-42.8	-39.3 (-44.1, -34.5)	<0.0001
HIGH FH[a]	140.9	-8.7	-39.0	-30.3 (-39.7, -20.9)	<0.0001
LONG TERM[a]	101.7	1.2	-52.8	-54.0 (-56.3, -51.7)	<0.0001
COMBO I[a]	91.0	-0.9	-36.7	-35.8 (-41.3, -30.3)	<0.0001
COMBO II[b]	94.0	-18.3	-40.7	-22.4 (-26.0, -18.8)	<0.0001
OPTIONS I[b]	93.1[c]	-12.0	-37.3	-25.3 (-32.2, -18.4)	<0.0001
OPTIONS II[b]	95.8[c]	-10.8	-32.2	-21.4 (-29.0, -13.9)	<0.0001
ALTERNATIVE[b]	141.7[c]	-11.2	-36.3	-25.1 (-29.8, -20.4)	<0.0001
MONO[b]	104.3	-11.0	-36.7	-25.8 (-32.3, -19.2)	<0.0001

a placebo-controlled
b ezetimibe-controlled
c alirocumab group only

Source: SCE, Figure 35, individual CSRs

40 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation (2002); 106(25): 3143-421.

41 The 2013 ACC/AHA cholesterol guidelines note, "One RCT…was identified that showed no additional ASCVD [atherosclerotic cardiovascular disease] event reduction from the addition of non-statin therapy to further lower non-HDL-C levels once an LDL-C goal had been reached. In AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low LDL/High Triglycerides and Impact on Global Health Outcomes), the additional reduction in non-HDL-C levels (as well as further reduction in apolipoprotein B, lipoprotein[a], and triglycerides in addition to HDL-C increases) with niacin therapy did not further reduce ASCVD risk in individuals treated to LDL-C levels of 40 to 80 mg/dL."

Table 51. Summary of Non-HDL-C Changes at Week 24, Phase 3 Trials

	Baseline Non-HDL-C (mg/dL)	Control (% change)	Alirocumab (% change)	LS Means Difference (95% CI)	p-value
FH I[a]	170.1	9.6	-42.8	-52.4 (-57.2, -47.6)	<0.0001
FH II[a]	158.5	3.1	-42.6	-45.7 (-51.8, -39.7)	<0.0001
HIGH FH[a]	226.4	-6.2	-41.9	-35.5 (-46.2, -24.9)	<0.0001
LONG TERM[a]	152.4	0.7	-51.6	-52.3 (-54.4, -50.2)	<0.0001
COMBO I[a]	131.1	-1.6	-39.1	-37.5 (-43.5, -31.4)	<0.0001
COMBO II[b]	138.3	-19.2	-42.1	-22.9 (-26.9, -18.9)	<0.0001
OPTIONS I[b]	137.3[c]	-17.6	-41.7	-24.1 (-31.8, -16.4)	<0.0001
OPTIONS II[b]	142.1[c]	-12.0	-36.7	-24.7 (33.7, -15.6)	<0.0001
ALTERNATIVE[b]	230.0[c]	-14.6	-40.2	-25.6 (-30.4, -20.8)	<0.0001
MONO[b]	165.7	-15.1	-40.6	-25.5 (-33.5, -17.4)	<0.0001

a placebo-controlled
b ezetimibe-controlled
c alirocumab group only

Source: SCE, Figure 36, individual CSRs

Table 52. Summary of Total Cholesterol Changes at Week 24, Phase 3 Trials

	Baseline Total-C (mg/dL)	Control (% change)	Alirocumab (% change)	LS Means Difference (95% CI)	p-value
FH I[a]	219.9	7.3	-31.4	-38.7 (-42.4, -35.0)	<0.0001
FH II[a]	211.6	2.1	-30.6	-32.8 (-37.4, -28.1)	<0.0001
HIGH FH[a]	274.4	-4.8	-33.2	-28.4 (-37.3, -19.6)	<0.0001
LONG TERM[a]	202.2	-0.3	-37.8	-37.5 (-39.1, -35.9)	<0.0001
COMBO I[a]	179.7	-2.9	-27.9	-25.0 (-29.3, -20.7)	<0.0001
COMBO II[b]	185.6	-14.6	-29.3	-14.7 (-17.7, -11.7)	<0.0001
OPTIONS I[b]	185.5[c]	-12.8	-30.0	-17.1 (-22.7, -11.5)	<0.0001
OPTIONS II[b]	192.8[c]	-9.9	-24.5	-14.6 (-21.0, -8.3)	<0.0001
ALTERNATIVE[b]	278.9[c]	-10.9	-31.8	-20.8 (-24.7, -17.0)	<0.0001
MONO[b]	222.8	-10.9	-29.6	-18.7 (-24.7, -12.7)	<0.0001

a placebo-controlled
b ezetimibe-controlled
c alirocumab group only

Source: SCE, Figure 37, individual CSRs

HDL-C and Fasting Triglycerides

Although low HDL-C and high TGs have been cited as independent risk factors for CVD, recent data from large clinical trials call into question whether increasing HDL-C and/or lowering fasting TGs with drugs in combination with statin therapy beneficially impacts risk of CV events.[2,3,4,5] Furthermore, there are no generally accepted treatment-related changes in these parameters that have been established as clinically meaningful. Early trials with fenofibrate in patients with primary hyperlipidemia and mixed dyslipidemia, demonstrated mean TG changes of -24% and -36% (compared with TG changes in placebo of +12% and +1%) respectively, and mean HDL-C changes

of +10% and +15% (compared with placebo +3% and +2%), respectively.[42] Niacin 2000 mg/day decreased TG by approximately 28% and increased HDL-C by approximately 22% as compared to placebo changes of 0% and +4%, respectively, in a similar patient population.[43] In cross-study comparisons, alirocumab's effects on these parameters as compared to placebo are generally less, and are variable, particularly for TG (only three of five trials were statistically significant). Compared to ezetimibe, alirocumab's effects on TG were not statistically significant. Statistically greater increases in HDL-C were observed in four of the five placebo-controlled trials and one of the five ezetimibe-controlled trials. The clinical significance of these changes is uncertain.

Table 53. Summary of Triglyceride Changes at Week 24, Phase 3 Trials

	Baseline TG (mg/dL)	Control (% change)	Alirocumab (% change)	LS Means Difference (95% CI)	p-value
FH I[a]	127.8	6.3	-9.6	-16.0 (-21.3, -10.6)	<0.0001
FH II[a]	121.0	0.5	-10.4	-10.9 (-17.5, -4.3)	0.0012
HIGH FH[a]	149.8	-1.9	-10.5	-8.7 (-20.2, 2.8)	0.1386
LONG TERM[a]	150.9	1.8	-15.6	-17.3 (-20.1, -14.6)	<0.0001
COMBO I[a]	147.5	-5.4	-6.0	-0.6 (-8.3, 7.0)	0.8699
COMBO II[b]	155.7	-12.8	-13.0	-0.3 (-5.1, 4.6)	0.9117
OPTIONS I[b]	138.5[c]	-8.1	-15.3	-7.2 (-14.6, 0.2)	0.0568
OPTIONS II[b]	142.2[c]	-9.9	-10.1	-0.2 (-9.0, 8.5)	0.9632
ALTERNATIVE[b]	186.2[c]	-3.6	-9.3	-5.7 (-13.3, 1.9)	0.1426
MONO[b]	129.9	-6.0	-10.3	-1.2 (-12.7, 10.3)	0.1827
a placebo-controlled b ezetimibe-controlled c alirocumab group only					

Source: SCE, Figure 27, individual CSRs

Table 54. Summary of HDL-C Changes at Week 24, Phase 3 Trials

	Baseline HDL-C (mg/dL)	Control (% change)	Alirocumab (% change)	LS Means Difference (95% CI)	p-value
FH I[a]	49.8	0.8	8.8	8.0 (5.0, 11.0)	<0.0001
FH II[a]	53.1	-0.8	6.0	6.8 (2.8, 10.7)	0.0009
HIGH FH[a]	48.1	3.9	7.5	3.7 (-2.9, 10.2)	0.2745
LONG TERM[a]	49.9	-0.6	4.0	4.6 (3.3, 5.9)	<0.0001
COMBO I[a]	48.5	-3.8	3.5	7.3 (3.6, 11.0)	0.0001
COMBO II[b]	47.3	0.5	8.6	8.1 (5.4, 10.7)	<0.0001
OPTIONS I[b]	47.7	1.0	6.2	4.8 (0.3, 9.3)	0.0306
OPTIONS II[b]	50.7[c]	0.8	8.1	7.3 (2.6, 12.0)	0.0026
ALTERNATIVE[b]	48.9[c]	6.8	7.7	0.9 (-3.8, 5.6)	0.6997
MONO[b]	57.1	1.6	6.0	4.4 (-1.0, 9.8)	0.1116
a placebo-controlled b ezetimibe-controlled c alirocumab group only					

Source: SCE, Figure 38, individual CSRs

42 Tricor (fenofibrate) prescribing information
43 Niaspan (niacin extended-release) prescribing information

The sponsor separately evaluated the effect of alirocumab in patients with mixed dyslipidemia; the definition utilized in this BLA is patients with hypercholesterolemia and TG ≥ 150 mg/dL, although other definitions include patients with low HDL-C.[44] A total of 2025 patients (38.2% of randomized) were considered to have mixed dyslipidemia by the sponsor's definition in the BLA. In this subgroup, effects on TG and HDL-C were similar to the overall population, and will not be described further.

Other Secondary Endpoints

Epidemiological studies suggest an independent association with Lp(a), an LDL particle with apoB-100 covalently modified by apolipoprotein(a), and atherosclerotic disease.[45] Nevertheless, it is unclear if modifying Lp(a) with PCSK9 inhibitors will beneficially impact cardiovascular risk among patients with well-controlled LDL-C but elevated Lp(a). In the alirocumab groups, mean percent change at week 24 from baseline in Lp(a) ranged from -17 to -30% across the trials, whereas placebo ranged from -4 to -10%, and ezetimibe -5 to -12%.

Apo A-1 is the main apolipoprotein associated with HDL, and epidemiological studies suggest that higher Apo A-1 is associated with lower CV risk.[46] In the alirocumab groups, mean percent change at week 24 from baseline in Apo A-1 ranged from +3 to +7% across the trials, whereas placebo ranged from -2.5 to +2%, and ezetimibe -1 to +3%.

6.1.6 Other Endpoints

Changes to Concomitant Lipid Modifying Therapies

All concomitant LMTs were to be at stable dose for at least 4 weeks before the screening visit, during the screening period, and throughout the study period. The lipid results from blood samples obtained after the randomization visit were not communicated to the site. However in some circumstances, investigators were allowed to make changes as a result of two specific types of alerts from the central laboratory:

44 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Final report. Circulation, 2002; 106: 3143-421.
45 Emerging Risk Factors Collaboration. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. 2009; 302(4): 412-23.
46 Luc G, et al. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-I/A-II in prediction of coronary heart disease: the PRIME study. Arterioscler Thromb Vasc Biol. 2002; 22(7): 1155-61.

- In all trials regardless of the duration of the study, a notification to sites was communicated for TG value ≥ 500 mg/dL at any time after randomization. For TG alert confirmed by repeat testing, investigators were allowed to modify the background LMT as per their medical judgment; as rescue LMT, only fenofibrate was allowed in the MONO study.

- In trials with a duration of at least 1 year, a notification to sites was communicated from the Week 24 visit and later for LDL-C increase >25%, as compared to randomization visit LDL-C, on two consecutive occasions. Investigators were asked to ensure that no reasonable explanation existed for insufficient LDL-C control (such as an alternative medical cause like corticosteroid use, or lack of compliance with diet/background LMT). If no reason could be found or if appropriate action failed to decrease LDL-C under the alert value, change in the background LMT as per investigators' medical judgment was allowed.

Changes to background LMTs could have the potential to influence the efficacy results. However, as seen in the sections below, the proportions of patients with changes to background therapies were small, and therefore unlikely to have a major impact on the results.

Dose Increase of Background LMT

Among the nine phase 3 trials where a background LMT was required or allowed (all trials but MONO), no dose increase was reported in HIGH FH, OPTIONS I, OPTIONS II, and ALTERNATIVE. In the other trials, the proportion of patients with an increase in the dose of the background LMT ranged from 1.2% to 3.8% in the placebo group as compared with 0.3% to 1.0% in the alirocumab group. In COMBO II, which was ezetimibe-controlled, the proportion was 0.6% and 0.4% for the alirocumab and ezetimibe groups, respectively.

Table 55. Proportion of Patients with Increase in Dose of Background LMT, Phase 3 Trials

	Control	Alirocumab
Placebo-controlled		
FH I	1.2%	0.3%
FH II	1.2%	0.6%
HIGH FH	0	0
LONG TERM	1.9%	1.0%
COMBO I	3.8%	1.0%
Ezetimibe-controlled		
COMBO II	0.4%	0.6%
OPTIONS I	0	0
OPTIONS II	0	0
ALTERNATIVE	0	0

Source: Request of 03-Mar-2015 Item #1 – Appendix, Tables 3.1 to 3.10

Addition of New LMT

Among the nine phase 3 trials where a background LMT was required or allowed, there was no addition of new background LMT during the OPTIONS II and ALTERNATIVE trials. Also in the MONO trial, in which background therapy was not permitted, there was no addition of any LMT. In the other trials, the proportion of patients with addition of a new background LMT ranged from 0.8% to 2.9% in the placebo group as compared with 0% to 1.0% in the alirocumab group. In COMBO II, which was ezetimibe-controlled, the proportion was 0.2% and 0% for alirocumab and ezetimibe groups, respectively. In one patient receiving rosuvastatin 40 mg in OPTIONS I, addition of ezetimibe was reported (not shown in the table below).

Table 56. Proportion of Patients with Addition of a New LMT during the Trial, Phase 3 Trials

	Control	Alirocumab
Placebo-controlled		
FH I	1.2%	0.9%
FH II	1.2%	0.6%
HIGH FH	2.9%	0
LONG TERM	0.8%	0.1%
COMBO I	0.9%	1.0%
Ezetimibe-controlled		
COMBO II	0	0.2%
OPTIONS I	0	0
OPTIONS II	0	0
ALTERNATIVE	0	0
MONO	0	0

Source: Request of 03-Mar-2015 Item #1 – Appendix, Tables 4.1 to 4.10

Decrease or Discontinuation of LMT

Among the nine phase 3 trials where a background LMT was required or allowed, the proportion of patients with decrease in dose or stopping background LMT ranged from 0.6% to 2.9% in the placebo group as compared with 0.6% to 4.2% in the alirocumab group. In the ezetimibe-controlled studies COMBO II and ALTERNATIVE, the proportion ranged from 0.8% to 4.1%, respectively, in the ezetimibe group, as compared with 0.4% to 1.6% in the alirocumab group. In total, 11 patients decreased dose of or discontinued a statin; all other changes were to non-statin LMT.

Table 57. Proportion of Patients who Decreased Dose of or Discontinued Background LMT, Phase 3 Trials

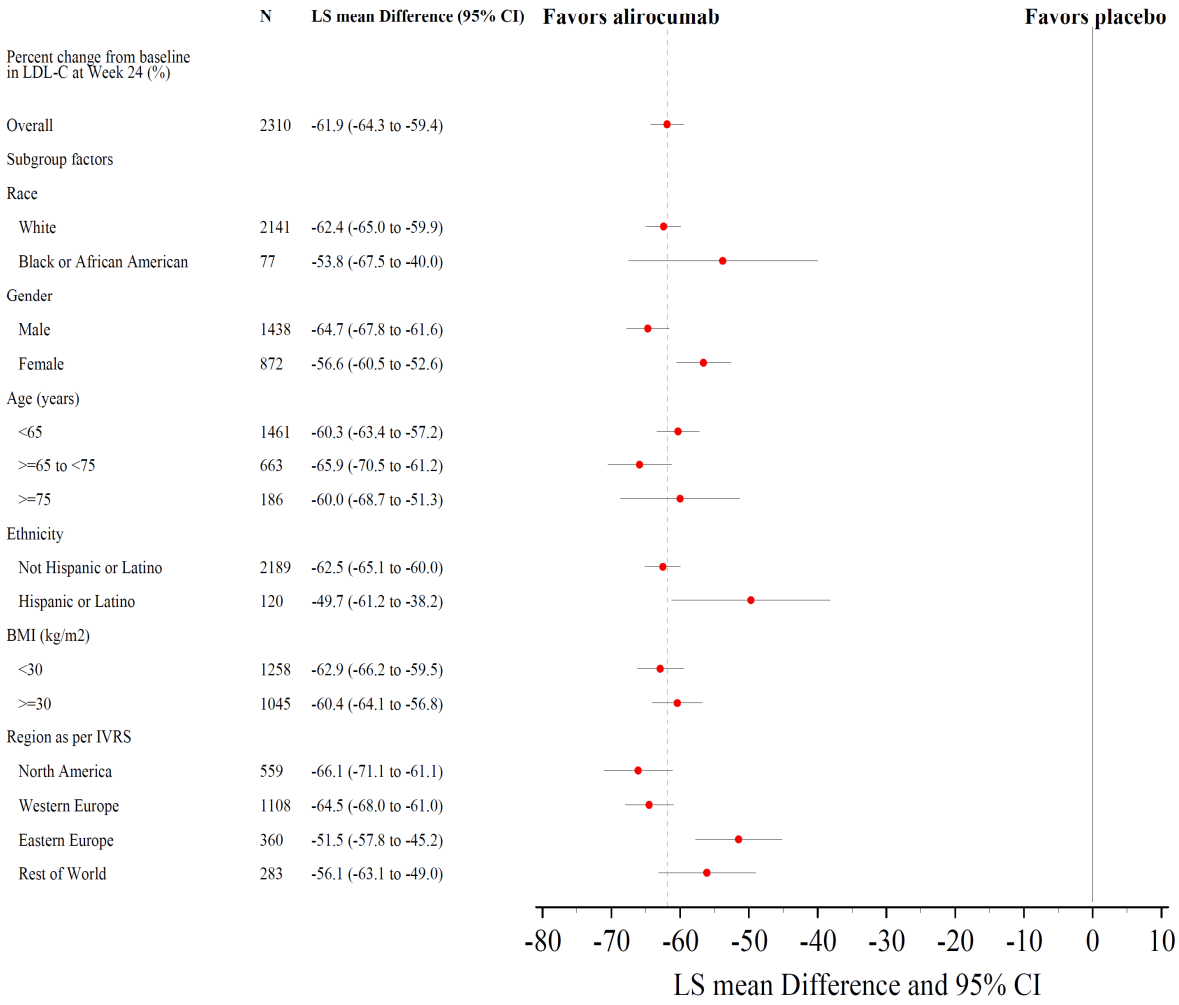
	Control	Alirocumab
Placebo-controlled		
FH I	0.6%	1.9%
FH II	1.2%	0.6%
HIGH FH	2.9%	4.2%
LONG TERM	1.3%	1.7%
COMBO I	1.9%	2.0%
Ezetimibe-controlled		
COMBO II	0.8%	0.4%
OPTIONS I	0	0
OPTIONS II	1.0%	0
ALTERNATIVE	4.1%	1.6%

Source: Request of 03-Mar-2015 Item #1 – Appendix, Tables 5.1 to 5.10

6.1.7 Subpopulations

In this review, the subgroups were primarily assessed in the LONG TERM trial because of its large size, with some explorations in the other phase 3 trials. The following figures present the primary analysis across subgroups defined by demographic or other baseline characteristics, including lipid values and background lipid therapies. In LONG TERM, interaction p-values < 0.1 were identified for sex, ethnicity, region, baseline PCSK9 level (total and free), CKD status, diabetes, baseline LDL-C, and baseline HDL-C. All were quantitative interactions.

Figure 11. Demographic Subgroup Analyses of the Primary Efficacy Endpoint, Trial LONG TERM



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction
Overall corresponds to primary analysis
N corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model
Interaction p-values: Race 0.2227, Sex 0.0014, Age 0.1313, Ethnicity 0.0324, BMI 0.3396, Region 0.0005
Source: CSR LTS11717, Figure 7

Race and ethnicity were explored further in the COMBO I trial, which was conducted solely in the United States, and might therefore be more relevant to the U.S. demographics.

Table 58. Percent Change from Baseline in LDL-C at Week 24 by Race, COMBO I

Subgroup factor Percent change from baseline in calculated LDL-C at week 24 (%)	Placebo (N=106)	Alirocumab 75 Q2W/Up150 Q2W (N=205)	Interaction p-value
Race			0.1859
White			
Number	88	167	
LS means (SE)	-2.7 (2.9)	-50.6 (2.1)	
LS mean difference (SE) vs placebo		-47.9 (3.6)	
95% CI		(-55.1 to -40.8)	
Black or African American			
Number	17	33	
LS means (SE)	-0.4 (6.9)	-36.3 (4.8)	
LS mean difference (SE) vs placebo		-35.9 (8.4)	
95% CI		(-52.4 to -19.4)	

Source: CSR EFC11568, Table 16.2.6.1.2.1

Although the percent change from baseline in LDL-C was similar in the Hispanic and non-Hispanic subgroups treated with alirocumab, the percent change from baseline was -22.5% in the placebo group in the Hispanic subpopulation, which impacted the treatment difference. This finding is based on a small number of patients, however, so the clinical significance is unclear.

Table 59. Percent Change from Baseline in LDL-C at Week 24 by Ethnicity, COMBO I

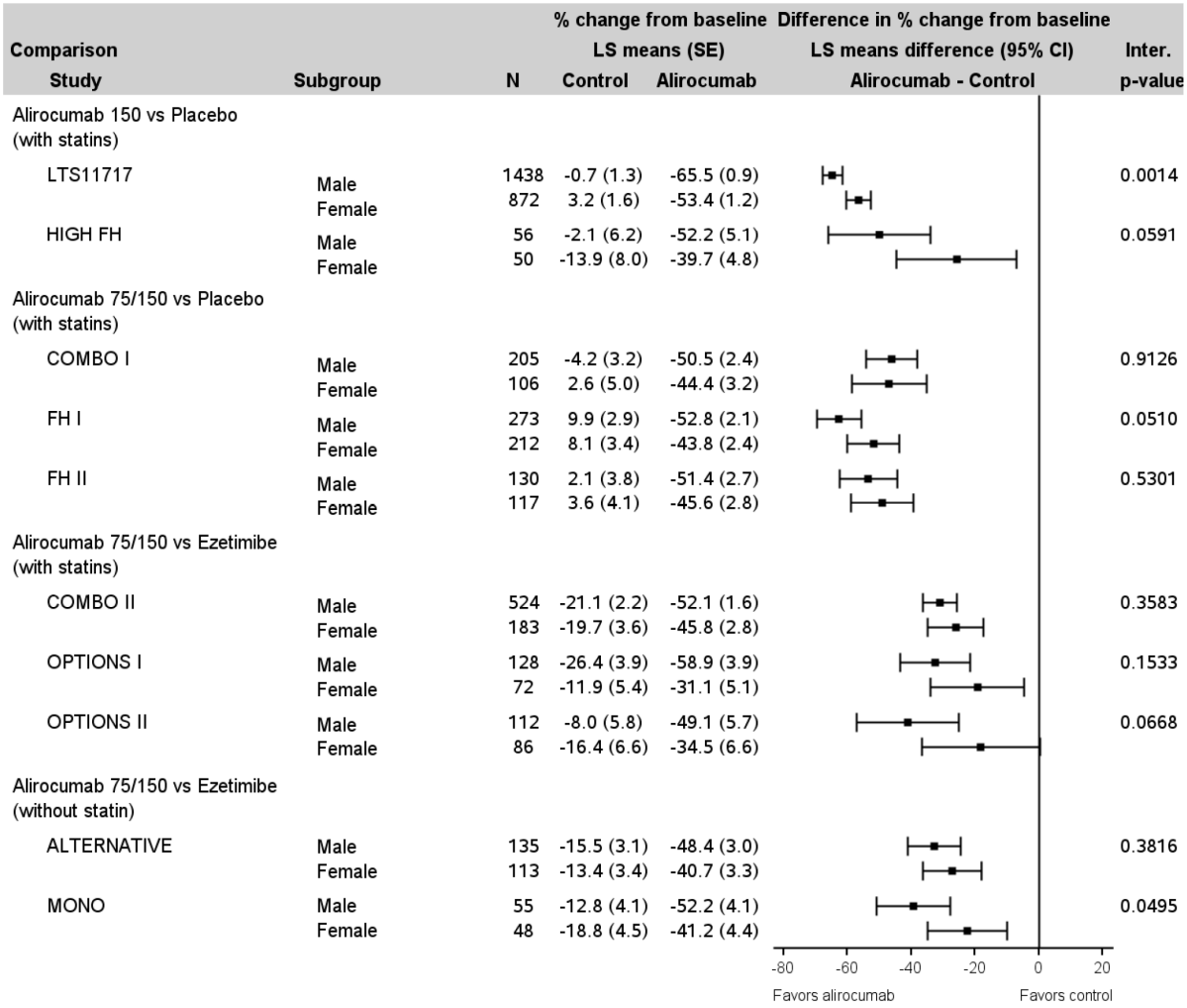
Subgroup factor Percent change from baseline in calculated LDL-C at week 24 (%)	Placebo (N=106)	Alirocumab 75 Q2W/Up150 Q2W (N=205)	Interaction p-value
95% CI		(-68.6 to -24.4)	
Ethnicity			0.0928
Not Hispanic or Latino			
Number	97	180	
LS means (SE)	-0.5 (2.8)	-47.8 (2.1)	
LS mean difference (SE) vs placebo		-47.4 (3.5)	
95% CI		(-54.2 to -40.5)	
Hispanic or Latino			
Number	9	25	
LS means (SE)	-22.5 (9.4)	-50.6 (5.7)	
LS mean difference (SE) vs placebo		-28.1 (10.9)	
95% CI		(-49.6 to -6.6)	

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.
Number corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model
The p-value is provided for descriptive purpose only

Source: CSR EFC11568, Table 16.2.6.1.2.1

The interaction for the sex subgroup in the LONG TERM trial was fairly consistently observed in the other phase 3 trials, with females demonstrating slightly less efficacy than males (Figure 12). There was no difference in alirocumab exposure by sex.

Figure 12. Primary Efficacy Endpoint by Sex Subgroup, Phase 3 Trials



Source: ISE, Figure 4.9.1.2

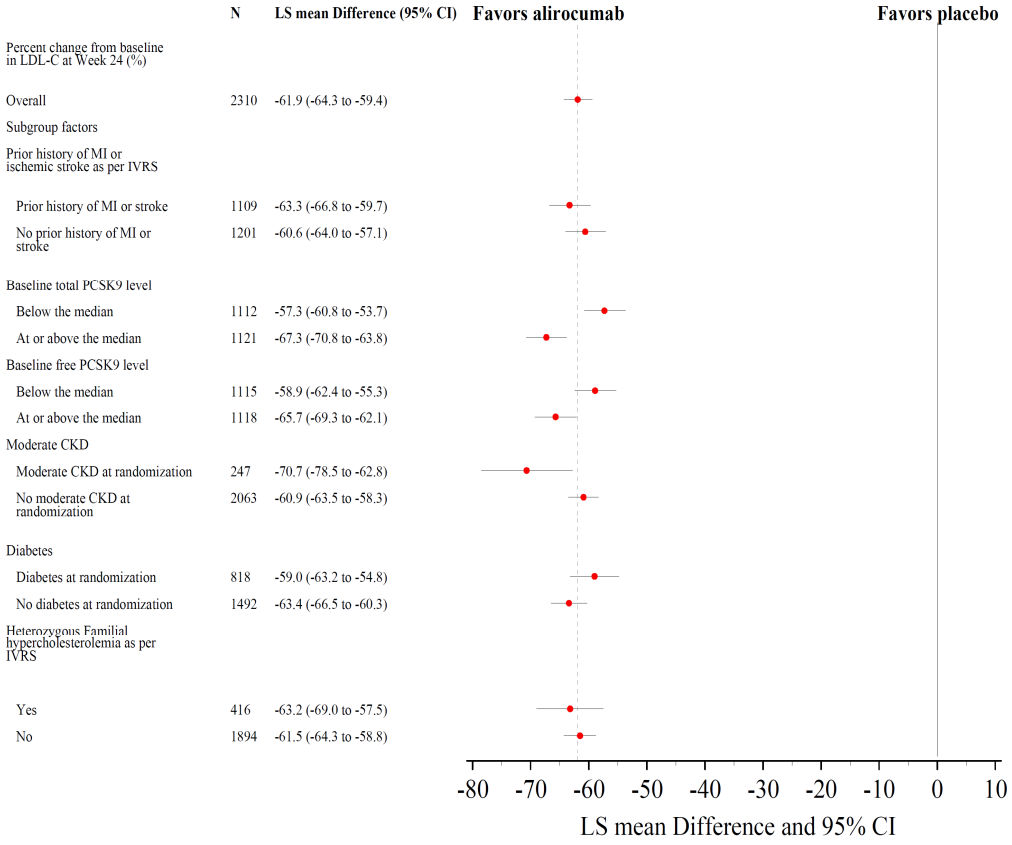
The reasons for this observed subgroup finding are unclear. As noted in Dr. McEvoy's review, baseline LDL-C concentrations were not found to be systematically different for males and females across trials. A recent publication reported that mean PCSK9 concentrations were actually higher in females than in males by 10% (which is supported three of the four phase 3 trials that measured total PCSK9 at baseline), and higher in postmenopausal than in premenopausal females by 22%.[47] Women included in the LONG TERM trial were predominantly post-menopausal. A subgroup analysis by menopausal status was explored in LONG TERM. Although a slightly lower reduction in LDL-C was seen in pre-menopausal women (-47.3%) as compared with post-menopausal women (-54.8%) in the alirocumab group, the treatment difference (from

47 Ghosh M, et al. Influence of physiological changes in endogenous estrogen on circulating PCSK9 and LDL cholesterol. J Lipid Res, 2015. 56: 463-9.

placebo) was similar in these two categories (LS mean difference for alirocumab versus placebo -58.6% (95% CI -69.0, -48.2) and -56.3% (95% CI -61.2, -51.3), respectively).

Other baseline characteristics subgroups were evaluated in LONG TERM. According to Figure 13, potential subgroups of interest include baseline total and free PCSK9 above and below the median, baseline diabetes status, and moderate chronic kidney disease (CKD) versus none to mild CKD (patients with calculated creatinine clearance < 30 mL/min were excluded from the trials).

Figure 13. Other Baseline Characteristics Subgroup Analyses, Primary Efficacy Endpoint, Trial LONG TERM



Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time
point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the
continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction
Overall corresponds to primary analysis
N corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model
Interaction p-values: MI or stroke history: 0.2835, baseline total PCSK9 <0.0001, baseline free PCSK9 0.0076, moderate CKD 0.0210, diabetes 0.0957, HeFH 0.6038
Source: CSR LTS11717, Figure 8

With respect to CKD, percent change from baseline in LDL-C was similar between the CKD subgroups in the alirocumab group (-62.0% and -60.9%, respectively); percent change from baseline in the placebo group was greater in the moderate CKD group as compared to the no to mild CKD group (+8.7% and 0%, respectively), which affected the apparent treatment difference. Interaction by CKD status was not consistent among the other phase 3 trials.

Similarly, percent change in LDL-C from baseline was similar across diabetes status in the alirocumab group (diabetes -60.0% and no diabetes -61.6%). In the other placebo-controlled trials (Figure 14), point estimates for percent LDL-C change in patients with diabetes are consistently slightly less than those without diabetes; however, the confidence intervals substantially overlap.

Figure 14. Percent Change from Baseline in LDL-C at Week 24 by Diabetes Status, Placebo-Controlled Phase 3 Trials

Comparison Study	Subgroup	N	% change from baseline LS means (SE) Control	Alirocumab	Difference in % change from baseline LS means difference (95% CI) Alirocumab - Control	Inter. p-value
Alirocumab 150 vs Placebo (with statins)						
LTS11717	Diabetes	818	-1.0 (1.8)	-60.0 (1.3)		0.0957
	No diabetes	1492	1.8 (1.3)	-61.6 (0.9)		
HIGH FH	Diabetes	15	-10.8 (12.4)	-35.0 (9.8)		0.3097
	No diabetes	91	-5.6 (5.4)	-47.3 (3.8)		
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	Diabetes	135	-2.6 (4.3)	-42.2 (2.8)		0.0841
	No diabetes	176	-2.0 (3.4)	-53.2 (2.6)		
FH I	Diabetes	56	0.2 (6.2)	-53.6 (5.1)		0.5508
	No diabetes	429	10.5 (2.4)	-48.3 (1.7)		
FH II	Diabetes	10	8.3 (12.5)	-39.2 (10.7)		0.8111
	No diabetes	237	2.5 (2.8)	-49.0 (2.0)		

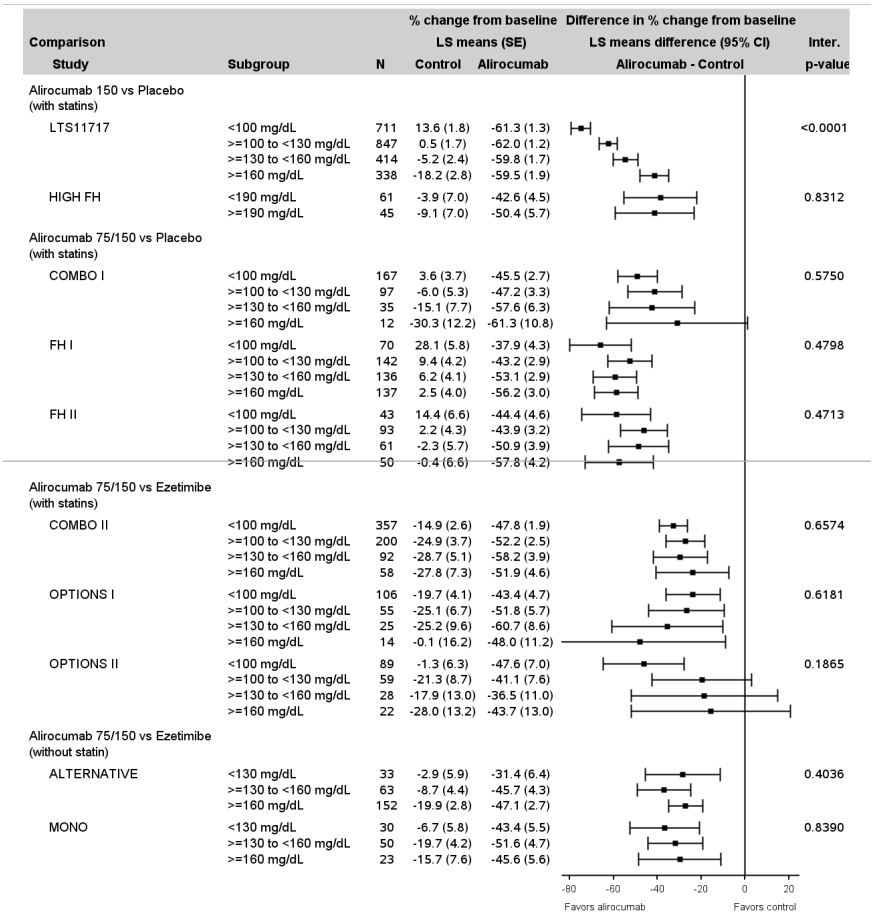
Source: ISE, Figure 4.9.1.10

Regarding baseline PCSK9 status, it is biologically plausible that a differential effect could be seen based on concentrations of the drug target. Nevertheless, robust LDL-C-lowering was seen in patients with relatively lower or higher PCSK9 concentrations (total and free).

Subgroup analyses were also conducted in LONG TERM by baseline lipid values (Figure 16). An apparent trend was observed in the baseline LDL-C subgroups, with the lowest baseline LDL-C associated with the greatest treatment effect. This subgroup finding in LONG TERM was not observed in the other phase 3 trials. Furthermore, the interaction appears entirely due to differences in the placebo group (with a mean increase observed in patients with the lowest LDL-C at baseline and vice versa),

possibly reflecting a regression to the mean phenomenon in the placebo group that might not be observed in the alirocumab group because maximal LDL-C lowering is achieved. Mean percent change from baseline in the alirocumab group ranged from 60 to 62% among the groups, whereas in the placebo group the range was -18 to +14%. (However, In the subgroup of patients in LONG TERM with baseline LDL-C ≥ 160 mg/dL *and* HeFH, mean percent change from baseline in LDL-C at week 24 was -51.8% in the alirocumab group – which mirrors more closely the LDL-C percent change in the alirocumab group from the HIGH FH trial – and -7.6% in the placebo group).

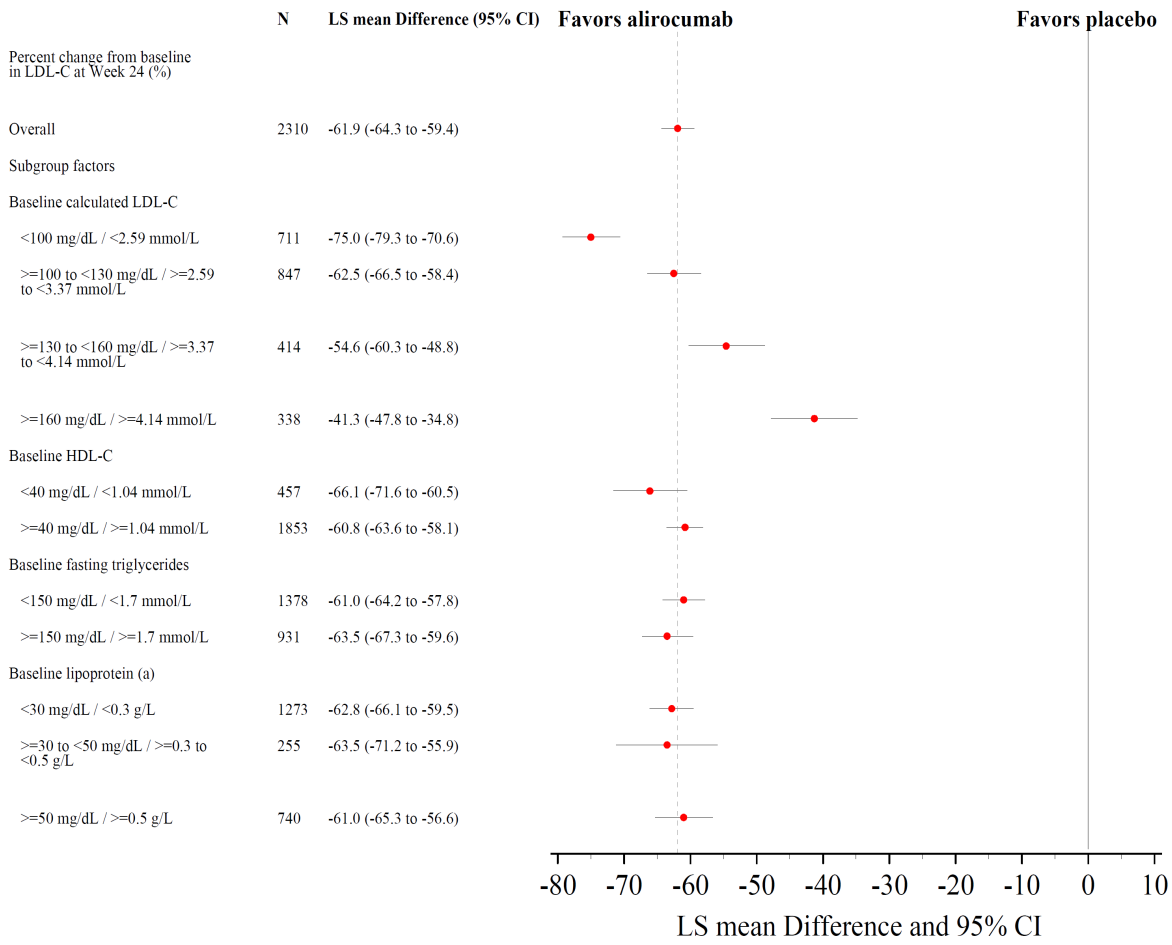
Figure 15. Percent Change from Baseline in LDL-C at Week 24 by Baseline LDL-C Subgroup, Phase 3 Trials



Source: ISE, Figure 4.9.1.15

No interaction was observed for baseline TG or Lp(a) subgroups in LONG TERM. An interaction p-value of 0.1 was observed for baseline HDL-C subgroups, but the quantitative difference between groups was small (see Figure 16, which also repeats the LDL-C subgroups from Figure 15).

Figure 16. Baseline Lipid Subgroup Analyses, Primary Efficacy Endpoint, Trial LONG TERM

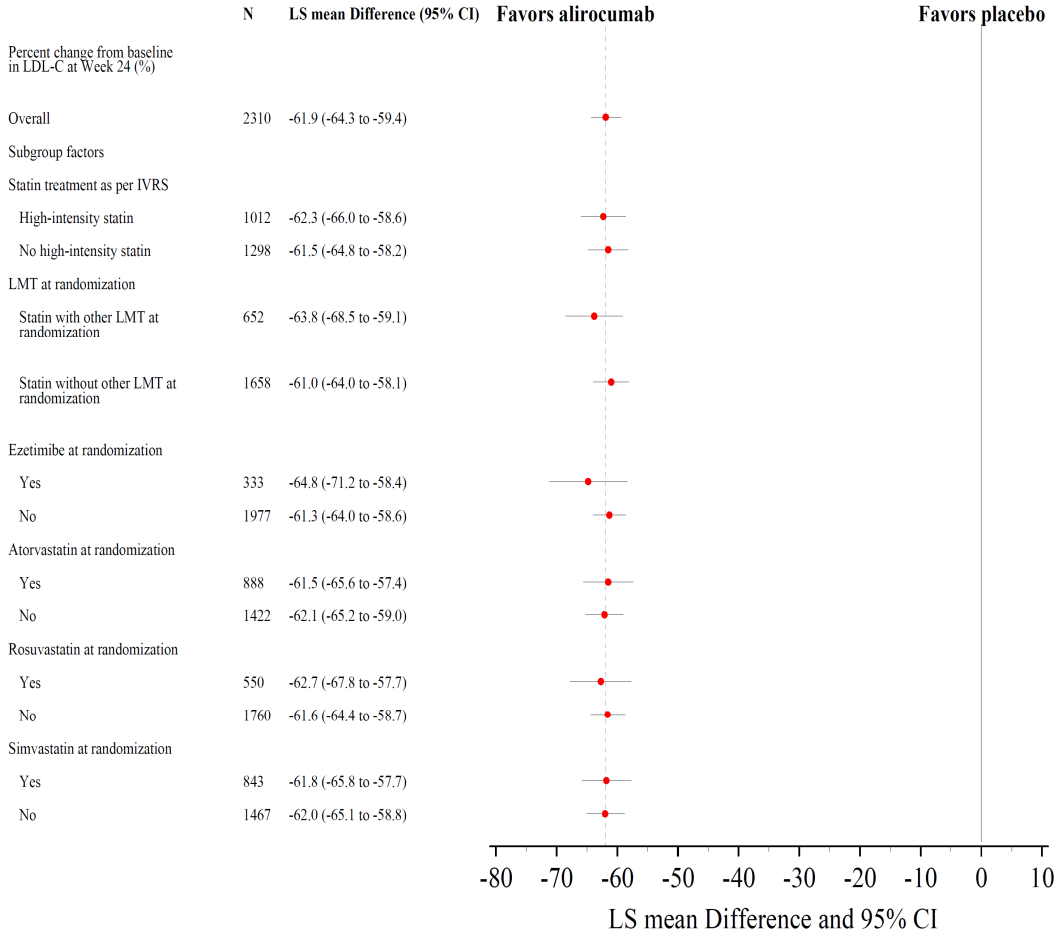


Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time
point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point for baseline LDL-C as subgroup factor.
For other subgroup factors, the model also includes the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction
Overall corresponds to primary analysis
N corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model
Interaction p-values: LDL-C in Figure 15, HDL-C 0.0989, TG 0.3431, Lp(a) 0.7622
Source: CSR LTS11717, Figure 9

One potentially important difference noted between the LONG TERM trial and other trials was that only 47% of patients were on high dose statin, as compared with 63 to 88% of patients enrolled in the other trials on maximally tolerated background statin

therapy (FH I, FH II, HIGH FH, COMBO I, and COMBO II, see Table 21). According to the subgroup analysis conducted, intensity of background statin did not appear to substantially impact the treatment effect in the LONG TERM trial (Figure 17).

Figure 17. Background LMT Subgroup Analyses, Primary Efficacy Endpoint, Trial LONG TERM

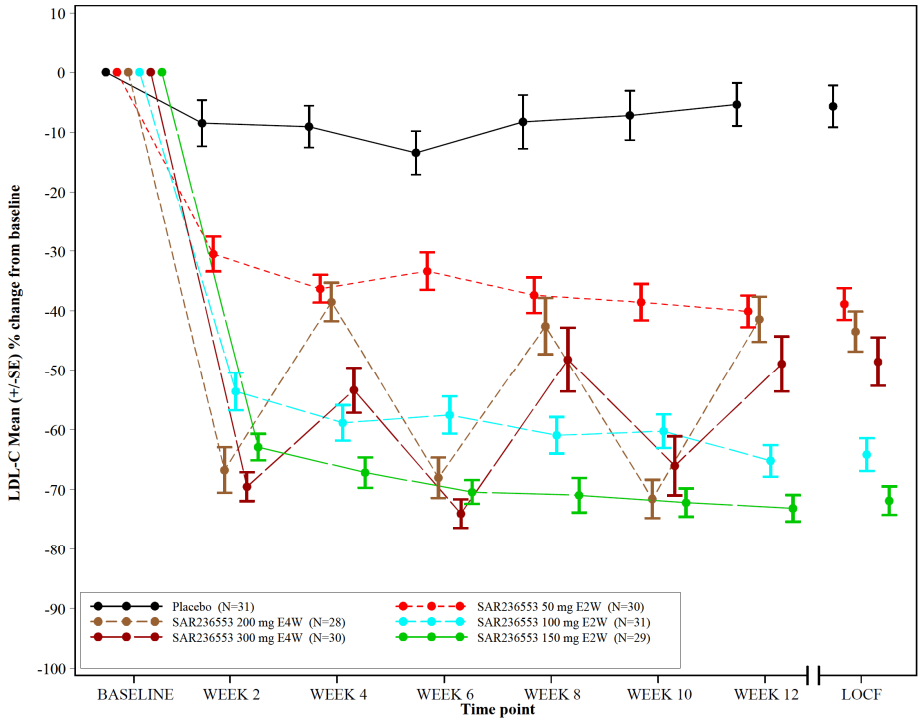


Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time
point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the
continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction
Overall corresponds to primary analysis
N corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model
Interaction p-values: Statin treatment 0.7543, LMT 0.3210, Ezetimibe 0.3273, Atorvastatin 0.8370, Rosuvastatin 0.6922, Simvastatin 0.9329
Source: CSR LTS11717, Figure 10

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

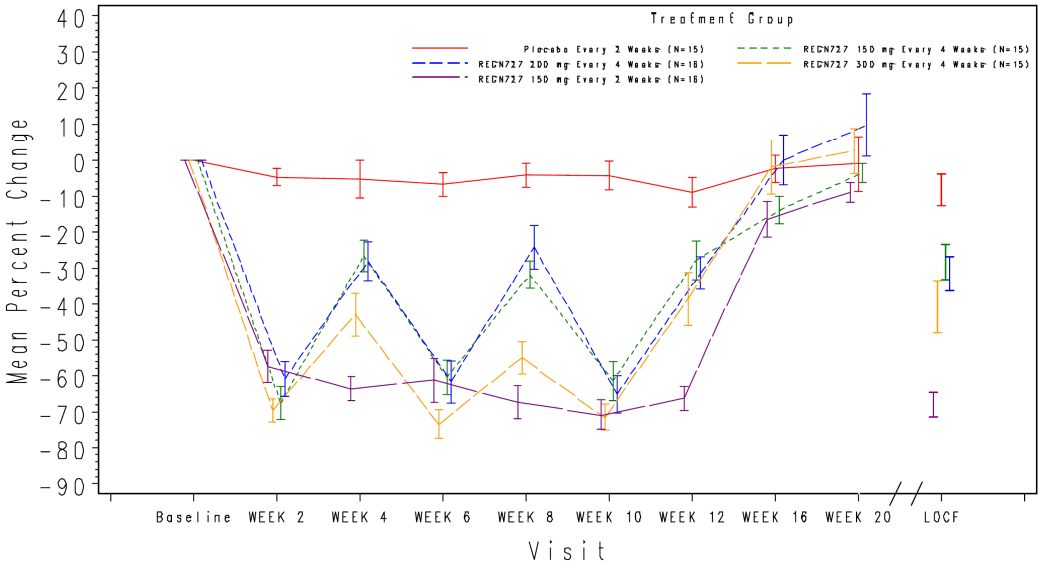
Phase 3 dosing regimens were selected after analyzing the results from the two dose-finding studies (DFI11565 and CL-1003) that evaluated 50, 100, 150 mg Q2W and 150, 200, 300 mg Q4W for 12 weeks in patients taking alirocumab concomitantly with a statin. See Figure 18 and Figure 19 for a graphical representation of LDL-C-lowering by dose over time. Of the Q2W dose regimens, the 150 mg Q2W regimen resulted in the greatest efficacy, ranging from -67.9% to -72.4%. Because the peak efficacy observed with 200 mg and 300 mg Q4W doses did not significantly exceed what was seen with 150 mg Q2W, and the effect was not fully maintained over the 4-week inter-dosing interval in the Q4W regimens, the 150 mg Q2W dose was considered the optimal dose to bring forward to phase 3.

Figure 18. LDL-C Mean Percent Change from Baseline, Phase 2 Trial DFI11565



Source: SCE, Figure 3

Figure 19. LDL-C Mean Percent Change from Baseline, Phase 2 Trial CL-1003



Source: SCE, Figure 4

There has been concern, however, regarding LDL-C going "too low" (see Dr. Roberts' review, section 7.3.5, for a discussion of low LDL-C and adverse events). Since the magnitude of effect observed with the 150 mg Q2W dose may not be needed to achieve individual target LDL-C in all patients, a lower dose that would provide an approximate 50% decrease in LDL-C from baseline was considered desirable. (Treatment guidelines have identified 50% as a target reduction in LDL-C in those high risk patients that cannot achieve absolute LDL-C targets.[7]) Because the lower doses – 50 and 100 mg Q2W – assessed in the phase 2 studies did not provide either the desired magnitude of LDL-C-lowering, or were not substantially different from the 150 mg dose, respectively, dose-response modeling was used to estimate the dose that would provide a 50% decrease in LDL-C; i.e., 75 mg Q2W.

The 75 mg and 150 mg Q2W doses were evaluated in the phase 3 trials. The use of an up-titration scheme was implemented in eight trials (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO). The dose of 75 mg Q2W was selected to initiate therapy, with up-titration to 150 mg Q2W after 12 weeks of treatment in patients not achieving their individual LDL-C target, based on a week 8 LDL-C value.[48]

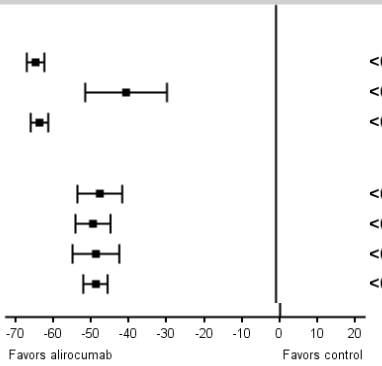
48 As a result of differences in the week 8 and week 12 values, it was noted that there were patients who were up-titrated at week 12 who did not need to be, and conversely, some patients who were not up-titrated at week 12 who should have been. For example, in COMBO I, 10/30 patients treated with alirocumab who were up-titrated in fact met their target LDL-C at week 12, and 19/152 patients who were not up-titrated because presumably they had reached their LDL-C target at week 8, were subsequently above their LDL-C target at week 12.

Because no trial randomized patients to 75 mg and 150 mg Q2W in parallel arms, a dose-response cannot be formally evaluated but rather only estimated from cross-study comparisons and post-hoc assessments of non-randomized groups.

The placebo-controlled week 12 analyses allow for an approximate – cross-study – comparison of the 150 mg doses (LONG TERM and HIGH FH) and the 75 mg doses (FH I, FH II, and COMBO I). (The 150 mg Q2W HIGH FH trial is a notable outlier. See section 6.1.4 for a discussion of this trial's primary efficacy results.)

Figure 20. Percent Change in LDL-C from Baseline at Week 12, Phase 3 Placebo-Controlled Trials

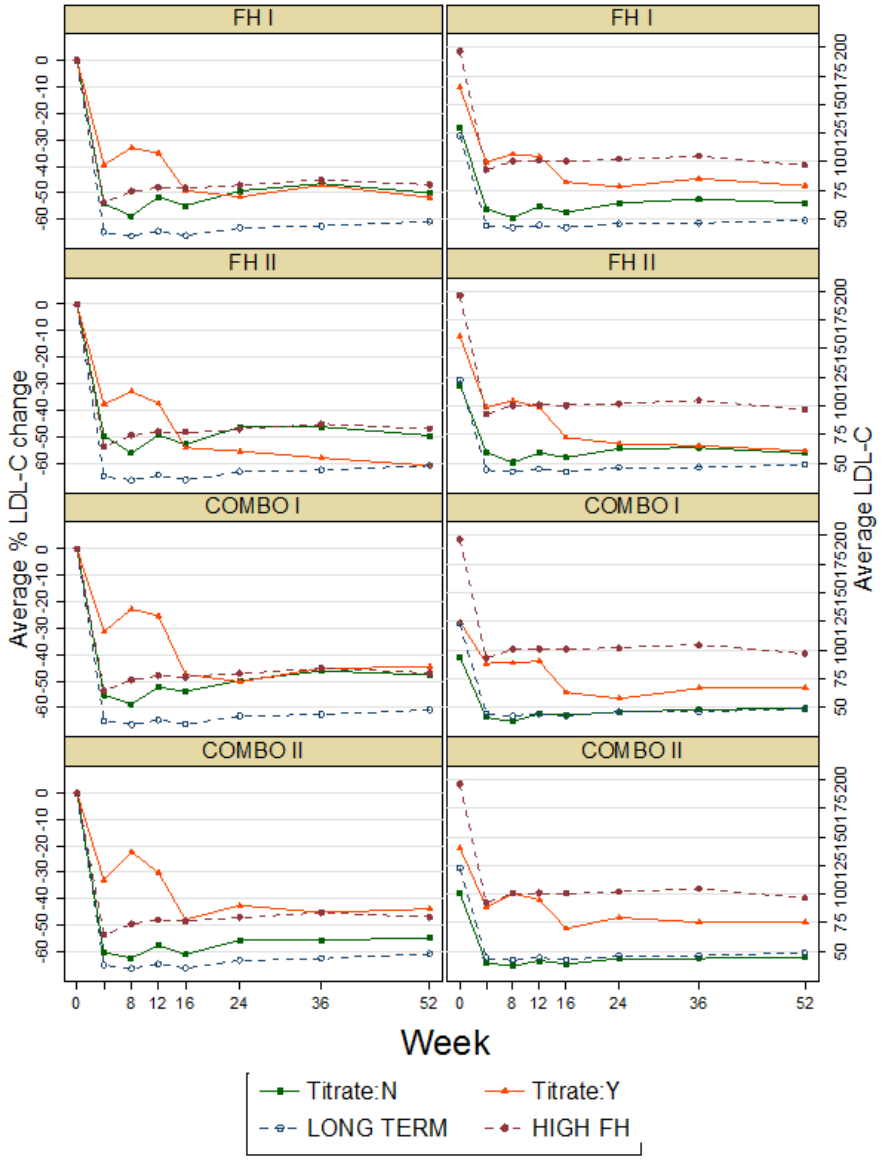
Comparison Study	% change from baseline LS means (SE) Control	Alirocumab	Difference in % change from baseline LS mean difference (95% CI) Alirocumab - Control	P-value	Number of patients Control	Alirocumab
Alirocumab 150 vs Placebo (with statins)						
LTS11717	1.5 (1.0)	-63.3 (0.7)		<0.0001	780	1530
HIGH FH	-6.6 (4.6)	-46.9 (3.2)		<0.0001	35	71
Pool	1.1 (1.0)	-62.6 (0.7)		<0.0001	815	1601
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	1.1 (2.5)	-46.3 (1.8)		<0.0001	106	205
FH I	5.7 (2.0)	-43.5 (1.4)		<0.0001	163	322
FH II	4.6 (2.6)	-43.8 (1.8)		<0.0001	81	166
Pool	4.1 (1.3)	-44.5 (1.0)		<0.0001	350	693



Note: LTS11717 = LONG TERM
Source: SCE, Figure 20

The figure below, by FDA statistician Dr. McEvoy, presents the LDL-C lowering over time in patients with and without up-titration in selected trials. The LDL-C lowering in the 150 mg dose-only trials, LONG TERM and HIGH FH, is presented for comparison.

Figure 21. Change in LDL-C Over Time by Titration Status, Placebo-Controlled Trials that Utilized the Titration Regimen (Percent Change, Left Panels; Absolute Change, Right Panels)



Source: B. McEvoy, FDA OBII

In patients who required up-titration, mean absolute and percent change in LDL-C did appear to decrease (improve) after up-titration (week 16 and thereafter). Furthermore, these figures suggest that the trajectory of LDL-C lowering in patients who required dose titration was "different" than in those who did not. Furthermore, patients who required up-titration were more likely to be female and have a higher LDL-C at baseline.

See Table 60, which outlines some demographic differences between those who did and did not up-titrate in the FH I and COMBO I trials (chosen as representative HeFH and high CV risk placebo-controlled trials, respectively, that utilized an up-titration scheme).

Table 60. Demographic and Baseline Characteristics in Alirocumab-Treated Patients With and Without Up-Titration, Trials FH I and COMBO I

	FH I		COMBO I	
	Not up-titrated N=176	**Up-titrated N=135**	**Not up-titrated N=159**	**Up-titrated N=32**
Age, yrs				
Mean (SD)	53.9 (12.5)	50.0 (12.9)	63.3 (9.1)	61.6 (10.6)
Sex, n (%)				
F	69 (39.2%)	68 (50.4%)	51 (32.1%)	18 (56.3%)
M	107 (60.8%)	67 (49.6%)	108 (67.9%)	14 (43.8%)
Race, n (%)				
White	165 (93.8%)	123 (91.1%)	135 (84.9%)	24 (75.0%)
Black	1 (0.6%)	1 (0.7%)	21 (13.2%)	8 (25.0%)
Other	10 (5.7%)	11 (8.1%)	3 (1.9%)	0
Ethnicity, n (%)				
Hispanic	10 (5.7%)	3 (2.2%)	21 (13.2%)	3 (9.4%)
Not Hispanic	163 (92.6%)	130 (96.3%)	138 (86.8%)	29 (90.6%)
Weight, kg				
Mean (SD)	80.7 (14.6)	87.8 (17.2)	93.9 (20.7)	94.1 (20.2)
BMI, kg/m^2				
Mean (SD)	28.0 (4.0)	30.4 (4.9)	32.4 (6.3)	33.3 (6.5)
Baseline LDL-C, mg/dL				
Mean (SD)	130.1 (42.5)	164.9 (55.1)	93.9 (23.2)	124.6 (39.8)

Source: CSR EFC12492, Tables 16.2.4.4.1 and 16.2.4.4.3; CSR EFC11568, Tables 16.2.4.4.1 and 16.2.4.4.3

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Trials with durations of at least 52 weeks were the FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM trials (for ongoing trials, all data cut-off dates included the last patient's week 52 visit). Results at weeks 12, 24, and 52 are shown below for these trials and demonstrate a persistence of response up to week 52.

Figure 22. Percent Change in LDL-C at Weeks 12, 24, and 52, Trial FH I

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 75 Q2W/Up150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	5.7 (2.0)	-43.5 (1.4)		<0.0001* K
		Week 24	9.1 (2.2)	-48.8 (1.6)		<0.0001* P
		Week 52	9.0 (2.6)	-47.1 (1.9)		<0.0001* K

Source: SCE, Figure 7

Figure 23. Percent Change in LDL-C at Weeks 12, 24, and 52, Trial FH II

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 75 Q2W/Up150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	4.6 (2.6)	-43.8 (1.8)		<0.0001* K
		Week 24	2.8 (2.8)	-48.7 (1.9)		<0.0001* P
		Week 52	8.4 (3.3)	-50.3 (2.3)		<0.0001* K

Source: SCE, Figure 8

Figure 24. Percent Change in LDL-C at Weeks 12, 24, and 52, Trial HIGH FH

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	-6.6 (4.6)	-46.9 (3.2)		<0.0001* K
		Week 24	-6.6 (4.9)	-45.7 (3.5)		<0.0001* P
		Week 52	-3.0 (5.9)	-42.1 (4.2)		<0.0001* K

Source: SCE, Figure 9

Figure 25. Percent Change in LDL-C at Weeks 12, 24, and 52, Trial COMBO I

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 75 Q2W/Up150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	1.1 (2.5)	-46.3 (1.8)		<0.0001* K
		Week 24	-2.3 (2.7)	-48.2 (1.9)		<0.0001* P
		Week 52	0.5 (3.6)	-42.5 (2.5)		<0.0001* K

Source: SCE, Figure 10

Figure 26. Percent Change in LDL-C at Weeks 12, 24, and 52, Trial COMBO II

Endpoint	Analysis	Time	% change from baseline LS means (SE) Ezetimibe	Alirocumab 75 Q2W/Up150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	-21.8 (1.8)	-51.2 (1.3)		<0.0001* K
		Week 24	-20.7 (1.9)	-50.6 (1.4)		<0.0001* P
		Week 52	-18.3 (2.1)	-49.5 (1.5)		<0.0001* K

Source: SCE, Figure 12

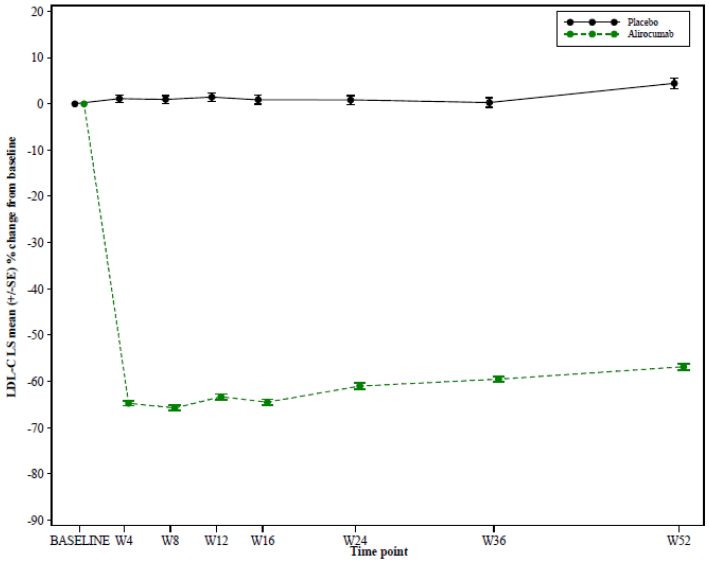
Figure 27. Percent Change in LDL-C at Weeks 12, 24, and 52, Trial LONG TERM

Endpoint	Analysis	Time	% change from baseline LS means (SE) Placebo	Alirocumab 150 Q2W	LS means difference (95% CI)	P-value
Calculated LDL-C	ITT	Week 12	1.5 (1.0)	-63.3 (0.7)		<0.0001* K
		Week 24	0.8 (1.0)	-61.0 (0.7)		<0.0001* P
		Week 52	4.4 (1.2)	-56.8 (0.8)		<0.0001

Source: SCE, Figure 11

The following figure also presents the mean percent change in LDL-C over time up to week 52 using the ITT analysis in LONG TERM. This figure demonstrates that LDL-C lowering was consistently observed, from week 4 onward.

Figure 28. LDL-C Mean Percent Change from Baseline over Time, Trial LONG TERM



Source: CSR LTS11717, Figure 2

6.1.10 Additional Efficacy Issues/Analyses

Immunogenicity

See section 7.3.4 for a discussion of the safety issues associated with immunogenicity.

In phase 3 trials, a treatment-emergent positive anti-drug antibody (ADA) response was defined as either no ADA-positive response at baseline but with any positive response in the post-baseline period (up to follow-up visit), or a positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (up to follow-up visit).

For treatment-emergent positive ADA, the duration of the ADA response was classified as: 1) persistent when an ADA positive response was detected in at least two consecutive post-baseline samples separated by at least a 12-week period, 2) indeterminate when ADA was present only at the last sampling time point, and 3) transient for a response that is considered neither persistent nor indeterminate.

In phase 3, pre-existing reactivity was observed in 1.1% of patients from the control group and 1.4% of patients from the alirocumab group. Treatment-emergent positive ADA responses were observed in 4.8% of patients in the alirocumab group and in 0.6% of patients in the control group. Most (63%) of these treatment-emergent ADA responses in the alirocumab group were classified as transient responses. The median time to the onset of treatment-emergent ADA response was 12 weeks (i.e., at the first post-baseline ADA assessment in most studies) in the alirocumab group.

Table 61. Summary of ADA, Phase 3 Trials

Anti-alirocumab antibody (ADA) n (%)	Control (N=1708)	Alirocumab (N=3033)
Pre-existing ADA[a] [n/N1 (%)]	18/1708 (1.1%)	41/3033 (1.4%)
Treatment-emergent ADA positive response[b] [n/N1 (%)]	10/1708 (0.6%)	147/3033 (4.8%)
Persistent [c] [n/N2 (%)]	2/10 (20.0%)	39/147 (26.5%)
Transient [d] [n/N2 (%)]	2/10 (20.0%)	93/147 (63.3%)
Indeterminate [e] [n/N2 (%)]	6/10 (60.0%)	15/147 (10.2%)
Time to onset of treatment-emergent ADA response (week)		
Number	10	147
Mean (SD)	43.74 (23.74)	13.00 (10.99)
Median	52.14	12.14
Q1 : Q3	24.14 : 64.29	4.29 : 12.43

Anti-alirocumab antibody (ADA) n (%)	Control (N=1708)	Alirocumab (N=3033)
Min : Max	11.3 : 78.1	1.6 : 63.7

Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)

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

Note: The denominator N1 (respectively N2) within a treatment group is the number of patients who had ADA assessed (respectively positive ADA status)

a patients with positive ADA response at baseline with less than 4-fold increase in titer in the post-baseline period

b patients with no positive ADA response at baseline but with any positive response in the post-baseline period OR with a positive ADA response at baseline and at least 4-fold increase in titer in the post-baseline period

c at least 2 consecutive post-baseline samples with positive ADA separated by at least a 12-week period

d any treatment-emergent positive ADA response neither considered persistent nor indeterminate; [e] ADA positive response present only at the last sampling time point

Source: Summary of Clinical Pharmacology, Table 13

Of the 147 alirocumab-treated patients with treatment-emergent ADA, 36 (24.5%) developed neutralizing antibodies. None of the placebo-treated patients developed neutralizing antibodies. In addition, 21 (14.3%) of the 147 alirocumab-treated patients who developed ADA had titers of 240 or greater.

Because statins and ezetimibe are considered immunomodulatory,[19] the sponsor also conducted analyses of ADA responses by background statin and ezetimibe therapy. FDA requested that data be limited to the first 6 months, as the trials without background statin therapy (ALTERNATIVE and MONO) were only 6 months in duration. Of note, the majority of alirocumab-treated patients who developed ADA presented in the first 6 months of the trial (137/147, 93%).

Table 62. Treatment-Emergent ADA During the First Six Months, Phase 3 Trials

	Control		Alirocumab	
	n/N (%)	95% mid-p CI	n/N (%)	95% mid-p CI
Treatment-emergent ADA positive response during the first 6 months[a]				
Patients not receiving statins or ezetimibe[1]				
ALTERNATIVE	0/118	(0.0% to 2.5%)	4/121(3.3%)	(1.1% to 7.8%)
MONO	0/49	(0.0% to 5.9%)	4/51(7.8%)	(2.5% to 17.8%)
Pool	0/167	(0.0% to 1.8%)	8/172(4.7%)	(2.2% to 8.6%)
Patients on statin and ezetimibe as background therapy[2]				
FH I	0/92	(0.0% to 3.2%)	9/170(5.3%)	(2.6% to 9.5%)
FH II	1/51(2.0%)	(0.1% to 9.3%)	8/111(7.2%)	(3.4% to 13.2%)
HIGH FH	0/12	(0.0% to 22.1%)	0/14	(0.0% to 19.3%)
COMBO I	0/9	(0.0% to 28.3%)	0/14	(0.0% to 19.3%)
LONG TERM	1/116(0.9%)	(0.0% to 4.2%)	12/210(5.7%)	(3.1% to 9.5%)
Pool	2/280(0.7%)	(0.1% to 2.3%)	29/519(5.6%)	(3.8% to 7.8%)

	Control		Alirocumab	
	n/N (%)	95% mid-p CI	n/N (%)	95% mid-p CI
Patients on statin background therapy but NOT receiving ezetimibe as background therapy[2]				
FH I	0/65	(0.0% to 4.5%)	7/137(5.1%)	(2.3% to 9.8%)
FH II	0/26	(0.0% to 10.9%)	5/52(9.6%)	(3.6% to 20.0%)
HIGH FH	0/23	(0.0% to 12.2%)	0/52	(0.0% to 5.6%)
COMBO I	0/90	(0.0% to 3.3%)	13/183(7.1%)	(4.0% to 11.6%)
COMBO II	1/231(0.4%)	(0.0% to 2.1%)	19/454(4.2%)	(2.6% to 6.3%)
LONG TERM	0/638	(0.0% to 0.5%)	51/1273(4.0%)	(3.0% to 5.2%)
OPTIONS I	0/93	(0.0% to 3.2%)	4/99(4.0%)	(1.3% to 9.5%)
OPTIONS II	0/95	(0.0% to 3.1%)	1/92(1.1%)	(0.1% to 5.2%)
Pool	1/1261(0.1%)	(0.0% to 0.4%)	100/2342(4.3%)	(3.5% to 5.1%)

[a]: patients with no positive ADA response at baseline but with any positive response during the first 6 months (up to Day 183) OR with a positive ADA response at baseline and at least 4-fold increase in titer during the first 6 months (up to Day 183).
[1] Pool of MONO and ALTERNATIVE studies
[2] Pool of LONG TERM, FH I, FH II, HIGH FH, COMBO I, COMBO II, OPTIONS I and OPTIONS II studies
Note: The denominator N within a treatment group is the number of patients who had ADA assessed
Source: Information on Clinical Topics Requested on 05 April 2015, Table 1

Reviewer comment: In the efficacy reviewer's opinion, background lipid-modifying therapy does not appear to influence the development of treatment-

emergent ADA, at least according to this analysis (which is limited because it relies on a cross-study comparison).

LONG TERM was selected to conduct an exploratory efficacy analysis (i.e., LDL-C-lowering) in patients with and without ADA:

- Out of 1530 patients randomized to alirocumab in the ITT population, 1483 had an ADA assessment. Therefore, a limitation to this analysis is that the sample is incomplete.

- A total of 71 patients developed a treatment-emergent positive ADA response, 5 in the placebo group (0.7%) and 66 in the alirocumab group (4.5%), which is similar to the incidence of ADA in the phase 3 program overall.

- As seen in the table below, the mean LDL-C reduction appears somewhat lower in patients with treatment-emergent ADA (-53.1%) compared to patients without an ADA response (-63.5%). However, out of the 6 patients with titers 240 or greater and 16 patients with neutralizing antibodies, the mean percent LDL-C lowering was -59.7% and -55.4%, respectively, making conclusions challenging (one might expect that neutralizing antibodies (NAbs) and / or higher titer Abs would be associated with greater loss of efficacy than ADA overall).

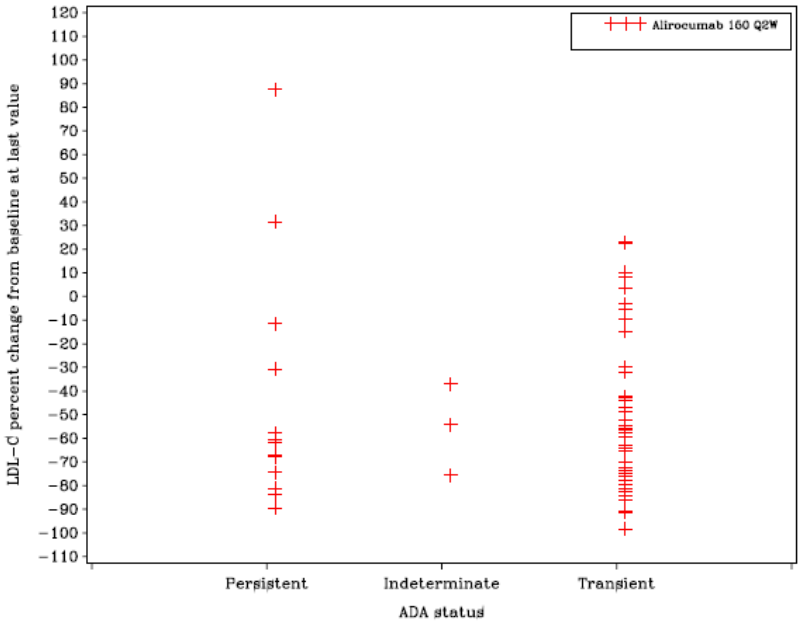
Table 63. Percent Change from Baseline in LDL-C at Week 24 by Development of Anti-Drug Antibodies in the Alirocumab Group, Trial LONG TERM

	Treatment-emergent ADA (N=1483)	
	Yes (N=66)	No (N=1417)
Percent change from baseline to Week 24 in calculated LDL-C		
Number	65	1407
Mean (SD)	-53.1 (30.3)	-63.5 (24.1)
Median	-61.9	-69.0
Q1 : Q3	-74.7 : -41.3	-79.4 : -54.1
Min : Max	-98 : 40	-100 : 102

Analysis based on calculated LDL-C values during the on-treatment period. Missing data at Week 24 imputed using last value on treatment (LOCF).
Source: Response to Agency Request #1, dated 3 Mar 2015, Table 2

- Among the patients in the alirocumab group in LONG TERM with a treatment-emergent positive ADA response, 15 patients had a response classified as persistent, 48 patients had a transient response, and 3 patients had an indeterminate response. The percent change in LDL-C from baseline at last value by ADA status in these patients is summarized in the following figure:

Figure 29. Percent Change in LDL-C among Patients with Positive ADA by ADA Status, Trial LONG TERM



Source: CSR LTS11717, Figure 16.2.5.5.2.4

In a review of patient-level data, many of the cases of ADA were transient and had no obvious effect on LDL-C. Other cases were uninterpretable, since NAbs were identified at dosing termination. However, as described in Appendix 9.1, there were nine cases of NAbs identified in the phase 3 program that appeared to be associated with loss of efficacy, including one patient who developed LDL-C concentrations above baseline in association with NAbs (Figure 49). In addition, there were two cases of NAbs potentially associated with enhanced efficacy.

Reviewer comment: There is not enough information at this time to fully characterize the effect of ADA on efficacy; however, in the efficacy reviewer's opinion, there is some evidence for a loss of effect (more so than evidence of enhancement) associated with NAbs. The association between ADA and loss of efficacy will be evaluated in a PMC study (see section 1.4).

Impact of Background Statin

Drug-drug interactions are discussed in other areas of this review; however, specific issues related to background statins on alirocumab efficacy are addressed here.

Because alirocumab is partially eliminated through target-mediated clearance, statins or other LMTs that impact the concentration of PCSK9 are expected to affect alirocumab PK and PD. Indeed, a population PK analysis demonstrates that statins increase

alirocumab clearance by 52%, which is reflected in the 28 to 29% decrease in alirocumab steady state exposure (AUC_{0-336}) at 75 mg and 150 mg Q2W administration.

Table 64. Alirocumab PK by Lipid-Modifying Therapy, Population PK

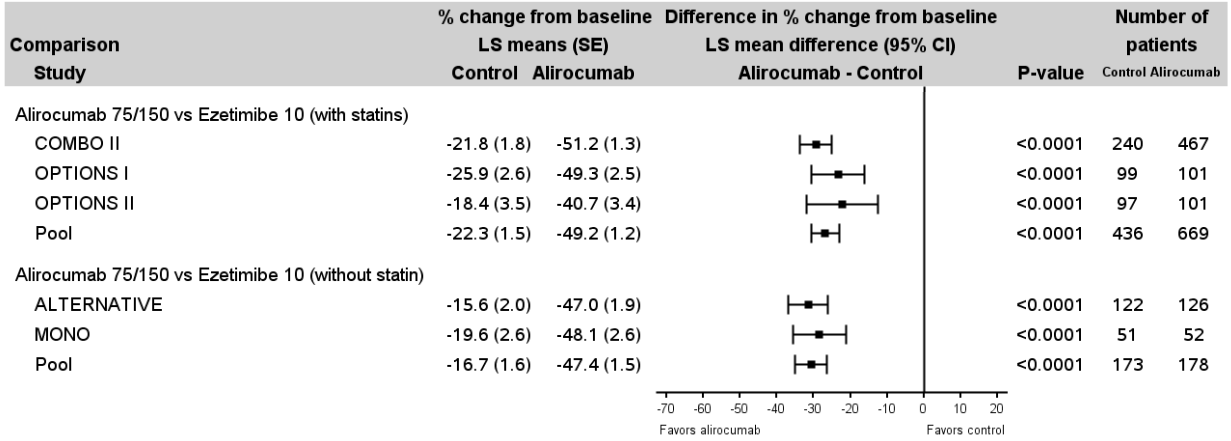
Covariate		75 mg Q2W			150 mg Q2W		
		n	C_{max} (mg/L)	AUC_{0-336} (mg.h/L)	n	C_{max} (mg/L)	AUC_{0-336} (mg.h/L)
Lipid modifying therapy	No statin	40	10.8 (41.0) [9.65]	3080 (47.2) [2750]	15	25.5 (47.8) [21.9]	7660 (51.7) [6330]
	Statin	514	7.93 (35.6) [7.63]	2150 (42.2) [1990]	1625	18.0 (46.5) [16.6]	5050 (53.2) [4520]
	No ezetimibe	441	8.01 (38.8) [7.53]	2180 (45.8) [1980]	1374	18.2 (47.7) [16.7]	5130 (54.4) [4550]
	Ezetimibe	113	8.64 (32.5) [8.26]	2350 (39.4) [2180]	266	17.3 (40.4) [16.4]	4790 (46.8) [4390]

Descriptive statistics are Mean (CV%) [Median]

Source: Summary of Clinical Pharmacology, Table 11

Despite the differential effect on PK, subgroup analyses demonstrated that LDL-C efficacy was not affected by intensity of background statin therapy (see Figure 17 in section 6.1.7). Furthermore, a cross-study comparison of ezetimibe-controlled trials, which included patients on (COMBO II, OPTIONS, I, and OPTIONS II) and not on (ALTERNATIVE, MONO) background statin suggests that there is not differential efficacy by background statin. The ezetimibe-controlled phase 3 trials were explored at week 12 to eliminate the impact of dose-titration (i.e., 75 mg Q2W dose only). Percent change from baseline was similar in the pool of the statin trials (-49.2%) and non-statin trials (-47.4%), see Figure 30.

Figure 30. Percent Change from Baseline in LDL-C at Week 12, Ezetimibe-Controlled Trials



Source: SCE, Figure 20

Nevertheless, the sponsor suggests that there could be a differential effect of alirocumab dose on LDL-C efficacy depending on use of concomitant statin. For example, Table 65 describes the effect on up-titration in alirocumab-treated patients in the 'background statin' pool (i.e., trials FH I, FH II, COMBO I, COMBO II, OPTIONS I, and OPTIONS II) and the 'without background statin' pool (i.e., trials ALTERNATIVE and MONO).

Table 65. Percent Change in LDL-C, Up-Titrated Alirocumab-Treated Patients, Trials with and without Background Statin

	Background Statin Pool N=1291	**Without Statin Pool N=155**
N (%) with up-titration	340 (26%)	68 (44%)
N[a,b]	305	55
% change from baseline to wk 12, mean (SD)	-33.3 (26.2)	-50.3 (13.1)
% change from baseline to wk 24, mean (SD)	-47.5 (34.7)	-53.5 (14.4)
Additional % change from wk 12 to wk 24, mean (SD)	-14.2 (30.5)	-3.1 (12.3)
At least 10% additional reduction from wk 12 to wk 24, %	58%	26%
a: up-titrated patients according to IVRS Week 12 transaction with at least one injection of alirocumab 150 mg afterwards. Denominator corresponding to patients with at least one injection post W12 IVRS transaction. b: Percent change from baseline to Week 12 and Week 24 is presented in patients with calculated LDL-C available both at Week 12 and Week 24 Additional percent change from Week 12 to Week 24 is calculated for each patient as (percent change from baseline to Week 24) - (Percent change from baseline to Week 12)		

Source: ISE, Table 4.10.2.1 and Table 4.10.2.2

Reviewer comments: The modest mean increase in efficacy when doubling the dose (-3.1% in patients not on background statins) could suggest that for most of the patients not receiving statins as background therapy, the near-maximal PCSK9-inhibiting effect is already reached with the dose of 75 mg Q2W (approximately 50% from baseline). In order to answer the question whether statins affect the dose response of alirocumab, patients would need to be randomized to background statin / no statin as well as randomized to various doses of alirocumab. Because this was not done, a formal assessment of the impact of statin on alirocumab cannot be conducted.

In summary, based on the information provided (albeit limited due to post-hoc and cross-study comparisons), the efficacy of alirocumab does not appear to be substantially affected by background statin. The development program overall supports alirocumab being administered as add-on to standard-of-care. In the efficacy reviewer's opinion, dosing recommendations based on background statin would not be supported by the available data.

7 Review of Safety

Safety Summary

The assessment of risk associated with alirocumab treatment is formed from an evaluation of four phase 2 trials and ten phase 3 studies encompassing a total of 3340 patients exposed to alirocumab as of the application cut-off date of August 31, 2014. The safety database is divided into two main safety pools based on the control employed – placebo or ezetimibe. Nine studies (4 phase 2 and 5 phase 3) compose the placebo-controlled pool and include patients with heterozygous familial hypercholesterolemia or non-familial hypercholesterolemia on maximally tolerated background statin therapy. Within this pool, 1999 (81%) patients were exposed to alirocumab for at least 1 year. The mean duration of exposure was 58 weeks. Five phase 3 studies compose the pool of ezetimibe-controlled studies. Four of the 5 studies were 24 weeks in duration. The mean duration of exposure within the pool of ezetimibe-controlled studies was 42 weeks, with 409 (47%) exposed to alirocumab for at least 1 year. The ezetimibe-controlled pool consists of patients with non-familial hypercholesterolemia who may have not been receiving statin therapy or were at less than maximal doses of statin therapy.

Treatment groups within the placebo-controlled (alirocumab versus placebo) and ezetimibe-controlled pools (alirocumab versus ezetimibe) were well matched for demographics and baseline characteristics. In the placebo-controlled pool the mean age was 59 years, 40% were women, 90% were Caucasian, and 30% participated at U.S. sites. In the ezetimibe-controlled pool the mean age was 62 years, 35% women, 87% Caucasian, and 50% participated at U.S sites. The majority of patients in both the placebo-controlled and ezetimibe-controlled pools had a history of CHD (60 to 70%) – with almost half of patients in both the placebo-controlled pool and ezetimibe-controlled pool reporting a coronary revascularization procedure and approximately a third of patients reporting a history of a myocardial infarction. In both of the main safety pools, approximately 70% reported a history of hypertension and an estimated 30% reported a history of diabetes mellitus. At randomization, 99.9% of patients within the placebo-controlled pool were on a background statin with 54% on a high intensity statin and approximately a quarter of patients on ezetimibe. In comparison, more patients (20% to 27%) were not receiving background statin therapy and fewer were on a high intensity statin, in the ezetimibe-controlled pool which reflects the inclusion criteria and objectives of particular studies within this group.

Although, this safety review presents data from both the placebo-controlled and ezetimibe-controlled pools, it should be kept in mind when reviewing the safety assessment of alirocumab that within the placebo-controlled pool, study design was most consistent, all patients were on maximally tolerated statin therapy, and the extent of exposure was greater.

All deaths were adjudicated by the clinical events committee (CEC) and categorized as cardiovascular, non-cardiovascular or undetermined based on the definitions pre-specified in the CEC charter document. In the global pool of phase 3 studies combined (placebo and ezetimibe controlled), there were a total of 37 on-study deaths: 17 deaths (0.9%) in the control group and 20 deaths (0.6%) in the alirocumab group. The majority of these deaths were adjudicated as cardiovascular – 11 occurring in the control group and 15 occurring in the alirocumab group which is not unexpected given the high cardiovascular risk profile of the population studied. Of import, the numbers are too small to draw any conclusions regarding the effect of alirocumab on reduction of risk of overall mortality.

In the pool of placebo-controlled studies, treatment-emergent serious adverse events (SAEs, fatal and non-fatal combined) were reported in 13.7% and 14.3% of patients in the alirocumab-treated and placebo-treated groups, respectively. Within the pool of ezetimibe-controlled studies, a slightly higher incidence of SAEs occurred in the alirocumab-treated (13.1%) versus the ezetimibe-treated (11.2 %) groups. The highest percentage of patients reporting a fatal and non-fatal SAE occurred in the "Cardiac disorders" SOC in both the placebo-controlled pool (4.5% placebo, 4.4% alirocumab) and ezetimibe-controlled pool (4.0% ezetimibe and 5.6% alirocumab). Within this SOC, the SAE of 'unstable angina' was reported with greater incidence in alirocumab-treated patients in both the pool of placebo-controlled studies (placebo 0.7% versus alirocumab 1.0%) and the pool of ezetimibe-controlled studies (ezetimibe 0.3% versus alirocumab 1.4%). Other SAEs, within this SOC, that occurred in at least 0.5% of patients and with greater incidence in alirocumab-treated versus placebo-treated group included 'angina pectoris' (0.5% placebo versus 0.6% alirocumab) and 'coronary artery disease' (0.2% versus 0.6%). In the pool of ezetimibe-controlled studies, these SAEs were 'acute myocardial infarction' (0.5% ezetimibe versus 1.3% alirocumab), 'atrial fibrillation' (0.5% versus 0.6%), and 'pneumonia' (0.3% versus 0.8%).

Within the placebo-controlled pool, a similar proportion of patients permanently discontinued treatment due to a treatment-emergent adverse event (TEAE): 5.1% patients in the placebo group and 5.3% patients in the alirocumab group. In the ezetimibe-controlled pool, the overall incidence of discontinuation due to a TEAE was 9.7% in the ezetimibe and 8.8% in the alirocumab group. In the placebo-controlled pool, the greatest absolute difference between treatment groups in discontinuations was noted in the "Skin and subcutaneous disorders" SOC. Ten (0.4%) alirocumab-treated patients compared with zero placebo-treated patients discontinued treatment due to adverse events within this category, mostly associated with pruritus and rash-related events. In the ezetimibe-controlled pool, the highest incidence of TEAE leading to treatment discontinuation were muscle-related, with 3.6% and 5.5% of alirocumab and ezetimibe-treated patients, respectively, reporting an event within the "Musculoskeletal and connective disorders" SOC. This is primarily a reflection of the ALTERNATIVE study, which included a patient population considered statin intolerant because of a history of muscle-related symptoms. Alirocumab-treated patients had a higher

incidence of TEAEs leading to discontinuation compared to ezetimibe-treated patients in the SOC “Investigations” (0.2% ezetimibe, 0.7% alirocumab) mostly related to abnormalities in liver enzymes.

Based on theoretical or identified concerns about PCSK9 inhibition or therapeutic protein products in general, or about alirocumab specifically, several adverse events of special interest (AESI) were prespecified for potential additional monitoring and reporting requirements. In order to evaluate these AESIs, the applicant utilized prespecified standardized MedDRA queries (SMQs), or company MedDRA queries (CMQs) which were developed when no appropriate SMQ was available. SMQs are groupings of MedDRA terms, usually at the preferred term (PT) level, which relate to a defined medical condition or area of interest. AESIs or special groupings of AEs evaluated were local injection site reactions, general allergic events, neurologic events, neurocognitive events, diabetes mellitus, hepatic-related disorders, and muscle-related disorders.

In the global pool (phase 2/3 studies), higher incidences of local injection site reactions were reported in patients receiving alirocumab injection (6.1%) versus sham injections (4.1%). Most injection site reactions were transient and of mild intensity and few patients discontinued treatment due to an injection site reaction (n=8, 0.2% alirocumab; n=6, 0.3% control). However, patients receiving the alirocumab injection reported a greater number of injection site reactions, had more reports of associated symptoms of erythema/redness, pain, and swelling, and had a longer average duration of injection site reactions than patients treated with placebo injections. In alirocumab-treated patients, those with treatment-emergent anti-drug antibodies (ADA) reported a higher incidence of local injection site reactions (10.2%) compared to ADA-negative patients (5.9%).

General allergic events occurred with a higher incidence in alirocumab-treated patients in both the pool of placebo-controlled studies and pool of ezetimibe-controlled studies (7.8% placebo versus 8.6% alirocumab; 5.3% ezetimibe versus 6.8% alirocumab). The proportion of patients with serious treatment-emergent adverse events was low and similar across treatment groups within both the placebo-controlled and ezetimibe-controlled pools. The most commonly reported treatment-emergent adverse events were rash and pruritus. However, there were several allergic events of note, including cases of angioedema that all occurred among alirocumab-treated patients (3 mentioned in the initial BLA submission, 1 in the 4-month safety update report), 2 cases of leukocytoclastic vasculitis (all alirocumab-treated: 1 in a patient administered 300 mg of alirocumab in a phase 2 study), and hypersensitivity. Patients with a medical history of allergy were more likely to report an allergic event compared to patients without a history of medical allergy. However, a similar proportion of patients with or without treatment-emergent positive ADA reported a general allergic event (8.8% positive ADA, 8.2% negative ADA).

Neurologic events related to myelin-sheath disorders or neuropathies were collected based on theoretical concerns that low LDL-C levels may impair myelination. Within the pool of placebo-controlled studies, the incidence of patients with a neurologic event of special interest was similar (3.5% in each treatment group). There was a slightly higher incidence of alirocumab-treated (3.4%) patients than ezetimibe-treated patients (2.4%) reporting an event within the pool of ezetimibe-controlled trials; however, there were no specific preferred terms that showed a large imbalance. Paresthesia was the only preferred term reported with a higher incidence in the alirocumab-treated group compared to the placebo-treated group or ezetimibe-treated group. These events occurring in the alirocumab group were not serious and the majority did not lead to treatment discontinuation. There were four alirocumab-treated patients that reported serious events that warrant mention – a case of Miller-Fisher syndrome (a variant of Guillain-Barre), optic neuritis, demyelination (multiple sclerosis), and transverse myelitis. With the exception of the Miller-Fisher syndrome case, none of the patients had two consecutive LDL-C levels less than 25 mg/dL or treatment-emergent anti-drug antibodies. After review of these cases a causal link with alirocumab or low LDL-C levels cannot be confirmed, based on potential alternative etiologies and the very small number of cases.

Neurocognitive adverse events were assessed in phase 2 and phase 3 trials using event terms that included deliria (including confusion), cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception and mental impairment disorders. Overall the number of patients reporting an event was low demonstrating similar frequencies between treatment groups in the pool of placebo-controlled studies (0.7% placebo, 0.8% alirocumab), and in the pool of ezetimibe-controlled studies (1.0% ezetimibe, 0.9% alirocumab). No alirocumab-treated patient discontinued due to an adverse neurocognitive event. Memory impairment was reported with greater incidence in alirocumab-treated patients compared to either placebo-treated or ezetimibe-treated patients. A total of 8 alirocumab-treated patients (n=5, 0.2% in placebo pool; n=3, 0.3% in ezetimibe pool) versus 1 (<0.1%) patient treated with placebo and none treated with ezetimibe reported this event. Of the 8 alirocumab-treated patients, memory impairment was not serious, no patient discontinued due to the event, only 1 patient had 2 consecutive LDL-C levels less than 25 mg/dL which occurred after the memory impairment event, and 2 patients had memory impairment in association with hospitalization for stroke. Outcomes of the 8 events were listed as “recovered” (n=3), “not recovered, stabilized” (n=2; occurring with a stroke event), and not recovered (n=3). Serious neurocognitive events occurred in very few patients and were associated with pre-existing medical conditions and other confounders.

On background of maximally tolerated statin therapy in placebo-controlled studies, treatment with alirocumab was associated with a higher percentage of patients reporting events within the SMQ “hepatic disorders” (1.8% placebo, 2.5% alirocumab). These events were primarily associated with abnormal hepatic laboratory values. Evaluation

of pre-specified categorical changes in ALT defined as ≥3x ULN (if baseline ALT < ULN) or twice baseline (if baseline ALT ≥ULN) demonstrated a slightly higher percentage of alirocumab-treated patients with this shift in ALT versus either placebo or ezetimibe-treated patients, however larger increases in (ALT >5x ULN or >10x ULN) were similar between treatment groups. There was a higher incidence of serious hepatic disorders associated with alirocumab treatment, with the majority associated with elevations of liver transaminases. Review of these cases suggested alternative etiologies such as hepatitis or concomitant medications as potential causative factors. Of the serious adverse events in which alirocumab was temporarily discontinued due to elevations in ALT, subsequent re-initiation of treatment resulted in negative rechallenge with the exception of 1 case of positive rechallenge(in this reviewer's opinion) with mild elevations in ALT that ultimately did not result in treatment discontinuation. An additional patient experienced an elevation in ALT that resolved with discontinuation of alirocumab, but experienced elevated ALT with rechallenge that led to permanent discontinuation of treatment. There were 3 cases (1 alirocumab-treated and 2 placebo-treated) that met the biochemical criteria for Hy's Law – however these cases do not qualify as Hy's Law cases based on alternative etiologies of hepatitis A, cholecystitis, and cholangitis, respectively.

Based on non-clinical observations of optic nerve degeneration and chorioretinal lesions in rats and monkeys, respectively, eye disorders were assessed using the SMQs 'optic nerve disorders', 'retinal disorders', and 'corneal disorders' in the overall safety population and with an ophthalmologic sub-study in a subset of patients in the placebo-controlled LONG TERM study. There were numerically higher incidences of ophthalmological TEAEs by SMQ in alirocumab-treated (1.8%) versus placebo-treated patients (1.4%) and alirocumab-treated (0.8%) versus ezetimibe-treated patients (0.5%). However, the TEAEs reported were varied within this category and did not demonstrate any specific pattern. An ophthalmological sub-study evaluated 139 patients (5.9% of LONG TERM study population) with additional ophthalmologic testing by either an ophthalmologist or optometrist throughout the study. Four (4.5%) patients in the alirocumab sub-study group had a TEAE within this SMQ, however 1 case of "demyelination" was considered more consistent with a neurological event of interest. Two (3.9%) placebo-treated patients in this sub-study reported an event (diabetic neuropathy and macular degeneration).

In the placebo-controlled safety pool in which all patients were on statin therapy, 15.1% patients in the alirocumab group versus 15.4% patients in the placebo group experienced a musculoskeletal-related CMQ defined TEAE. TEAEs that occurred in ≥2% of patients and with greater incidence in the alirocumab group included myalgia (4.2% alirocumab versus 3.4% placebo), muscle spasms (3.1% versus 2.4%), and musculoskeletal pain (2.1% versus 1.6%). Two cases of rhabdomyolysis in alirocumab-treated patients were reported; 1 occurring in a 81-year-old patient on atorvastatin 80 mg who experienced a fall and concurrent diagnosis of pneumonia; the other case was later downgraded to myositis. Muscle-related AEs were less common in patients

considered statin intolerant treated with alirocumab compared to patients treated with atorvastatin or ezetimibe.

Approximately 31% of patients in the global safety pool (combined phase 2 and 3 studies) at baseline were normoglycemic, 37% had impaired fasting glucose and 32% were diabetic. Distribution according to these glycemic categories was comparable between treatment groups in both the placebo-controlled and ezetimibe-controlled pools at baseline. Regardless of baseline glycemic status, a slightly higher percentage of patients treated with alirocumab (4.2%) had a diabetes-related TEAE compared to patients treated with placebo (3.8%). This was not observed in the ezetimibe-controlled pool (alirocumab 2.9%; ezetimibe 3.6%). Mean change in fasting glucose and HbA1c over time did not demonstrate meaningful differences between treatment groups by baseline glycemic status. However looking at measures of central tendency in laboratory values and adverse events independently may not convey clinically significant changes in glycemic status.

Therefore, in exploratory analyses, shifts in glycemic status during the TEAE period were conducted using adverse events, HbA1c, and fasting plasma glucose values. In the pool of phase 3 placebo-controlled studies, 224 (31.2%) alirocumab-treated patients versus 97 (26.6%) placebo-treated patients who were normoglycemic at baseline shifted to the impaired fasting glucose category. In the ezetimibe-controlled pool, a total of 59 (26.5%) and 42 (24.1%) patients in the alirocumab and ezetimibe groups, respectively shifted from normoglycemic to the category of impaired fasting glucose. Conversely, in patients with impaired fasting glucose at baseline, a total of 178 (20.6%) and 76 (18.1%) patients in the alirocumab and placebo groups, respectively, in the placebo-controlled pool, and 94 (28.2%) and 77 (31.7%) patients in the alirocumab and ezetimibe groups, respectively, in the ezetimibe-controlled pool returned to the normoglycemic category at least once. The proportion of patients meeting the criteria for diabetes diagnosed either by adverse event or laboratory value for the placebo-controlled pool was 3.2% in the alirocumab group and 2.2% in the placebo group and for the ezetimibe-controlled pool was 2.5% in the alirocumab group and 1.9% in the placebo group with most meeting these criteria by laboratory data only.

The applicant has provided the following caveats in interpreting the results from the analyses on glucose control with alirocumab treatment: (1) many patients had values at baseline close to the thresholds between categories, so small changes between baseline and “worse value during TEAE period” could lead to a category change, (2) HbA1c was infrequently measured, and (3) changes in drugs and other factors that can affect glucose control/levels are not accounted for. While these are reasonable considerations in the interpretation of these results, the following must be kept in mind, the mean baseline glucose and HbA1c values were well matched across glucose control categories and treatment groups. Therefore, both the alirocumab and control treated groups at baseline were probably equally likely to cross glycemic thresholds by

chance. In addition, mean changes only incorporate scheduled visits and therefore may not capture all laboratory assessments, unlike categorical shift analyses which should include all laboratory values collected during the treatment period and therefore may more accurately depict glucose control. This reviewer agrees that post-randomization changes in diabetes medications are confounding factors as there was no standardized algorithm for managing glucose values. Therefore, conclusions regarding the contribution of medication changes in the overall pattern of glycemic control are limited. Lastly, for the majority of patients, glucose control remained stable and serious diabetes-related adverse events were few. It is uncertain whether the observed shifts represent a true risk for worsening glycemic control with alirocumab treatment. Glycemic control is monitorable and treatable, factors which should be considered when evaluating the benefits and risks associated with alirocumab.

Within the “Cardiac disorders” SOC treatment-emergent cardiac disorders were reported by investigators in 8.0% of alirocumab-treated patients and 9.0% of placebo-treated patients. Serious TEAEs were similar in frequency between treatment groups (4.4% alirocumab, 4.5% placebo). In the pool of ezetimibe-controlled studies, a slightly higher proportion of alirocumab-treated patients reported a TEAE (8.8%) and SAE (5.6%) compared to ezetimibe-treated patients (TEAE 7.1%, SAE 4.0%). In both safety pools, the preferred term ‘unstable angina’ was reported with higher incidence in alirocumab-treated patients compared with placebo or ezetimibe-treated patients. In the placebo-controlled pool, ‘unstable angina’ was reported in 1.2% alirocumab patients (1.1 per 100-patient years) and 0.9% placebo patients (0.8 per 100-patient years). In the ezetimibe-controlled pool, 1.4% (1.6 per 100-patient years) and 0.3% (0.4 per 100-patient years) of alirocumab and ezetimibe treated patients, respectively reported an event.

Unstable angina along with other suspected cardiovascular events were adjudicated by the CEC. In the global pool of phase 3 studies, adjudicated MACE events defined as CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization occurred in 52 (1.6%) patients in the alirocumab group and in 33 (1.8%) patients in the control group, with HR 0.81 (95% CI 0.52 to 1.25). An expanded evaluation which included MACE, hospitalization for congestive heart failure, or coronary revascularization procedure occurred in 110 (3.5%) patients in the alirocumab group and in 53 (3.0%) patients in the control group, with HR 1.08 (95% CI 0.78 to 1.50). The majority of events within this grouping were revascularization procedures. Significant treatment interactions ($p<0.10$) between the expanded MACE endpoints and type of hypercholesterolemia (HeFH, non-FH) and dose of statin at baseline were noted.

While cardiovascular events within this application are of interest, the number of adjudicated events is too small overall and within subgroups to make any reliable conclusions regarding the effect of alirocumab on risk of cardiovascular events. The ongoing event-driven cardiovascular OUTCOMES study with an estimated enrollment of

18,000 patients with acute coronary syndrome is designed to establish the effect of alirocumab on cardiovascular morbidity and mortality.

The incidence of anti-drug antibody development after receiving at least 1 dose of alirocumab in the global pool of phase 3 studies was 4.8% of alirocumab-treated patients compared with 0.6% in the control groups. The presence of antibodies occurred at a median of 12 weeks. For the majority of patients, a positive treatment-emergent ADA response was transient. In general, patients with a treatment-emergent positive ADA response were more apt to report local injection site reactions (10.2%) versus ADA-negative patients (5.2%). A similar proportion of patients with or without treatment-emergent positive ADA reported a general allergic event (8.8% positive ADA, 8.2% negative ADA). Neutralizing antibodies were detected in 1.2% of patients treated with alirocumab. There did not appear to be a correlation with neutralizing antibodies and safety.

Approximately 20% and 40% of patients treated with alirocumab had at least one calculated LDL-C value less than 15 mg/dL and 25 mg/dL, respectively compared to less than 1% of control treated patients. The majority of patients were receiving 150 mg of alirocumab every two weeks at the time of these LDL-C values. The time to the first LDL-C value less than 25 mg/dL or 15 mg/dL was on average 12 to 16 weeks, respectively. A total of 796 (23.8%) of alirocumab-treated patients had two consecutive LDL-C values less than 25 mg/dL. As expected, significant prognostic factors for patients that achieved LDL-C less than 25 mg/dL include baseline LDL-C and dose of alirocumab. As mentioned previously, conclusions generated from comparisons of groups defined by factors post-randomization are extremely limited and subject to bias. In addition, the duration of exposure is on average 1 year and therefore, it is uncertain what, if any, adverse effects of prolonged exposure to very low levels of LDL-C will be. However, at this time review of adverse events divided by levels of LDL-C achieved did not demonstrate a safety signal.

Because the potential for increased HCV infectivity in alirocumab-treated participants is a theoretical possibility, analyses were performed to assess potential cases of hepatitis C. Within the primary safety database there were no cases of RNA confirmed hepatitis C. In the four month safety update report, there was one documented case of acute hepatitis C infection in an alirocumab-treated patient participating in an ongoing trial not included in the primary safety database.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Integrated Summary of Safety (ISS) covers development of alirocumab through the cut-off date of 31 August 2014. This safety review focuses on data from 4 completed

phase 2 clinical studies and 10 phase 3 studies (Table 66). Five of the phase 3 trials are complete and 5 are ongoing. The ongoing trials were included because Week 52 assessments were obtained and approximately 600 patients had completed the 18-month double-blind treatment period from the LONG TERM study. For the phase 3 ongoing studies, analyses are referred to as the "first-step analyses" which describes all primary and secondary efficacy endpoints (up to Week 52) and all safety data up to each individual study cut-off date.

All phase 2 studies were of 12 weeks duration except study DFI11566 (which was 8 weeks). All the placebo-controlled phase 3 studies had a planned duration of 18 months, except COMBO I (completed, 12 months duration). All ezetimibe-controlled phase 3 studies were of 6 months duration, except COMBO II (ongoing, 24 months).

Excluded from this review of safety are four blinded, ongoing, phase 3 studies that did not reach the timepoint for first-step analysis or final analysis before the cut-off date of 31 August 2014. They are the CV outcome trial (OUTCOMES), EFC 13672, CHOICE I, and CHOICE II and 3 ongoing open label extension (OLE) studies/periods.

The phase 3 studies are placebo-controlled or ezetimibe-controlled. The placebo-controlled studies were conducted on top of maximally tolerated statin therapy whereas the ezetimibe-controlled studies include studies with and without concomitant statin therapy.

Table 66. Primary studies reviewed in the Integrated Summary of Safety

Phase	Study	Treatment Group			Duration	Main objectives (background therapy)
		Placebo N[3]	Alirocumab N[3]	Ezetimibe N[3]		
Phase 2						
Placebo-controlled	CL-1003	15	16[1]	0	12 wks	Dose-finding study in heFH (add-on to statins±eze)
	DFI11565	31	31[1]	0	12 wks	Dose-finding study (add-on to atorvastatin)
	DFI11566	31	61	0	8 wks	Safety and efficacy (add-on to 10 and 80 mg of atorvastatin
	DFI12361	25	50[2]	0	12 wks	Dose-finding study in Japan (add-on to statins)
Total		*102*	*158*	*0*		
Phase 3						
Placebo-controlled	FH I [(1st)]	163	322	0	78 wks	Efficacy and safety in heFH (add-on to MTD statins ± other LMT)
	FH II [(1st)]	81	167	0	78 wks	Efficacy and safety in heFH (add-on to MTD statins ± other LMT)
	HIGH FH [(1st)]	35	72	0	78 wks	Efficacy and safety in heFH LDL ≥160 mg/dL (add-on to MTD statins ± other LMT)
	COMBO I	107	207	0	52 wks	Efficacy and safety in high CV risk non-FH (add-on to MTD statins ± other LMT)

Phase	Study	Treatment Group			Duration	Main objectives (background therapy)
		Placebo N[3]	Alirocumab N[3]	Ezetimibe N[3]		
	LONG TERM [(1st)]	788	1550	0	78 wks	Long-term safety and efficacy in heFH and in high CV risk non-FH (add-on to MTD statins ± other LMT)
Total		*1174*	*2318*			
Ezetim be-controlled	COMBO II [(1st)]	0	479	241	104 wks	Efficacy and safety in high CV risk non-FH (add-on to MTD statins)
	OPTIONS I	0	104	101	24 wks	Efficacy and safety in high CV risk patients (add-on to non-max rosuvastatin ± other LMT)
	OPTIONS II	0	103	101	24 wks	Efficacy and safety in high CV risk patients (add-on to non-max rosuvastatin ± other LMT)
	ALTERNATIVE	0	126	124	24 wks	Efficacy and safety in statin intolerant patients (monotherapy or add-on to non-statin LMT)
	MONO	0	52	51	24 wks	Efficacy and safety in moderate CV risk patients (monotherapy)
Total			*864*	*618*		
Phase 3 total		*1174*	*3182*	*618*		
Grand Total		***1276***	***3340***	***618***		

Source: Adapted from BLA 125559 ISS Table 1, Clinical Overview Table 1; submitted 26 November 2014 (SD 1)
1st: Ongoing trial with first-step analysis included in ISS
1: Number of patients included in the alirocumab 150 mg Q2W group only
2: Number of patients included in the alirocumab 75 mg and 150 mg Q2W groups
3: Number randomized and exposed

7.1.2 Categorization of Adverse Events

Treatment-emergent adverse events (TEAE) were defined as events occurring or worsening from the time of the first dose of double-blind treatment up to the day of last dose + 70 days (10 weeks), as a residual effect of alirocumab is expected until 10 weeks after the dosing.

Post-treatment adverse events were defined as events occurring or worsening after the end of the TEAE period.

The on-study observation period was defined as the time from the day of first dose of study drug until the last protocol planned visit of the patient. The last protocol planned visit was defined as the follow-up visit if done, or else 86 weeks after the randomization of the patient. A patient may be off treatment but could still be considered on-study.

The safety population was defined as all randomized patients exposed to at least 1 dose or part of a dose regardless of the amount received.

There were several adverse events identified as being of special interest (AESI) such as hypersensitivity reactions, neurocognitive events, muscle-related events which may have required additional reporting in case report forms or monitoring. In order to identify

these AESIs, the applicant utilized prespecified standardized MedDRA queries (SMQs), or company MedDRA queries (CMQs) which were developed when no appropriate SMQ was available. SMQs are groupings of MedDRA terms, usually at the preferred term (PT) level that relate to a defined medical condition or area of interest. See the Appendix for a summary of definitions, monitoring procedures, and assessments for AESI.

Adverse events were coded using MedDRA version 17.0.

The applicant had a three tiered approach to analyzing adverse events.

Tier 1: Treatment-emergent adverse events prospectively defined based on non-clinical findings or theoretical risks. This group Includes AESIs, groupings of specific AEs, and CV events confirmed by adjudication as follows:

- Local injection site reactions
- General allergic events
- Neurological events, focusing on myelin sheath-related disorders
- Neurocognitive disorders
- Musculoskeletal related disorders (only for ALTERNATIVE)
- Diabetes mellitus
- Hepatic disorders
- Ophthalmologic events
- CV events confirmed by adjudication

These events were analyzed in each of the main safety data pools with a pre-defined analytical approach to include incidence, event rate per 100 patient-years, hazard ratio using a Cox model stratified on the study, an assessment of the consistency of treatment effect across studies, assessments of risk over time using study-adjusted Kaplan-Meier estimates, and treatment effect across subgroups.

Tier 2 represented “common” TEAEs that were not pre-specified. These TEAEs were screened statistically for a signal by the applicant. Additional analyses were conducted if a clinically significant signal was detected. “Common” events were defined as those for which there were at least 9 patients with an event overall in the placebo-controlled pool or 6 patients with an event in the ezetimibe-controlled pool. The applicant selected these thresholds because if all the events occurred in the alirocumab group and none in the control group the lower bound of the 95% CI for the HR of alirocumab versus control would not exceed 1.

Tier 3 represented infrequent TEAEs which were assessed clinically and summarized with descriptive statistics.

Cardiovascular Adjudication Procedures

In phase 3 studies, the following suspected cardiovascular events and all deaths that occurred from randomization until the follow-up visit were to be sent to the Clinical Events Committee (CEC) with an adjudication package:

- Myocardial infarction;
- Cerebrovascular events;
    - Stroke, TIA, intracranial bleeding, ischemia or bleeding of spine or retina
- Unstable angina requiring an emergency room visit or requiring/prolonging hospitalization;
- Congestive heart failure requiring an emergency room visit or requiring/prolonging hospitalization;
- All coronary revascularization procedures
- All deaths (including congestive heart failure death)

The CEC also reviewed abnormal values of CK, CK-MB, troponin I or T and coronary revascularization events to identify any additional MI and unstable angina requiring hospitalization that have not been identified by the Investigators as potential CV events.

The CEC, managed by the Duke Clinical Research Institute (DCRI), is composed of experts in the field of cardiovascular diseases, independent from the applicant and investigators. The CEC reviewers are tasked with defining, validating, and classifying, while blinded to treatment assignment and LDL-C results, pre-specified cardiovascular events and all deaths.

The suspected CV events/coronary revascularization procedures are reviewed as shown in the diagram below:

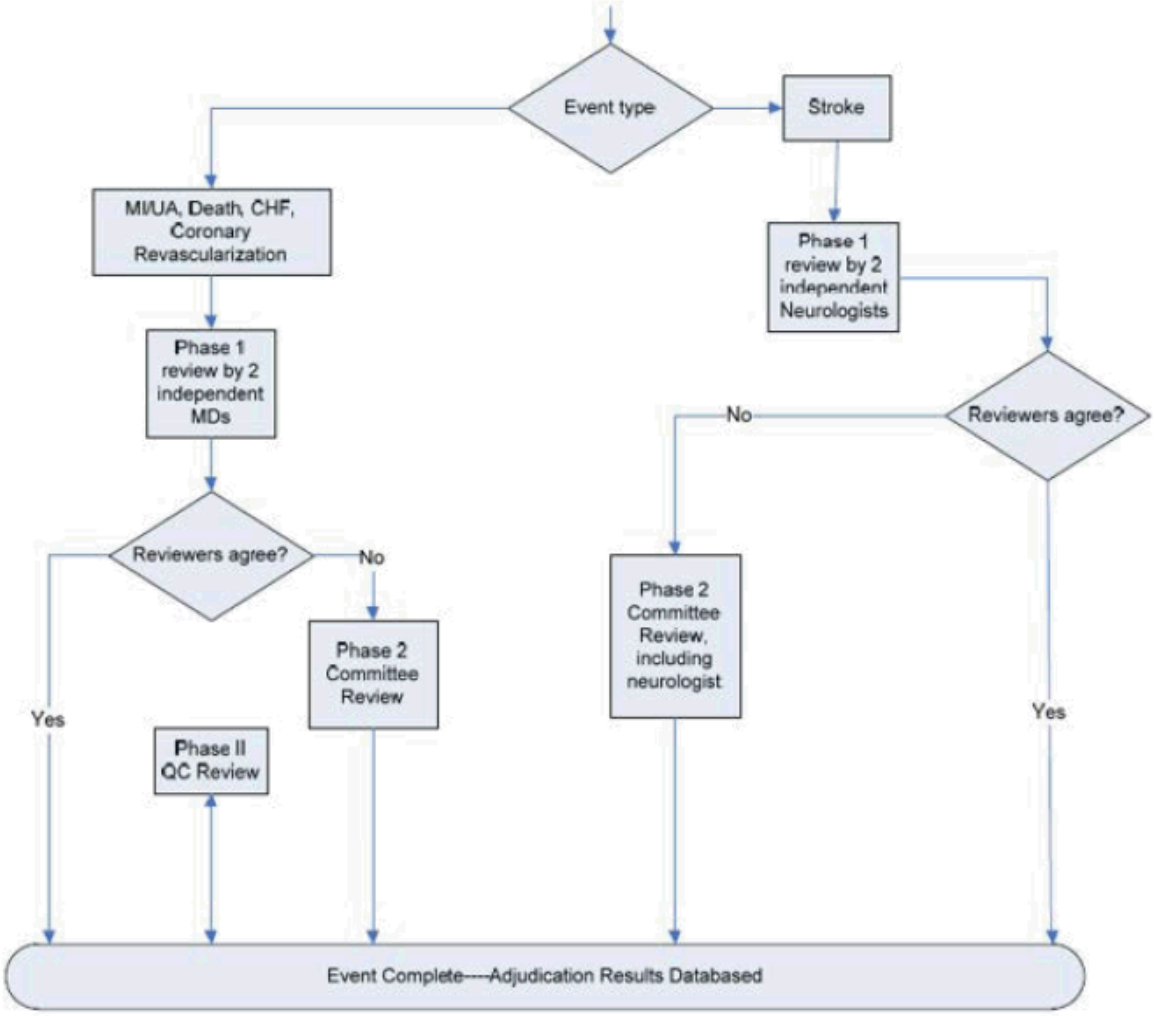


Figure 31. Adjudication review flow chart

Source: NDA 125559 Module 1.2 Adjudication reviewer guide Figure 2

The events were adjudicated by the CEC into the following event categories:

- CHD death;
- Nonfatal MI
- Fatal and nonfatal stroke
- Unstable angina requiring hospitalization
- CHF requiring hospitalization
- Ischemia-driven coronary revascularization procedure

Monitoring for low LDL-C

Monitoring was put into place for assessing the safety of LDL-C <25 mg/dL in Phase 3 studies with a treatment duration of more than 6 months. An independent physician working in coordination with a member of the Data Monitoring Committee (DMC) was responsible for monitoring patients with low LDL-C levels of <25 mg/dL. After notification by the central laboratory of all patients who achieved two consecutive calculated LDL-C <25 mg/dL, the independent physician was to review all available data on the patient including any AEs potentially associated with low LDL-C. After review of the information, the independent physician would communicate with the responsible DMC member, who in consultation with the independent physician would decide whether or not to notify the site.

If the site was not notified, the patient would continue study treatment and visits as per the study protocol. The independent physician would continue to periodically monitor the patient's data and inform the designated DMC member as needed.

Site notification, once decided, was done by the central lab. No actual lipid values were communicated to the investigator. In order to maintain integrity of the study blind, sham alerts were also made to sites. An alerted investigator was to follow recommended steps regarding alerts for patients with low LDL-C levels. These steps included:

- Call the patient as soon as possible to inquire about interval occurrence of AEs
- Decide whether the patient should be requested to have an unscheduled site visit, or if assessment could be done at the next scheduled visit
- At the study visit, based on investigator judgment, the need for conducting clinical investigations, arranging specialist consultations as needed and any relevant additional work-up was to be assessed. In addition the need for study treatment temporary or permanent discontinuation was to be considered.

The DMC also analyzed the aggregate date for all patients who achieved LDL-C <25 mg/dL during DMC periodic reviews.

Overall, 7 alerts were issued, including 3 sham alerts. No patients permanently discontinued therapy as a result of an LDL-C alert and only 1 patient in the alirocumab group, 11569-840-986-001, temporarily discontinued study medication as a result of the alert.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of clinical trials

All completed double-blind phase 2 and 3 studies and all phase 3 studies with a completed first step analysis are included in the integrated clinical safety database and were the primary focus of the safety review.[49]

[49] Completed phase 2 study CL-1010 was not included – studied patients with PCSK9 or ApoB mutations.

Two main pools are the primary source for analyses and conclusions of safety and are based on the control group (placebo or ezetimibe). Table 67 lists the studies included in each of the safety pools evaluated in the ISS.

The placebo pool contains phase 2 and phase 3 trials. The phase 2 trials were of a much shorter duration (8 to 12 weeks) compared to the phase 3 trials (52 to 78 weeks). Pooling analyses of phase 2 and 3 placebo-controlled studies was considered a reasonable approach to identify safety signals with alirocumab versus control, especially those occurring in the first few weeks of treatment.

Table 67. Studies included in the safety pools evaluated in the ISS

Study Name	Pbo pool	Eze pool	Global	P3 pbo pool	P3 pool
DFI 11565	X		X		
DFI 11566	X		X		
CL-1003	X		X		
DFI 12361	X		X		
FH I	X		X	X	X
FH II	X		X	X	X
HIGH FH	X		X	X	X
COMBO I	X		X	X	X
LONG TERM	X		X	X	X
COMBO II		X	X		X
ALTERNATIVE		X	X		X
MONO		X	X		X
OPTIONS I		X	X		X
OPTIONS II		X	X		X

Source: Reviewer generated table

In some cases parameters and endpoints were not assessed in the phase 2 trials (e.g. adjudicated CV events, hemolytic anemia, medical history of patient's allergies), therefore a pool of placebo-controlled phase 3 studies was used.

A global pool included placebo and ezetimibe-controlled studies and was used to conduct specific safety analyses which included anti-drug antibodies, deaths, injection site reactions, and AEs in patients with 2 consecutive LDL-C <25 mg/dL. A phase 3 pool was used to evaluate CV events.

Throughout the review, the studies generating the data presented in tables will be supplied by pool (in table title) and study name (at bottom of table).

Pooling of alirocumab doses

Two doses, 75 mg and 150 mg, administered subcutaneously once every two weeks (Q2W), were used in the phase 2 and 3 studies. The applicant seeks approval of both doses. Eight phase 3 studies used an up-titration scheme (initiation of alirocumab with 75 mg Q2W, and potential titration to 150 mg Q2W). Up-titration was done at Week 12 if

patients initially treated with the 75 mg dose did not achieve their predetermined target LDL-C at Week 8 (70 mg/dL or 100 mg/dL), depending on the study and the patient's individual CV risk. Of the 3188 patients randomized to alirocumab in phase 3 trials, approximately half (N=1563) participated in the 8 studies using an up-titration scheme. The other two phase 3 studies, LONG TERM and HIGH FH, and all the phase 2 studies (with the exception of DFI12361) used 150 mg Q2W throughout the study.

The applicant has pooled both doses of alirocumab for its main safety analyses. This pooling of alirocumab doses is acceptable based on analyses further discussed in Section 7.5.1 which did not demonstrate a meaningful difference in adverse events by dose or treatment regimen.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure to study drug

Within the phase 2 and 3 studies, a total of 3340 patients were treated with either 75 or 150 mg alirocumab and 1894 were treated with either placebo (n=1276) or ezetimibe (n=618). In the placebo-controlled pool, most of the patients (81% in alirocumab group; 79% in placebo group) were exposed for at least 52 weeks. The mean duration of exposure was 58 weeks. In the ezetimibe-controlled pool, a total of 1482 patients were treated, 864 patients were exposed to alirocumab and 618 patients were exposed to ezetimibe. Total exposure was 692 patient-years for alirocumab and 419 patient-years for ezetimibe. The mean extent of exposure for alirocumab was 42 weeks in the alirocumab group and 35.5 weeks in the ezetimibe group, consistent with the 24-week duration for all studies except COMBO II and with the 2:1 randomization ratio in COMBO II.

Table 68. Exposure[1] to study drug (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Cumulative injection exposure (pt-years)	1408	2759	419	692
Duration of injection exposure (weeks)				
n[2]	1275	2470	617	861
Mean	58	58	35	42
Median	65	65	24	27
Number (%) of patients exposed by time period				

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
≥1 day to <4 wks	13 (1.0)	24 (1.0)	15 (2.4)	21 (2.4)
≥4 wks to <8 wks	20 (1.6)	54 (2.2)	26 (4.2)	27 (3.1)
≥8 wks to <12 wks	47 (3.7)	105 (4.3)	18 (2.9)	15 (1.7)
≥12 wks to <16 wks	93 (7.3)	111 (4.5)	18 (2.9)	18 (2.1)
≥16 wks to <24 wks	20 (1.6)	41 (1.7)	53 (8.6)	59 (6.9)
≥24 wks to <36 wks	35 (2.7)	66 (2.7)	277 (44.9)	297 (34.5)
≥36 wks to <52 wks	37 (2.9)	70 (2.8)	1 (0.2)	15 (1.7)
≥52 wks to<64 wks	277 (21.7)	576 (23.3)	132 (21.4)	250 (29.0)
≥64 wks to <76 wks	444 (34.8)	848 (34.3)	47 (7.6)	95 (11.0)
≥76 wks	289 (22.7)	575 (23.3)	30 94.9)	64 (7.4)

Source: NDA 125559 ISS Table 6
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I); phase 2 (DFI11565, DFI 11566, CL-1003, DFI12361)
Ezetim be-controlled studies: (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1: Duration of injection exposure in weeks is defined as (last injection date +14 days-first injection date)/7, regardless of intermittent discontinuations
2 Only patients without missing first or last injection dates were used in the exposure calculations

In phase 2 and 3 studies, there were 717 and 861 patients in the placebo-controlled and ezetimibe-controlled studies, respectively, initiating treatment with alirocumab 75 mg Q2W. Approximately 30% (n=228) and 20% (n=179), respectively were uptitrated to 150 mg Q2W at Week 12 based on LDL-C failure to achieve LDL-C goals. The following table lists the number and patient-years of exposure by alirocumab dose.

Table 69. Patient-year exposure by alirocumab dose (safety population) – pool of placebo-controlled and pool of ezetimibe controlled studies

	Placebo-controlled		Ezetimibe-controlled	
	Alirocumab N=2470		Alirocumab N=861	
	n (%)	Patient-year	n (%)	Patient-year
75 mg Q2W[1]	717 (29.0)	534.9	861 (100)	595.2
150 mg Q2W[2]	1981 (80.2)[3]	2223.6	179 (20.8)	96.9

Source: NDA 125559 ISS Appendix 1.2.1.6
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Note: Patients are considered in the treatment group they actually received.
1: For up-titrated patient, duration of exposure to 75 mg Q2W initial dose, until up-titration
2: For up-titrated patient, duration of exposure after up-titration to 150 mg Q2W.
3: Includes 1753 patients who initiated treatment at 150 mg Q2W

Demographics and other characteristics of safety population

The alirocumab patient population included patients with heterozygous familial hypercholesterolemia (HeFH) and patients with non-familial hypercholesterolemia

representing roughly 27% and 73% of the safety population, respectively.[50] The mean duration of time from hypercholesterolemia diagnosis was 10 years.

Baseline characteristics of the placebo-controlled and ezetimibe-controlled populations are summarized in Table 70. The treatment groups were well-matched for demographic and baseline characteristics. In the placebo-controlled and ezetimibe-controlled pools, the mean age was 59 and 62 years, respectively, roughly 60% of the subjects were male, and approximately 90% were Caucasian in both pools. Thirty percent and approximately 50% of patients in the placebo-controlled and ezetimibe-controlled pools, respectively were from sites within the United States.

Table 70. Baseline demographic and baseline characteristics (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

		Placebo-controlled pool		Ezetimibe-controlled pool	
		Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Demographic characteristics					
Age (years)	Mean (SD)	58.5 (11.3)	58.6 (11.6)	62.1 (9.5)	61.9 (9.4)
	≥65 years, n (%)	398 (31.2)	805 (32.5)	243 (39.3)	353 (40.9)
Sex, n (%)	Female	513 (40.2)	994 (40.1)	231 (37.4)	283 (32.8)
Race, n (%)	White	1136 (89.0)	2232 (90.1)	546 (88.3)	745 (86.2)
	Black/African American	57 (4.5)	101 (4.1)	37 (6.0)	50 (5.8)
Ethnicity, n (%)	Hispanic	77 (6.2)	153 (6.3)	41 (6.7)	50 (5.8)
Baseline characteristics					
Current smoker	n (%)	250 (19.6)	480 (19.4)	118 (19.1)	146 (16.9)
Diabetes	n (%)	403 (31.6)	754 (30.5)	201 (32.5)	308 (35.6)
BMI (kg/m^2)	Mean (SD)	30.2 (5.6)	29.9 (5.6)	30.0 (5.7)	30.2 (6.0)
	≥30 kg/m2	558 (43.8)	1054 (42.7)	281 (45.5)	376 (43.5)
HbA1c (%)	Mean (SD)	6.05 (0.93)	6.02 (0.91)	5.99 (0.78)	6.05 (0.80)
	≥5.7 to <6.5	511 (40.2)	1010 (40.9)	257 (41.6)	352 (40.9)
hsCRP (mg/L)	Median	1.41	1.59	1.73	1.66
Lipids/lipoproteins					
LDL-C (mg/dL)	Mean (SD)	126.6 (43.8)	126.6 (45.3)	125.5 (56.9)	123.2 (51.5)
	<100 mg/dL, n (%)	357 (28.0)	685 (27.7)	245 (39.7)	329 (38.1)
HDL-C (mg/dL)	Mean (SD)	50.0 (13.1)	50.5 (13.6)	49.7 (14.3)	48.5 (13.8)
	<40 mg/dL, n (%)	270 (21.2)	528 (21.3)	139 (22.5)	248 (28.7)
Fasting TG (mg/dL)	Median	125.0	126.5	133.5	132.0
	≥200 mg/dL, n (%)	236 (13.5)	457 (13.5)	136 (22.0)	197 (22.8)
eGFR ($mL/min/1.73m^2$)					
	≥90, n (%)	293 (23.0)	512 (20.7)	101 (16.3)	142 (16.4)
	≥60 to <90, n (%)	794 (62.2)	1557 (62.9)	413 (66.8)	570 (66.0)
	≥30 to <60, n (%)	188 (14.7)	402 (16.2)	102 (16.5)	151 (17.5)
	≥15 to <30, n (%)	0	3 (0.1)	2 (0.3)	1 (0.1)

50 Percentages based on a safety population (n=5005), which excluded phase 2 studies except CL-1003 as the type of hypercholesterolemia was not collected.

		Placebo-controlled pool		Ezetimibe-controlled pool	
		Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Region, n (%)	United States	384 (30.1)	725 (29.3)	310 (50.2)	397 (45.9)

Source: ISS Table 7, ISS Appendix 1.3.6.3, 1.3.6.9, 1.3.6.14, 1.3.6.17, 1.3.7.14
Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Medical history

Patients' CV history and CV risk factors are provided only for phase 3 studies since patients were only specifically questioned about pre-specified CHD and CHD risk equivalents in these studies. The majority of patients in both the placebo and ezetimibe pools had a history of CHD (60 to 70%) – with almost half of patients reporting a coronary revascularization procedure and approximately a third of patients reporting a history of a myocardial infarction. Approximately 70% reported a history of hypertension and an estimated 30% reported a history of diabetes mellitus. The majority of patients were considered either high or very high CV risk based on United States or European guidelines current at the time of study initiation.[21,40,51,52]

Table 71. Cardiovascular medical history/risk factors (safety population) – pool of phase 3 placebo-controlled studies and pool of ezetimibe controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1174 n (%)	Alirocumab N=2318 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Any cardiovascular history/risk factors	**964 (82.1)**	**1870 (80.7)**	**618 (100)**	**861 (99.7)**
Coronary heart disease	766 (65.2)	1450 (62.6)	388 (62.8)	611 (70.7)
Acute Myocardial Infarction	421 (35.9)	757 (32.7)	206 (33.3)	352 (40.7)
Silent myocardial infarction	22 (1.9)	75 (3.2)	15 (2.4)	27 (3.1)
Unstable angina	167 (14.2)	274 (11.8)	87 (14.1)	141 (16.3)
Coronary revascularization procedures	522 (44.5)	1003 (43.3)	289 (46.8)	455 (52.7)
Other clinically significant CHD	322 (27.4)	616 (26.6)	203 (32.8)	305 (35.3)
Coronary heart disease risk equivalents per CRF[1]	408 (34.8)	804 (34.7)	155 (25.1)	232 (26.9)
Ischemic stroke/transient ischemic attack	86 (7.3)	199 (8.6)	42 (6.8)	67 (7.8)
Peripheral arterial disease	56 (4.8)	97 (4.2)	17 (2.8)	33 (3.8)
Known history of diabetes (type 1 or 2) AND	207 (17.6)	387 (16.7)	57 (9.2)	84 (9.7)

51 The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J. 2011;32:1769-1818.
52 Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts).

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1174 n (%)	Alirocumab N=2318 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
additional risk factors[2]				
Moderate chronic kidney disease	138 (11.8)	284 (12.3)	50 (8.1)	82 (9.5)
Other medical history				
Hypertension	820 (69.8)	1570 (67.7)	438 (70.9)	641 (74.2)
Type 2 diabetes	343 (29.2)	680 (29.3)	189 (30.6)	279 (32.3)
Family history of premature CHD	435 (37.1)	837 (36.1)	153 (24.8)	192 (22.2)
Current smoker	230 (19.6)	453 (19.5)	118 (19.1)	146 (16.9)
Moderate chronic kidney disease	138 (11.8)	284 (12.3)	50 (8.1)	82 (9.5)

Source: ISS Table 8, 9;
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1 Table only includes categories that were assessed in placebo and ezetimibe controlled trials
2 At least 2 of the following risk factors: ankle-brachial index ≤0.90, hypertension, nephropathy, retinopathy or family history of premature CHD in LONG TERM, FH I, FH II, HIGH FH, COMBO I, COMBO II studies

In the phase 3 studies, the majority of patients entered studies on maximally tolerated background statin therapy. Roughly half of patients were taking a high intensity statin defined as atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily. A higher percentage of patients in the ezetimibe-controlled pool were not on background statin therapy reflecting two studies within this pool that were conducted in patients who did not receive statins (MONO and ALTERNATIVE).

Table 72. Background lipid modifying therapy at randomization (safety population) – phase 3 placebo and ezetimibe controlled pools

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1174 n (%)	Alirocumab N=2318 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
No background statin	1 (<0.1)	2 (<0.1)	165 (26.7)	176 (20.4)
Taking high intensity statin[1]	633 (53.9)	1268 (54.7)	259 (41.9)	421 (48.7)
Atorvastatin	423 (36.0)	891 (38.4)	226 (36.6)	344 (39.8)
Rosuvastatin	374 (31.9)	727 (31.4)	180 (29.1)	242 (28.0)
Simvastatin	378 (32.2)	700 (30.2)	53 (8.6)	107 (12.4)
Other statins[2]	0	0	1 (0.2)	0
Other lipid modifying therapy (LMT)[3]				
Any LMT other than dietary supplements	399 (34.0)	740 (31.9)	88 (14.2)	94 (10.9)
Ezetimibe	291 (24.8)	536 (23.1)	NA	NA

Source: ISS Table 13
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. High intensity statin corresponds to atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily
2. Patients not receiving atorvastatin, rosuvastatin or simvastatin at randomization.
3. In combination with statins or not

In both the phase 3 placebo-controlled and the ezetimibe-controlled pools, 87% to 90% of patients received concomitant CV medications. Antithrombotic agents were taken by

more than 70% of patients; acetylsalicylic acid was the most frequently reported concomitant CV medication.

7.2.2 Explorations for Dose Response

See Section 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

Please see the non-clinical review team's assessment for further information.

7.2.4 Routine Clinical Testing

The types of routine clinical testing performed in the safety evaluation of alirocumab were adequate. The following tables summarize the timing of blood sample collection for clinical laboratories across the phase 2 and 3 studies.

Table 73. Summary of clinical laboratory collection

Studies	D0[a]	W4	W8	W12	W16	W24	W36	W52	W64	W76[a] W78	W104
Standard hematology[b], chemistry (other than liver tests)											
DFI11566	X	X	X (EOT)								
Other phase 2	X	X	X	X (EOT)							
OPTIONS, MONO, ALTERNATIVE	X			X		X (EOT)					
COMBO I	X			X		X	X	X (EOT)			
LTS, FH I-II, High FH	X			X		X	X	X	X	X (EOT)	
COMBO II	X			X		X	X	X		X	X (EOT)
Liver tests (ALT, AST, ALP, Total Bilirubin)[b]											
DFI11566	X	X	X (EOT)								
Other phase 2	X	X	X	X (EOT)							
OPTIONS, MONO, ALTERNATIVE	X			X		X (EOT)					
COMBO I	X	X	X	X	X	X	X	X (EOT)			
LTS, FH I-II, High FH	X	X	X	X	X	X	X	X	X	X (EOT)	
COMBO II	X	X	X	X	X	X	X	X		X	X (EOT)

a D0: baseline (screening or randomization sample); W76 for Combo II; EOT: End of Treatment

b Also include erythrocyte counts for monitoring of hemoglobin decrease and GGT, LDH for liver tests in phase 3 and in DFI12361
Glucose was only measured as baseline, W6 and W12 in DFI11565, CL-1003, DFI12361 and baseline and W8 in DFI11566

Studies	D0[a]	W4	W8	W12	W24	W52	W78	W104
Hs-CRP								
DFI11566	X	X	X (EOT)					
Other phase 2	X	X	X	X (EOT)				
OPTIONS, MONO	X			X	X (EOT)			
ALTERNATIVE	X				X (EOT)			
COMBO I	X				X	X (EOT)		
LTS11717, FH I-II, High FH	X			X(LTS)	X	X	X (EOT)	
COMBO II	X				X	X		X (EOT)
HbA1C								
DFI11566	X		X (EOT)					
Other phase 2	X	W6		X (EOT)				
OPTIONS, MONO	X			X	X (EOT)			
ALTERNATIVE	X				X (EOT)			
COMBO I	X				X	X (EOT)		
LTS11717, FH I-II, High FH	X			X	X	X	X (EOT)	
COMBO II	X				X	X		X (EOT)

EOT: End of Treatment
a D0: baseline (screening or randomization sample)

Source: NDA 125559 ISS SAP Table 11, 12

7.2.5 Metabolic, Clearance, and Interaction Workup

See the clinical pharmacology review team's evaluation for further details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The following table provides an overview of identified, potential, and theoretical risks associated with alirocumab treatment and the action plans for assessment of these concerns within the phase 3 program. The procedures to evaluate predefined safety concerns were adequate.

Table 74. Overview of alirocumab safety concerns and action plan

Risk description *	Risk type	Source of data (non-clinical, clinical, literature..)	Action plans for evaluating important safety risks (AESI, specific monitoring, specific study..)	Status (New / Ongoing / Closed)
Immunogenicity	Identified	Nonclinical, Clinical, Literature (mAbs)	Assessment of ADA in phase 3.	Ongoing
Injection site reaction	Identified	Clinical	Assessment in Phase 3 (AESI)	Ongoing
Hypersensitivity	Potential	Clinical, Literature (biologics)	Assessment in Phase 3 (AESI, correlation with ADA titers)	Ongoing
Myelin-sheath – related disorders including optic neuropathy / Neuropathy	Theoretical	Preclinical (questionable) Clinical (3 SUSARs)	Assessment in Phase 3 (AESI) Ophthalmologic substudy in LTS11717	Ongoing
Neurocognitive disorders / aggravation of Alzheimer's disease	Potential	Health Authority (based on clinical data from competitor), Literature	Assessment in Phase 3 (specific AE evaluation)	New (Feb 2014) / ongoing
Increased incidence of cancers incl. colorectal cancers	Theoretical	Literature	Assessment in Phase 3.	Ongoing
Impairment of gonadal and adrenal steroidogenesis	Theoretical	Preclinical (questionable), Literature	Assessment in Phase 3. Laboratory Measures in LTS11717	Ongoing
Immunomodulation and increased risk of infections	Theoretical	Literature, Clinical (nasopharyngitis)	Assessment in Phase 3	Ongoing
Increased susceptibility to hepatitis C	Theoretical	Literature, Interaction with Health Authority	Assessment in Phase 3 Specific algorithm (laboratory data)	Ongoing
Predisposition to haemorrhagic stroke	Theoretical	Literature	Assessment in Phase 3	Ongoing
Clinical consequence of liposoluble vitamin deficiency	Theoretical	Literature	Assessment in Phase 3. Laboratory Measures in LTS11717	Ongoing
Hemolytic anemia	Theoretical	Literature	Assessment in Phase 3 (AESI), algorithm for specific examinations in case of serum hemoglobin decrease > 1.5g/dL	Ongoing
Risk description *	**Risk type**	**Source of data (non-clinical, clinical, literature..)**	**Action plans for evaluating important safety risks (AESI, specific monitoring, specific study..)**	**Status (New / Ongoing / Closed)**
Impairment of glucose tolerance/hyperglycaemia	Theoretical	Literature	Assessment in Phase 3	Ongoing
OTHER (statin-induced)				
Elevation of transaminase levels	Identified	Statin Labelling	Assessment in Phase 3	Ongoing
Muscle symptoms (i.e., pain, soreness, weakness, and/or cramps) or signs (myopathy or creatine phosphokinase [CPK] elevations)				

Source: NDA 125559 ISS SAP Table 2

7.3 Major Safety Results

The following is a summary of treatment emergent adverse events (TEAE) within the safety population of placebo-controlled studies (phase 2/3) and ezetimibe-controlled studies (phase 3).

Table 75. Overview of TEAE (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Patients with any TEAE	975 (76.4)	1876 (75.8)	421 (68.1)	607 (70.3)
Patients with any treatment emergent SAE	182 (14.3)	340 (13.7)	69 (11.2)	113 (13.1)
Patients with any TEAE leading to death	11 (0.9)	13 (0.5)	7 (1.1)	2 (0.2)
Patients with any TEAE leading to treatment discontinuation	65 (5.1)	131 (5.3)	60 (9.7)	76 (8.8)

Source: ISS Table 14
Placebo-controlled studies phase 3: LONG TERM, FH I, FH II, HIGH FH, COMBO I; phase 2 DFI11565, DFI 11566, CL-1003, DFI12361
Ezetim be-controlled studies phase 3: COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE

The following table presents the incidence and hazard ratios for TEAEs that were considered adverse events of special interest based on theoretical or non-clinical concerns. Further discussion of these events may be found in subsequent sections.

Table 76. Incidence and HR for treatment emergent AEs of special interest

	Placebo-controlled pool			Ezetimibe-controlled pool		
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	HR (95% CI)[1]	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)	HR (95% CI)
Local injection site reaction TEAE	65 (5.1)	179 (7.2)	1.48 (1.12-1.97)	13 (2.1)	26 (3.0)	1.58 (0.80-3.09)
General allergic 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)
Neurologic TEAE	45 (3.5)	86 (3.5)	0.98 (0.68-1.41)	15 (2.4)	29 (3.4)	1.43 (0.76-2.69)
Neurocognitive TEAE	9 (0.7)	21 (0.8)	1.18 (0.54-2.58)	6 (1.0)	8 (0.9)	0.94 (0.32-2.74)
Diabetes mellitus/diabetic complication TEAE	49 (3.8)	103 (4.2)	1.07 (0.76-1.50)	22 (3.6)	25 (2.9)	0.71 (0.40-1.26)
Hepatic TEAE	23 (1.8)	61 (2.5)	1.36 (0.84-2.20)	14 (2.3)	16 (1.9)	0.69 (0.34-1.43)
Ophthalmological TEAE	18 (1.4)	44 (1.8)	1.24 (0.72-2.15)	3 (0.5)	7 (0.8)	1.36 (0.35-5.31)
Hemolytic anemia	0	0	NA	0	0	NA

Source: NDA 125559 ISS Appendix 1.4.1.1.1, ISS Table 21, 23, 24, 26, 27, ISS Addendum Table 25 (1 April 2015 SD#25),
[1]HR calculated using a Cox model stratified on the study

7.3.1 Deaths

The analysis of deaths is presented in the following ways:

- Deaths on-study according to adjudication
- TEAEs leading to death according to Investigator's opinion

On-study was defined as time period occurring after the start of the treatment up to the last protocol planned visit of the patient. Patients did not need to be on-treatment to be included in this group.

On-treatment was defined as up to 70 days after last administration of study drug but before the last protocol planned visit.

Post-study defined as occurring after the last planned protocol visit

No patients died in the phase 1 or phase 2 studies.

In the global pool of phase 3 studies, there were a total of 37 on-study deaths: 20 deaths (0.6%) in the alirocumab and 17 deaths (0.9%) in the control group reported on-study. The applicant's definition of on-study was defined as the time period occurring after the start of the treatment up to the last protocol planned visit of the patient. Five of these deaths (all in alirocumab-treated patients) occurred outside the "on-treatment" period which was defined as up to 70 days after administration of study drug but before the last protocol planned visit.

Table 77 summarizes the cause of death as determined by adjudication as of the application's cut-off date of 31 August 2014.

Table 77. Summary of deaths by adjudication (safety population) – pool of phase 3 studies

Primary cause of death as per adjudication	Control N=1792 n (%)	Alirocumab N=3182 n (%)
Death on-study	**17 (0.9)**	**20 (0.6)**
Any cardiovascular	11 (0.6)	15 (0.5)
Acute myocardial infarction	0	4 (0.1)
Cardiovascular hemorrhage	1 (<0.1)	2 (<0.1)
Cardiovascular procedure	1 (<0.1)	1 (<0.1)
Heart failure or cardiogenic shock	1 (<0.1)	1 (<0.1)
Stroke-hemorrhagic	0	1 (<0.1)
Sudden cardiac death	8 (0.4)	6 (0.2)
Any non-cardiovascular	6 (0.3)	4 (0.1)
Accidental	1 (<0.1)	1 (<0.1)
Pancreatic	1 (<0.1)	1 (<0.1)
Pulmonary	2 (0.1)	2 (<0.1)
Suicide	1 (<0.1)	0
Other non-cardiovascular	1 (<0.1)	0
Non-cardiovascular: Infection	1 (<0.1)	0
Non-cardiovascular: Malignant	2 (0.1)	2 (<0.1)
New malignancy	1 (<0.1)	1 (<0.1)
Worsening prior malignancy	1 (<0.1)	1 (<0.1)
Not adjudicated	0	1 (<0.1)

Source: ISS Table 16
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Only the primary cause of death is adjudicated
1. Includes all deaths that occurred after the start of the treatment up to the last protocol planned visit of the patient

Deaths were also evaluated by treatment-emergent adverse events leading to death in the global pool of phase 2 and phase 3 trials. There were a total of 33 deaths: 15 deaths (0.4%) in the alirocumab group and 18 deaths (1.0%) in the control group. The difference in deaths between on-study (n=37) and TEAEs leading to death (n=33) is due to the fact that 5 patients in the on-study group died of events that began more than 70 days after the last administration of study drug but resulted in death before the last protocol planned visit of the patient (which defines the end of the on-study period). In addition, 1 patient (patient ID 011568-840-803-004) in the control group had a TEAE leading to death that occurred after the last protocol planned visit of the patient: the death was included as a TEAE leading to death (Table 78) but not counted in the on-study deaths (Table 77). The highest incidence of deaths occurred in the cardiac disorders system organ class (SOC) and general disorders SOC which was mainly due to sudden death or sudden cardiac death.

Table 78. Number (%) of patients with TEAE(s) leading to death by primary SOC and PT (safety population) – global pool (phase 2/3 studies)

Primary SOC Preferred term	Control N=1894 n (%)	Alirocumab N=3340 n (%)
Any class	**18 (1.0)**	**15 (0.4)**
Cardiac disorders	**6 (0.3)**	**7 (0.2)**
Acute myocardial infarction	1 (<0.1)	3 (0.1)
Cardiac arrest	1 (<0.1)	1 (<0.1)
Cardiac failure	0	1 (<0.1)
Coronary artery disease	1 (<0.1)	1 (<0.1)
Myocardial infarction	1 (<0.1)	1 (<0.1)
Angina pectoris	1 (<0.1)	0
Atrial fibrillation	1 (<0.1)	0
Cardiogenic shock	1 (<0.1)	0
Defect conduction intraventricular	1 (<0.1)	0
Ventricular fibrillation	1 (<0.1)	0
Ventricular tachycardia	1 (<0.1)	0
General disorders and administration site conditions	**6 (0.3)**	**2 (<0.1)**
Multi-organ failure	2 (0.1)	1 (<0.1)
Sudden cardiac death	2 (0.1)	1 (<0.1)
Death	1 (<0.1)	0
Sudden death	1 (<0.1)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	**4 (0.2)**	**3 (<0.1)**
Metastatic lymphoma	0	1 (<0.1)
Non-small cell lung cancer metastatic	0	1 (<0.1)
Pancreatic carcinoma metastatic	0	1 (<0.1)
Acute myeloid leukemia	1 (<0.1)	0
Lung neoplasm malignant	1 (<0.1)	0
Esophageal adenocarcinoma metastatic	1 (<0.1)	0
Pancreatic carcinoma	1 (<0.1)	0

Primary SOC / Preferred term	Control N=1894 n (%)	Alirocumab N=3340 n (%)
Vascular disorders	**1 (<0.1)**	**3 (<0.1)**
Aortic aneurysm rupture	0	1 (<0.1)
Aortic dissection	0	1 (<0.1)
Thrombosis	0	1 (<0.1)
Peripheral ischemia	1 (<0.1)	0
Injury, poisoning, and procedure complications	**1 (<0.1)**	**2 (<0.1)**
Fall	0	1 (<0.1)
Traumatic intracranial hemorrhage	0	1 (<0.1)
Subdural hematoma	1 (<0.1)	0
Respiratory, thoracic, and mediastinal disorders	**2 (0.1)**	**1 (<0.1)**
Pulmonary embolism	0	1 (<0.1)
Acute respiratory distress syndrome	1 (<0.1)	0
Pulmonary edema	1 (<0.1)	0
Nervous system disorders	**1 (<0.1)**	**1 (<0.1)**
Hemorrhagic stroke	0	1 (<0.1)
Dementia	1 (<0.1)	0
Psychiatric disorders	**1 (<0.1)**	**0**
Completed suicide	1 (<0.1)	0
Infections and infestations	**1 (<0.1)**	**0**
Neutropenic sepsis	1 (<0.1)	0

Source: ISS Table 17
Placebo-controlled trials: phase 3: (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled trials phase 3: (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

A breakdown of the 33 TEAEs leading to death is shown in the table below by study.

Table 79. TEAEs leading to death stratified by study (safety population) - global pool (phase 2/3 studies)

	Control n/N (%)	Alirocumab n/N (%)
Placebo-controlled studies	11/1276 (0.9)	13/2476 (0.5)
LONG-TERM	8/788 (1.0)	7/1550 (0.5)
FH I	0/163 (0)	4/322 (1.2)
FH II	0/81 (0)	0/167 (0)
HIGH FH	0/35 (0)	0/72 (0)
COMBO I	3/107 (2.8)	2/207 (1.0)
DFI 11565	0/31 (0)	0/31 (0)
DFI 11566	0/31 (0)	0/61 (0)
CL-1003	0/15 (0)	0/16 (0)
DFI 12361	0/25 (0)	0/50 (0)
Ezetimibe-controlled studies	7/618 (1.1)	2/864 (0.2)
COMBO II	4/241 (1.7)	2/479 (0.4)
MONO	0/51 (0)	0/52 (0)
OPTIONS I	2/101 (2.0)	0/104 (0)
OPTIONS II	1/101 (1.0)	0/103 (0)
ALTERNATIVE	0/124 (0)	0/126 (0)

Source: NDA 125559 ISS Table 18

Narratives of alirocumab-treated patient deaths are provided in the Appendix. Review of deaths in patients treated with alirocumab did not strongly suggest a causal relationship between alirocumab and the fatal event.

7.3.2 Nonfatal Serious Adverse Events

Within the placebo-controlled pool, 13.5% of alirocumab-treated patients versus 13.7% of placebo-treated patients reported a non-fatal serious adverse event (SAE). When including cases leading to death, the incidence was 13.7% in the alirocumab group and 14.3% in the placebo group. In the ezetimibe-controlled pool, 13.0% of alirocumab-treated patients versus 10.4% of ezetimibe-treated patients reported a non-fatal SAE. When including fatal SAEs, the incidence was 13.1% in the alirocumab group and 11.2% in the ezetimibe-treated group.

Table 80. Fatal and non-fatal treatment-emergent SAEs (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

System organ class	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Total	**182 (14.3)**	**340 (13.7)**	**69 (11.2)**	**113 (13.1)**
Cardiac disorders	58 (4.5)	109 (4.4)	25 (4.0)	48 (5.6)
Nervous system disorders	19 (1.5)	47 (1.9)	10 (1.6)	15 (1.7)
Infections and infestations	26 (2.0)	44 (1.8)	7 (1.1)	23 (2.7)
Neoplasms	24 (1.9)	35 (1.4)	5 (0.8)	10 (1.2)
Musculoskeletal and connective disorders	19 (1.5)	33 (1.3)	4 (0.6)	5 (0.6)
Injury, poisoning, and procedural complications	17 (1.3)	27 (1.1)	4 (0.6)	13 (1.5)
Gastrointestinal disorders	18 (1.4)	22 (0.9)	4 (0.6)	13 (1.5)
Respiratory, thoracic, and mediastinal disorders	14 (1.1)	22 (0.9)	2 (0.3)	5 (0.6)
General disorders and administration site conditions	11 (0.9)	19 (0.8)	8 (1.3)	5 (0.6)
Renal and urinary disorders	8 (0.6)	15 (0.6)	3 (0.5)	2 (0.2)
Vascular disorders	11 (0.9)	16 (0.6)	4 (0.6)	4 (0.5)
Metabolism and nutrition disorders	8 (0.6)	12 (0.5)	0	0
Psychiatric disorders	7 (0.5)	8 (0.3)	5 (0.8)	2 (0.2)
Eye disorders	5 (0.4)	7 (0.3)	1 (0.2)	2 (0.2)
Hepatobiliary disorders	5 (0.4)	8 (0.3)	1 (0.2)	1 (0.1)
Investigations	1 (<0.1)	7 (0.3)	0	1 (0.1)
Reproductive system and breast disorders	1 (<0.1)	4 (0.2)	0	1 (0.1)
Blood and lymphatic system	1 (<0.1)	2 (<0.1)	2 (0.3)	1 (0.1)
Immune system disorders	2 (0.2)	2 (<0.1)	1 (0.2)	1 (0.1)
Endocrine disorders	0	1 (<0.1)	0	1 (0.1)
Ear and labyrinth disorders	2 (0.2)	1 (<0.1)	1 (0.2)	0
Skin and subcutaneous disorders	0	2 (<0.1)	1 (0.2)	0
Social circumstances	0	1 (<0.1)	0	0
Pregnancy, puerperium, and perinatal conditions	1 (<0.1)	0	0	0
Congenital, familial, and genetic disorders	2 (0.2)	0	0	0

Source: ISS Table 41

Placebo-controlled pool
With the exception of the SOCs of Nervous system disorders, Investigations, and Reproductive system and breast disorders, Skin and subcutaneous tissue disorders, Endocrine disorders, and Social circumstances, the proportion of SAEs occurring in the alirocumab treatment group was the same or slightly lower than the proportion occurring in the placebo treatment group. As would be expected given the patient population at increased cardiovascular risk, the SOC of cardiac disorders had the highest proportion of patients with an event. The SAEs by preferred term within the cardiac disorders SOC that occurred with higher incidence in the alirocumab group versus placebo group (incidence ≥0.5%) were unstable angina (1.0% alirocumab versus 0.7% placebo), angina pectoris (0.6% versus 0.5%), and coronary artery disease (0.6% versus 0.2%). However, several preferred terms with the Cardiac disorders SOC also had an incidence ≥0.5% but favored the alirocumab group: acute myocardial infarction (0.5% alirocumab versus 0.9% placebo), atrial fibrillation (0.4% versus 0.7%), and acute coronary syndrome (<0.1% versus 0.5%).

Within the SOC of Nervous System disorders in the placebo-controlled pool the majority of the events were related to stroke or syncopal events. There were 11 patients (0.4%) reporting syncopal events in the alirocumab group versus 7 (0.5%) in the placebo group. There were several alirocumab-treated patients reporting stroke-related events that were not reported in the placebo-treated group. These preferred terms were cerebrovascular accident (n=5 alirocumab), transient ischemic attack (n=5 alirocumab), hemorrhagic stroke (n=2 alirocumab), lacunar infarction (n=2 alirocumab), brain stem infarction (n=1 alirocumab), cerebellar infarction (n=1 alirocumab). Fatal and non-fatal ischemic stroke events would have been triggered for adjudication and are included in the post-hoc assessment of major adverse cardiovascular events. Adjudicated ischemic stroke was observed in 3 (0.2%) control-treated patients and 12 (0.4%) alirocumab-treated patients.

Seven patients (0.3%) treated with alirocumab versus 1 patient (<0.1%) treated with placebo experienced a SAE within the Investigations SOC. The majority (n=3) were ALT elevations. One of the cases of 'ALT increase' occurred in a 36-year-old white male (patient ID 011717-380-001-003), with a history of elevations in liver enzymes and fatty liver who demonstrated several episodes of elevated ALT during alirocumab treatment. Peak ALT was 233 (5.4x ULN) and AST 162 (4.5x ULN), alkaline phosphatase and bilirubin were within normal limits. Viral serologies were negative. Liver ultrasound confirmed fatty liver infiltration. Study drug was temporarily interrupted for 5 weeks and liver function tests returned to baseline 4 weeks after discontinuation. After reintroduction of study drug, this patient had five additional episodes of increased ALT (>2x ULN but less or equal to 3x ULN) alternating with ALT values <1.5 ULN, no further action regarding the study drug was taken, and the patient completed the study. New information provided by the applicant states this event was downgraded to non-serious by the investigator.

Within the Reproductive system/breast disorders SOC, 4 alirocumab versus 1 placebo patient reported a SAE. No preferred term occurred in more than 1 patient.

There were 2 serious adverse events reported in the Skin/subcutaneous tissue SOC (allergic dermatitis and nummular eczema) which ocurred in alirocumab-treated patients. No SAEs in this SOC were reported for placebo-treated patients.

Ezetimibe-controlled pool
The SOCs which had a higher proportion of alirocumab-treated patients reporting a SAE compared to placebo-treated patients included Cardiac disorders (5.6% versus 4.0%), Infections and infestations (2.7% versus 1.1%), Gastrointestinal disorders (1.5% versus 0.6%), Neoplasms benign, malignant and unspecified (1.2% versus 0.8%), Injury, poisoning, and procedural complications (1.5% versus 0.6%), Nervous system disorders (1.7% versus 1.6%), and Respiratory disorders (0.6% versus 0.5%).

The Cardiac disorders SOC had the highest incidence of patients reporting events overall. Alirocumab-treated patients had higher incidence of unstable angina (n=12; 1.4%) versus ezetimibe-treated patients (n=2; 0.3%). Similarly, in the placebo-control pool, more alirocumab-treated patients (n=25, 1.0%) reported unstable angina than placebo-treated patients (n=9, 0.7%). Acute MI also occurred with greater incidence in the alirocumab group (n=11; 1.3%) compared to the ezetimibe group (n=3; 0.5%). This imbalance was not observed in the placebo-controlled pool (0.5% alirocumab versus 0.9% placebo).

The difference in the Infections and infestations SOC was primarily due to pneumonia, which was reported in 7 (0.8%) patients in the alirocumab group versus 2 (0.3%) in the ezetimibe group. This imbalance was not observed in the placebo-control pool [pneumonia 6 (0.2%) alirocumab, 6 (0.5) placebo]. Diverticulitis occurred in 3 (0.3%) alirocumab-treated patients versus none in the ezetimibe-treated group, this imbalance was also seen in the placebo-control pool [4 (0.2%) alirocumab-treated patients versus none in the placebo-treated group].

Gastrointestinal disorders were observed in a higher proportion of alirocumab-treated patients versus ezetimibe-treated patients. The majority of the events were gastric ulcer hemorrhage which occurred in 3 (0.3%) alirocumab-treated patients versus 0 ezetimibe-treated patients; other events occurring in more than 1 patient (all alirocumab-treated) were hemorrhoids (n=2; 0.2%) and vomiting (n=2; 0.2%).

Neoplasms occurred in a higher proportion of alirocumab (1.2%) versus ezetimibe-treated patients (0.6%). The serious neoplastic events that occurred in greater than 1 patient included prostate cancer [3 (0.3%) alirocumab-treated patients, no ezetimibe-treated patients] and malignant melanoma [2 (0.2%) alirocumab-treated patients, no ezetimibe-treated patients]. In the pool of placebo-controlled studies there was a lower

incidence of serious neoplasms in the alirocumab-treated (1.4%) compared to placebo-treated (1.9%). Overall, there was no specific increased incidence at any specific site.

In the Injury, poisoning, and procedural complications, the only preferred term occurring in more than 1 patient was hip fracture (n=2, 0.2% all alirocumab-treated).

Selected SAEs of interest
Within the placebo and ezetimibe phase 2/3 safety pools there were four suicide attempts: 3 occurring in alirocumab-treated patients, and 1 occurring in a placebo-treated patient. There was one completed suicide in a placebo-treated patient. The 3 cases the alirocumab-treated patients attempting suicide experienced a situational trigger or had a history of depression including one patient with a previous suicide attempt. None of the patients reported treatment with anti-depressant medication at the time of the event, including the patient completing suicide.

Table 81. Narratives of suicide attempt/completed suicide events: pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	AE verbatim term	AE preferred term	Action taken with study drug/ Outcome	Summary
11569-643-929-016 COMBO II Ezetim be Russia	61/W/M	Completed suicide	Completed suicide	None/Death	On Day 367 of the study (b) (6), reported event as completed suicide. Per investigator, patient complained to his wife of depression and unwillingness to live due to the severity of his coronary artery disease. The patient did not complain to investigators of depression during site visits, but he did report moderate anxiety/depression and severe anxiety/depression on EQ-5D questionnaire (quality of life survey) at his last visit. No antidepressant medication started.

11717-250-009-005 LONG TERM Placebo France	51/W/M	Suicide attempt-the patient cut his wrists	Suicide attempt	None/Recovered	Approx 13 months after starting placebo (Sept 2013), patient with no history of depression, reported suicidal depression. No psychosocial stressor provided. Patient given alprazolam as treatment. Two months later (Day 469, patient cut wrists and overdosed on alprazolam and tetrazapam. Patient was hospitalized and treated and discharged. Patient completed study.
11568-840-811-017 COMBO I Alirocumab 150 mg Q2W USA	52/W/F	Suicide attempt	Suicide attempt	Drug discontinued/ Recovered	Day 163 of study, and 8 days after uptitration to 150 mg alirocumab, patient attended wedding, drank too much alcohol, became depressed and overdosed on alprazolam. Unspecified corrective treatment given. Study drug discontinued.
11717-724-001-001 LONG TERM Alirocumab 150 mg Q2W Spain	72/W/F	Suicide attempt	Suicide attempt	Drug discontinued/ Recovered	Patient with a history of anxious depressive syndrome and previous suicide attempt, on Day 169 of study, had an intentional overdose of propranolol, rosuvastatin and ezetimibe as a suicide attempt. She was hospitalized and treated. She had not been on antidepressants or receiving counseling at the time of the event.
11717-840-075-011 LONG TERM Alirocumab 150 mg Q2W USA	69/W/F	Suicide attempt	Suicide attempt	None/recovered	Day 56 of study, the patient with a history of chronic depression, attempted suicide by intentional overdose of 15 Percocet 5/325 mg tablets. Unspecified corrective treatment was provided. Dose of study drug was unchanged, patient continued in study. Patient receiving counselling.

Source: LONG TERM, COMBO I, COMBO II CSR SAE narratives

Intracranial hemorrhagic events (fatal and non-fatal)

Based on epidemiological observations of an association between low LDL-C levels and intracerebral hemorrhage there has been concern that pharmacological reduction of

LDL-C may increase risk of hemorrhagic stroke.[53] Although, post-hoc analysis of large statin cardiovascular outcome trials[54,55] and meta-analyses of statin trials[56,57] have not confirmed a causal relationship between low LDL-C levels and increased bleeding risk, an examination of reports of intracranial hemorrhage in the alirocumab development program by the application cut-off date was performed to evaluate this theoretical safety concern.

Adverse events of intracranial hemorrhage were selected based on standard MedDRA query 'Haemorrhagic cerebrovascular conditions' and include 12 patients with treatment-emergent AEs (Table 82). Of the nine patients treated with alirocumab with an event, 2 were adjudicated as a cerebral hemorrhage. The remaining cases, including patients who received placebo or ezetimibe, were either adjudicated as "ischemic stroke" or "no stroke".

Table 82. Fatal and non-fatal TEAEs coded under SMQ "Hemorrhagic cerebrovascular conditions" (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Standardized MedDRA Query / Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Hemorrhagic cerebrovascular conditions (SMQ)	**1 (<0.1)**	**8 (0.3)**	**2 (0.3)**	**1 (0.1)**
Cerebrovascular accident[1]	0	6 (0.2)	0	1 (0.1)
Hemorrhagic stroke	0	2 (<0.1)	1 (0.2)	0
Cerebral hemorrhage	1 (<0.1)	0	1 (0.2)	0
Subarachnoid hemorrhage	0	0	1 (0.2)	0
Subdural hematoma	0	0	1 (0.2)	0

Source: Response FDA information request 9 February 2015, Table 1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361) Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Non-hemorrhagic events

In the post-treatment period (defined as occurring greater than 70 days after last dose of study drug) there were 2 additional alirocumab-treated patients with intracerebral hemorrhages (fatal hemorrhagic stroke occurred 374 days after last study drug injection and basal ganglia hemorrhage occurring 309 days after last study drug injection).

53 Noda H et al. Low-Density Lipoprotein Cholesterol Concentrations and Death Due to Intraparenchymal Hemorrhage: The Ibaraki Prefectural Health Study. Circulation. 2009;119:2136-2145
54 Goldstein LB et al. Secondary analysis of hemorrhagic stroke in the Stroke Prevention by aggressive Reduction in Cholesterol Levels (SPARCL) study. Neurology. 2008;70:2364-2370
55 Everett BM et al. Safety profile of subjects treated to very low low-density lipoprotein cholesterol levels (<30 mg/dL) with rosuvastatin 20 mg daily (from JUPITER). Am J Cardiol. 2014;114(11):1682-9
56 Hacam DG et al. Statins and intracerebral hemorrhage: collaborative systematic review and meta-analysis. Circulation.2011;124:2233-2242
57 McKinney JS et al. Statin therapy and the risk of intracerebral hemorrhage: a meta-analysis of 31 randomized controlled trials. Stroke. 2012;43:214902156

Summaries of patients with an event under SMQ 'Hemorrhagic cerebrovascular conditions' are found in the table below, with the exception of the 7 events coded as "cerebrovascular accident," since hemorrhage was ruled out according to brain CT scan or MRI reports for these events. Where available the calculated LDL-C values for the patients in this table are included. The two alirocumab-treated patients with adjudicated cerebral hemorrhage during the treatment-emergent period had a LDL-C value between 25 and 50 mg/dL closest to the time of the event. The number of cases of intracranial hemorrhage is too few to reliably assess any association of intracerebral hemorrhage with the levels of LDL-C obtained.

Table 83. Treatment-emergent adverse events under the SMQ "Hemorrhagic cerebrovascular conditions"[1] (safety population) – global pool

Pt. ID Study Treatment	Age (y)/ Race/ Sex/	AE verbatim term	AE preferred term	Action taken with study drug/ Outcome	Adjudicated outcome	Summary
Alirocumab-treated						
11717-578-003-016 LONG-TERM Alirocumab 150 mg Q2W	82 W M	Hemorrhagic stroke possibly due to HTN	Hemorrhagic stroke	D/C tx Recovered with sequelae Short term memory loss	Cerebral hemorrhage	Day 95, severe HA, vomiting confusion. Neuro exam hemianopsia, walking difficulties, aphasia. CT left parieto-occipital bleed LDL 88 mg/dL (BL) LDL 29 mg/dL (W8 – Day 57) LDL 31 mg/dL (W12 – Day 82)
11717-840-165-013 LONG-TERM Alirocumab 150 mg Q2W	61 W M	Aortic dissection Hemorrhagic stroke	Hemorrhagic stroke	Fatal	Cerebral hemorrhage	Day 287 patient hospitalized for aortic dissection. Immediate post-op experienced hemorrhagic stroke Patient died 1 wk post-op underlying cause was reported to be type A aortic dissection and repair of aortic dissection LDL 113 mg/dL (BL) LDL 25 mg/dL (W12 – Day 85) LDL 38 mg/dL(W36 –Day 253)
Control-treated						
11717-826-001-010 LONG-TERM Placebo	49 W M	Multiple cerebral hemorrhages Neutropenic sepsis Multi-organ failure Acute myeloid leukemia Tumor lysis syndrome	Cerebral hemorrhage	Fatal	No stroke	On an unknown date in (b) (6) the patient had a new serious adverse event of severe intensity, reported as multiple cerebral hemorrhages. The patient was already hospitalized for acute myeloid leukemia and did not undergo any further procedure to investigate/correct cerebral hemorrhage. Corrective treatment was given, but not further specified. The CEC did not classify this event as a positively adjudicated cardiovascular event. The patient died while hospitalized in ICU for acute myeloid leukemia and neutropenic sepsis

001118-840-487-001 OPTIONS II Ezetim be	62 W M	Subarachnoid hemorrhage Rt. Cerebellar hemorrhagic stroke Hemorrhage within right splenium of corpus callosum	Subarachnoid hemorrhage Hemorrhagic stroke Cerebral hemorrhage	D/C tx Recovered with sequelae	Not an ischemic stroke	Three events occurred on Day 78. This event was not originally submitted for adjudication. Based on the investigator's judgment, the event was viewed as a definitive hemorrhagic event/stroke with no ischemic component and as such did not meet protocol requirement for adjudication at that time. The applicant made several queries to the investigative site requesting submission for adjudication; however, the investigator never sent the case for adjudication. Based on FDA inquiry, this event has been submitted for adjudication. Although the study has been completed and unblinded, no treatment assignment information for this patient has been communicated to the adjudication committee and as such they remained blinded. The adjudication committee determined that this event reported as right cerebellar hemorrhagic stroke by the Investigator did not qualify as an adjudication endpoint of stroke. LDL 92 mg/dL (BL) LDL 78 mg/dL (Day 63) LDL 235 mg/dL (Day 112)
001118-840-870-011 OPTIONS II Ezetim be	71 W M	Subdural hematoma	Subdural hematoma	Fatal	No stroke	On Day 56 of the study the patient with history of warfarin therapy since 1990 had a new serious adverse event of severe intensity, reported as subdural hematoma. On (b) (6), the subject was found unresponsive, and emergency medical services were called. The patient was hospitalized on the same day and underwent a head CT scan revealing clinically significant abnormalities ('subdural hematoma'). Glasgow Coma Scale was 3 on admission. INR was found to be > 18. The patient was known to take warfarin regularly and never had significant issues with elevated levels. The patient did not have any recent head trauma that preceded this incident, history of falls, difficulty with balance, or any recent illness or other significant medical conditions. The final diagnosis was considered to be a 'subdural hematoma'. The patient's family elected comfort care rather than aggressive treatment. LDL 97 mg/dL (BL) LDL 59 mg/dL (Day 23) LDL 55 mg/dL (Day 51)

Source: Response to FDA IR 9 February 2015, Table 3 submitted 4 March 2015 (SD 14) and respective CSR narratives

1. Does not include AEs listed as cerebrovascular accident as these were non-hemorrhagic

Table 84. Post treatment adverse events under SMQ "Hemorrhagic cerebrovascular conditions" (safety population) – global pool

Pt. ID Study Treatment	Age (y)/ Race/ Sex/	AE verbatim term	AE preferred term	Action taken with study drug/ Outcome	Adjudicated outcome	Summary
11717-826-007-103 LONG-TERM Alirocumab 150 mg Q2W	64 W M	Hemorrhagic stroke	Hemorrhagic stroke	Off drug (post-treatment) Fatal	Cerebral hemorrhage	Patient had discontinued alirocumab treatment on Day 76 due to ALT increase. On Day 377, 10 months after last study dose administration, the patient was admitted to hospital with Glasgow coma scale of 12/15 after sudden collapse. On (b) (6) a CT head scan showed 'massive cerebral haemorrhagic stroke at left frontal lobe.' The neurosurgical team reviewed that patient was not suitable for intervention thus no procedures were undertaken. The patient rapidly deteriorated and died on (b) (6)
11717-724-003-010 LONG-TERM Alirocumab 150 mg Q2W	68 W M	Basal ganglia hemorrhage	Basal ganglia hemorrhage	Off drug (post-treatment) Recovered with sequelae	Cerebral hemorrhage	Last day of treatment was Day 128 and onset of event was Day 437

Source: Response to FDA IR 9 February 2015, Table 3 submitted 4 March 2015 (SD 14) and respective CSR narratives

7.3.3 Dropouts and/or Discontinuations

In the placebo-controlled pool, a similar proportion of patients did not complete the study treatment period as per the case report form (CRF) (16.8% placebo; 17.5% alirocumab). Of the patients randomized, 5.5% of alirocumab-treated patients and 5.2% of placebo-treated patients permanently discontinued treatment due to an adverse event. A higher percentage of discontinuation was due to a revised "Other reasons" reported by 214 (8.6%) patients in the alirocumab group and 91 (7.1%) patients in the placebo group. A breakdown of "Other reasons" is provided in the table below. The most common reasons for discontinuations in this category were "other-withdrawal of patient consent" and "other-other". Review of the text recorded with the withdrawals of consent did not reveal safety/tolerability issues. The majority of "other-other" reasons were due to the timing of the final visit.

In the ezetimibe-controlled pool a total of 155 (17.9%) patients in the alirocumab group and 128 (20.6%) patients in the ezetimibe group did not complete the study treatment period (as per the CRF). The most frequently reported reasons for not completing the study treatment period were discontinuations due to AEs, reported by 76 (8.8%) patients in the alirocumab group and 60 (9.7%) in the ezetimibe group, and "Other reasons" reported by 61 (7.1%) patients in the alirocumab group and 54 (8.7%) patients in the ezetimibe group. The largest group of discontinuations in this category was "other-withdrawal of patient consent" and "other-other". Review of the text recorded with the withdrawals of consent did not reveal safety/tolerability issues.

Table 85. Patient disposition (randomized population) – pool of placebo-controlled studies and pool of ezetimibe controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1277 n (%)	Alirocumab N=2482 n (%)	Ezetimibe N=620 n (%)	Alirocumab N=864 n (%)
Randomized but not treated	1 (<0.1)	6 (0.2)	2 (0.3)	0
Randomized and treated	1276 (>99.9)	2476 (99.8)	618 (99.7)	864 (100)
Did not complete the study treatment period (as per CRF)	214 (16.8)	435 (17.5)	128 (20.6)	155 (17.9)
Treatment ongoing	713 (55.8)	1377 (55.5)	206 (33.2)	406 (47.0)
Reason for not completing the study treatment period (as per CRF)	**214**	**435**	**128**	**155**
Adverse event	**66 (5.2)**	**136 (5.5)**	**60 (9.7)**	**76 (8.8)**
Death	**6 (0.5)**	**6 (0.2)**	**6 (1.0)**	**2 (0.2)**
Poor compliance with protocol	**50 (3.9)**	**79 (3.2)**	**14 (2.3)**	**18 (2.1)**
Other reasons	**91 (7.1)**	**214 (8.6)**	**48 (7.7)**	**59 (6.8)**
Physician decision	2 (0.2)	5 (0.2)	3 (0.5)	2 (0.2)
Patient moved	7 (0.5)	25 (1.0)	2 (0.3)	10 (1.2)

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1277 n (%)	Alirocumab N=2482 n (%)	Ezetimibe N=620 n (%)	Alirocumab N=864 n (%)
Patient withdrew consent	37 (2.9)	83 (3.3)	13 (2.1)	14 (1.6)
Related to IMP administration	6 (0.5)	16 (0.6)	2 (0.3)	2 (0.2)
Did not like injections	*3 (0.2)*	*12 (0.5)*	*2 (0.3)*	*2 (0.2)*
Injection too frequent	*3 (0.2)*	*3 (0.1)*	*0*	*0*
Device use not convenient	*1 (<0.1)*	*0*	*0*	*0*
Temperature storage condition	*1 (<0.1)*	*1 (<0.1)*	*0*	*0*
Other	39 (3.1)	85 (3.4)	28 (4.5)	31 (3.6)
Planned treatment duration completed but outside visit window[1]	*23 (1.8)*	*54 (2.2)*	*14 (2.3)*	*17 (2.0)*
At least 1 exclusion criterion finally met	*1 (<0.1)*	*4 (0.2)*	*0*	*2 (0.2)*
Site closure	*6 (0.5)*	*10 (0.4)*	*3 (0.5)*	*4 (0.5)*
Potential lost to follow-up	*2 (0.2)*	*3 (0.1)*	*4 (0.6)*	*4 (0.5)*
Miscellaneous	*7 (0.5)*	*14 (0.6)*	*7 (1.1)*	*4 (0.5)*
Missing	**1 (<0.1)**	**0**	**0**	**0**

Source: Response to FDA IR dated 13 March 2015, Table 3
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Note: Percentages are calculated using the number of patients randomized as denominator.
Only the main reason for stopping treatment was entered in e-CRF
1. Planned treatment duration completed but final visit outside the pre-specified visit window.

Permanent discontinuation of treatment due to a treatment-emergent adverse event

Within the placebo-controlled pool, there were 65 (5.1%) patients in the placebo group and 131 (5.3%) in the alirocumab group permanently discontinuing treatment due to the TEAE (Table 86). Please note the difference of 6 patients discontinuing due to an adverse event between Table 85 and Table 86 is primarily due to when an adverse event occurred (pre-treatment, treatment-emergent, post-treatment). Table 86 includes only treatment-emergent adverse events leading to discontinuation. In the ezetimibe-controlled pool, the overall incidence of discontinuation due to TEAE was 8.8% in the alirocumab and 9.7% in the ezetimibe group.

In the placebo-controlled pool, 10 (0.4%) alirocumab-treated patients compared with zero placebo-treated patients discontinued treatment due adverse events within the Skin and subcutaneous disorders SOC. The most common reported event was pruritus and rash-related events within this SOC. Further descriptions of these events are described in Section 7.3.4 regarding allergic events. In the alirocumab group, the most frequently reported (in at least 3 patients) TEAEs and occurring at a higher incidence than in the placebo group were ALT increased, myalgia, (n=4 [0.2%] each); and anemia, vertigo, and pruritus (n=3 [0.1%] each).

In the ezetimibe-controlled pool, the highest incidences of TEAEs leading to treatment discontinuation were muscle-related with 3.6% and 5.5% of alirocumab and ezetimibe-treated patients, respectively reporting an event. This is primarily a reflection of the

ALTERNATIVE study which enrolled a patient population considered intolerant to statins because of muscle-related symtpoms. In the alirocumab group, the most frequently reported (in at least 3 patients) TEAE and occurring at a higher incidence than in the ezetimibe group was injection site reaction (n=3 [0.3%]).

Table 86. Number (%) of patents with TEAE leading to permanent treatment discontinuation (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Primary SOC / Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Total Discontinuations due to TEAE	**65 (5.1)**	**131 (5.3)**	**60 (9.7)**	**76 (8.8)**
General disorders and administration site conditions	**10 (0.8)**	**17 (0.7)**	**5 (0.8)**	**8 (0.9)**
Injection site reaction	4 (0.3)	5 (0.2)	1 (0.2)	3 (0.3)
Fatigue	4 (0.3)	4 (0.2)	1 (0.2)	2 (0.2)
Malaise	1 (<0.1)	2 (<0.1)	1 (0.2)	0
Non-cardiac chest pain	1 (<0.1)	2 (<0.1)	0	0
Asthenia	0	1 (<0.1)	2 (0.3)	1 (0.1)
Feeling hot	0	1 (<0.1)	0	0
Local swelling	0	1 (<0.1)	0	0
Multi-organ failure	0	1 (<0.1)	0	0
Chest discomfort	0	0	0	2 (0.2)
Injection site pruritus	1 (<0.1)	0	0	0
Edema peripheral	0	0	1 (0.2)	0
Investigations	**6 (0.5)**	**15 (0.6)**	**1 (0.2)**	**6 (0.7)**
ALT increased	1 (<0.1)	4 (0.2)	1 (0.2)	2 (0.2)
Electrocardiogram QT prolonged	1 (<0.1)	2 (<0.1)	0	0
Hepatic enzyme increased	0	2 (<0.1)	0	0
Blood pressure increased	0	1 (<0.1)	0	0
Electrocardiogram ST segment depression	0	1 (<0.1)	0	0
GGT increased	0	1 (<0.1)	0	0
Neutrophil count decreased	0	1 (<0.1)	0	0
Transaminases increased	0	1 (<0.1)	0	2 (0.2)
Weight decreased	0	1 (<0.1)	0	0
White blood cell count increased	0	1 (<0.1)	0	0
AST increased	0	0	0	1 (0.1)
Blood corticotrophin decreased	1 (<0.1)	0	0	0
Blood cortisol decreased	2 (0.2)	0	0	0
Blood creatine phosphokinase increased	2 (0.2)	0	0	1 (0.1)
Hemoglobin decreased	0	0	0	1 (0.1)
Musculoskeletal and connective tissue disorders	**9 (0.7)**	**14 (0.6)**	**34 (5.5)**	**31 (3.6)**
Myalgia	1 (<0.1)	4 (0.2)	23 (3.7)	21 (2.4)

Primary SOC Preferred term	Placebo-controlled pool Placebo N=1276 n (%)	 Alirocumab N=2476 n (%)	Ezetimibe-controlled pool Ezetimibe N=618 n (%)	 Alirocumab N=864 n (%)
Arthralgia	1 (<0.1)	2 (<0.1)	4 (0.6)	2 (0.2)
Muscle spasms	0	2 (<0.1)	2 (0.3)	1 (0.1)
Pain in extremity	1 (<0.1)	2 (<0.1)	2 (0.3)	2 (0.2)
Back pain	3 (0.2)	1 (<0.1)	2 (0.3)	2 (0.2)
Musculoskeletal discomfort	0	1 (<0.1)	1 (0.2)	0
Myositis	0	1 (<0.1)	0	0
Osteopenia	0	1 (<0.1)	0	0
Pain in jaw	0	1 (<0.1)	0	0
Rhabdomyolysis	0	1 (<0.1)	0	0
Arthritis reactive	0	0	1 (0.2)	0
Bone disorder	0	0	0	1 (0.1)
Muscle tightness	0	0	0	1 (0.1)
Muscular weakness	1 (<0.1)	0	3 (0.5)	1 (0.1)
Musculoskeletal chest pain	1 (<0.1)	0	0	0
Musculoskeletal pain	0	0	0	2 (0.2)
Musculoskeletal stiffness	0	0	0	1 (0.1)
Systemic lupus erythematosus	1 (<0.1)	0	0	0
Cardiac disorders	**7 (0.5)**	**12 (0.5)**	**1 (0.2)**	**5 (0.6)**
Acute myocardial infarction	0	2 (<0.1)	0	1 (0.1)
Acute coronary syndrome	0	1 (<0.1)	0	0
Angina unstable	0	1 (<0.1)	0	1 (0.1)
Aortic valve stenosis	1 (<0.1)	1 (<0.1)	0	0
Atrioventricular block	0	1 (<0.1)	0	0
Bradycardia	0	1 (<0.1)	0	0
Cardiac arrest	0	1 (<0.1)	0	1 (0.1)
Cardiac failure	0	1 (<0.1)	0	0
Cardiac failure congestive	1 (<0.1)	1 (<0.1)	0	0
Coronary artery disease	1 (<0.1)	1 (<0.1)	0	0
Myocardial infarction	2 (0.2)	1 (<0.1)	0	0
Palpitations	0	1 (<0.1)	0	0
Supraventricular tachycardia	0	1 (<0.1)	0	1 (0.1)
Atrial fibrillation	2 (0.2)	0	0	2 (0.2)
Atrial flutter	1 (<0.1)	0	1 (0.2)	0
Cardiac aneurysm	1 (<0.1)	0	0	0
Intracardiac thrombus	1 (<0.1)	0	0	0
Ischemic cardiomyopathy	1 (<0.1)	0	0	0
Nodal arrhythmia	1 (<0.1)	0	0	0
Sick sinus syndrome	1 (<0.1)	0	0	0
Gastrointestinal disorders	**9 (0.7)**	**12 (0.5)**	**9 (1.5)**	**5 (0.6)**
Nausea	2 (0.2)	5 (0.2)	2 (0.3)	2 (0.2)
Diarrhea	2 (0.2)	3 (0.1)	1 (0.2)	1 (0.1)
Abdominal discomfort	0	1 (<0.1)	2 (0.3)	1 (0.1)
Abdominal pain	2 (0.2)	1 (<0.1)	1 (0.2)	0
Abdominal pain upper	1 (<0.1)	1 (<0.1)	1 (0.2)	0
Constipation	0	1 (<0.1)	0	1 (<0.1)
Dry mouth	0	1 (<0.1)	0	0
Dyspepsia	0	1 (<0.1)	1 (0.2)	0

Primary SOC / Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Enterocolitis	0	1 (<0.1)	0	0
Pancreatitis relapsing	0	1 (<0.1)	0	0
Vomiting	1 (<0.1)	1 (<0.1)	0	0
Flatulence	0	0	0	1 (0.1)
Gastrointestinal mucocoele	0	0	1 (0.2)	0
Gastroesophageal reflux disease	1 (<0.1)	0	0	0
Nervous system disorders	**7 (0.5)**	**12 (0.5)**	**6 (1.0)**	**10 (1.2)**
Ischemic stroke	0	2 (<0.1)	0	0
Decreased vibratory sense	0	1 (<0.1)	0	0
Dizziness	3 (0.2)	1 (<0.1)	1 (0.2)	2 (0.2)
Hemorrhagic stroke	0	1 (<0.1)	1 (0.2)	0
Headache	2 (0.2)	1 (<0.1)	3 (0.5)	3 (0.3)
Hypoesthesia	0	1 (<0.1)	0	0
Lethargy	0	1 (<0.1)	0	1 (0.1)
Miller Fisher syndrome	0	1 (<0.1)	0	0
Optic neuritis	0	1 (<0.1)	0	0
Polyneuropathy idiopathic progressive	0	1 (<0.1)	0	0
Presyncope	0	1 (<0.1)	0	0
Brain injury	0	0	0	1 (0.1)
Cerebrovascular accident	0	0	0	1 (0.1)
Dementia	2 (0.2)	0	0	0
Disturbance in attention	0	0	1 (0.2)	0
Hypersomnia	0	0	0	1 (0.1)
Myelitis transverse	0	0	0	1 (0.1)
Neuralgia	0	0	0	1 (0.1)
Paraesthesia	1 (<0.1)	0	0	1 (0.1)
Syncope	1 (<0.1)	0	0	1 (0.1)
Transient global amnesia	0	0	1 (0.2)	0
Tremor	1 (<0.1)	0	0	0
Skin and subcutaneous tissue disorders	**0**	**10 (0.4)**	**4 (0.6)**	**4 (0.5)**
Pruritus	0	3 (0.1)	0	0
Angioedema	0	1 (<0.1)	0	0
Drug eruption	0	1 (<0.1)	0	0
Eczema nummular	0	1 (<0.1)	0	0
Hyperhidrosis	0	1 (<0.1)	0	0
Rash	0	1 (<0.1)	1 (0.2)	1 (0.1)
Rash generalized	0	1 (<0.1)	0	0
Rash maculopapular	0	1 (<0.1)	0	0
Dermatitis contact	0	0	0	1 (0.1)
Hypersensitivity vasculitis	0	0	0	1 (0.1)
Pain of skin	0	0	0	1 (0.1)
Psoriasis	0	0	1 (0.2)	0
Skin irritation	0	0	1 (0.2)	0
Urticaria	0	0	1 (0.2)	0
Eye disorders	**1 (<0.1)**	**8 (0.3)**	**1 (0.2)**	**2 (0.2)**

Primary SOC / Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Cararact	0	1 (<0.1)	0	0
Dark circles under eyes	0	1 (<0.1)	0	0
Diplopia	0	1 (<0.1)	0	0
Endocrine ophthalmopathy	0	1 (<0.1)	0	0
Eye pain	0	1 (<0.1)	0	0
Eye pruritus	0	1 (<0.1)	0	0
Vision blurred	0	1 (<0.1)	0	2 (0.2)
Vitreous floaters	0	1 (<0.1)	0	0
Eye irritation	1 (<0.1)	0	0	0
Glaucoma	0	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**8 (0.6)**	**7 (0.3)**	**3 (0.5)**	**1 (0.1)**
B-cell lymphoma	0	1 (<0.1)	0	0
Breast cancer	0	1 (<0.1)	0	0
Metastatic lymphoma	0	1 (<0.1)	0	0
Non-small cell lung cancer metastatic	0	1 (<0.1)	1 (0.2)	0
Pancreatic carcinoma metastatic	0	1 (<0.1)	0	0
Rectal adenocarcinoma	0	1 (<0.1)	0	0
Rectal cancer	0	1 (<0.1)	0	0
Chronic myeloid leukemia	1 (<0.1)	0	0	0
Endometrial cancer	1 (<0.1)	0	0	0
Gastrointestinal stromal tumor	0	0	1 (0.2)	0
Lung adenocarcinoma	0	0	0	1 (0.1)
Lung neoplasm malignant	0	0	1 (0.2)	0
Esophageal adenocarcinoma metastatic	1 (<0.1)	0	0	0
Esophageal carcinoma	1 (<0.1)	0	0	0
Pancreatic carcinoma	1 (<0.1)	0	0	0
Prostate cancer	1 (<0.1)	0	0	0
Prostate cancer recurrent	1 (<0.1)	0	0	0
Squamous cell carcinoma of lung	1 (<0.1)	0	0	0
Renal and urinary disorders	**2 (0.2)**	**8 (0.3)**	**3 (0.5)**	**4 (0.5)**
Hematuria	0	2 (<0.1)	0	0
Renal failure	0	2 (<0.1)	0	1 (0.1)
Nephrolithiasis	0	1 (<0.1)	0	0
Polyuria	0	1 (<0.1)	0	0
Renal failure chronic	0	1(<0.1)	0	1 (0.1)
Renal impairment	0	1 (<0.1)	1 (0.2)	0
Pollakiuria	0	0	1 (0.2)	0
Renal cyst	1 (<0.1)	0	0	2 (0.2)
Renal failure acute	1 (<0.1)	0	0	0
Renal tubular necrosis	0	0	1 (0.2)	0
Psychiatric disorders	**4 (0.3)**	**8 (0.3)**	**3 (0.5)**	**3 (0.3)**
Depressed mood	0	2 (<0.1)	0	0
Depression	1 (<0.1)	2 (<0.1)	0	1 (0.1)
Suicide attempt	0	2 (<0.1)	0	0
Alcohol abuse	1 (<0.1)	1 (<0.1)	0	1 (0.1)

Primary SOC / Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Insomnia	0	1 (<0.1)	1 (0.2)	0
Panic attack	0	1 (<0.1)	0	0
Abnormal dreams	0	0	1 (0.2)	0
Anxiety	1 (<0.1)	0	0	0
Confusional state	0	0	1 (0.2)	0
Mental disorder due to a general medical condition	1 (<0.1)	0	0	0
Nervousness	1 (<0.1)	0	0	0
Sleep disorder	0	0	0	1 (0.1)
Infections and infestations	**2 (0.2)**	**5 (0.2)**	**4 (0.6)**	**2 (0.2)**
Conjunctivitis	0	2 (<0.1)	0	0
Nasopharyngitis	1 (<0.1)	1 (<0.1)	0	0
Osteomyelitis	0	1 (<0.1)	0	0
Vulvovaginal candidiasis	0	1 (<0.1)	0	0
Peritonitis	0	0	1 (0.2)	0
Pneumonia staphylococcal	0	0	1 (0.2)	0
Pulmonary tuberculosis	0	0	0	1 (0.1)
Spinal cord infection	0	0	1 (0.2)	0
Upper respiratory tract infection	0	0	0	1 (0.1)
Urinary tract infection	0	0	1 (0.2)	0
Viral infection	1 (<0.1)	0	0	0
Blood and lymphatic system disorders	**2 (0.2)**	**6 (0.2)**	**0**	**0**
Anemia	0	3 (0.1)	0	0
Neutropenia	1 (<0.1)	2 (<0.1)	0	0
Thrombocytopenia	1 (<0.1)	1 (<0.1)	0	0
Metabolism and nutrition disorders	**0**	**6 (0.2)**	**1 (0.2)**	**0**
Diabetes mellitus	0	2 (<0.1)	0	0
Gout	0	2 (<0.1)	1 (0.2)	0
Dehydration	0	1 (<0.1)	0	0
Hyperuricemia	0	1 (<0.1)	0	0
Vascular disorders	**2 (0.2)**	**5 (0.2)**	**1 (0.2)**	**3 (0.3)**
Aortic dissection	0	1 (<0.1)	0	0
Flushing	0	1 (<0.1)	0	1 (0.1)
Hot flush	0	1 (<0.1)	0	0
Hypertension	0	1 (<0.1)	1 (0.2)	1 (0.1)
Hypotension	0	1 (<0.1)	0	0
Aortic arteriosclerosis	0	0	0	1 (0.1)
Intermittent claudication	1 (<0.1)	0	0	0
Venous insufficiency	1 (<0.1)	0	0	0
Respiratory, thoracic and mediastinal disorders	**2 (0.2)**	**3 (0.1)**	**1 (0.2)**	**3 (0.3)**
Dyspnea	1 (<0.1)	1 (<0.1)	1 (0.2)	1 (0.1)
Interstitial lung disease	0	1 (<0.1)	0	0

Primary SOC Preferred term	Placebo-controlled pool Placebo N=1276 n (%)	 Alirocumab N=2476 n (%)	Ezetimibe-controlled pool Ezetimibe N=618 n (%)	 Alirocumab N=864 n (%)
Pulmonary embolism	0	1 (<0.1)	0	1 (0.1)
Cough	0	0	1 (0.2)	0
Epistaxis	1 (<0.1)	0	0	0
Sneezing	0	0	0	1 (0.1)
Hepatobiliary disorders	**1 (<0.1)**	**3 (0.1)**	**0**	**1 (0.1)**
Cholelithiasis	0	2 (<0.1)	0	0
Hepatitis alcoholic	0	1 (<0.1)	0	0
Hepatic lesion	0	0	0	1 (0.1)
Hepatic steatosis	1 (<0.1)	0	0	0
Injury, poisoning and procedural complications	**1 (<0.1)**	**3 (0.1)**	**0**	**2 (0.2)**
Intentional overdose	0	2 (<0.1)	0	0
Procedural dizziness	0	1 (<0.1)	0	0
Fall	1 (<0.1)	0	0	0
Fibula fracture	0	0	0	1 (0.1)
Joint dislocation	0	0	0	1 (0.1)
Muscle rupture	0	0	0	1 (0.1)
Rib fracture	0	0	0	1 (0.1)
Upper limb fracture	1 (<0.1)	0	0	0
Ear and labyrinth disorders	**1 (<0.1)**	**3 (0.1)**	**1 (0.2)**	**0**
Vertigo	1 (<0.1)	3 (0.1)	1 (0.2)	0
Immune system disorders	**2 (0.2)**	**2 (<0.1)**	**0**	**2 (0.2)**
Hypersensitivity	1 (<0.1)	2 (<0.1)	0	2 (0.2)
Anaphylactic reaction	1 (<0.1)	0	0	0
Endocrine disorders	**1 (<0.1)**	**1 (<0.1)**	**0**	**0**
Addison's disease	0	1 (<0.1)	0	0
Adrenal insufficiency	1 (<0.1)	0	0	0
Pregnancy puerperium and perinatal conditions	**1 (<0.1)**	**0**	**0**	**0**
Pregnancy	1 (<0.1)	0	0	0
Reproductive system and breast disorders	**0**	**0**	**1 (0.2)**	**1 (0.1)**
Erectile dysfunction	0	0	0	1 (0.1)
Gynecomastia	0	0	1 (0.2)	0

Source: ISS Table 42
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

7.3.4 Significant Adverse Events

Local injection site reactions
Local injection site reactions are presented using the global pool of phase 2/3 studies (global pool) as sham injections were used regardless of actual control (placebo or ezetimibe) group.

The proportion of patients reporting a local injection site reaction was higher in patients receiving an alirocumab injection (6.1%) compared to patients receiving a sham injection (4.1%) with a HR 1.5 (95% CI 1.15-1.95).

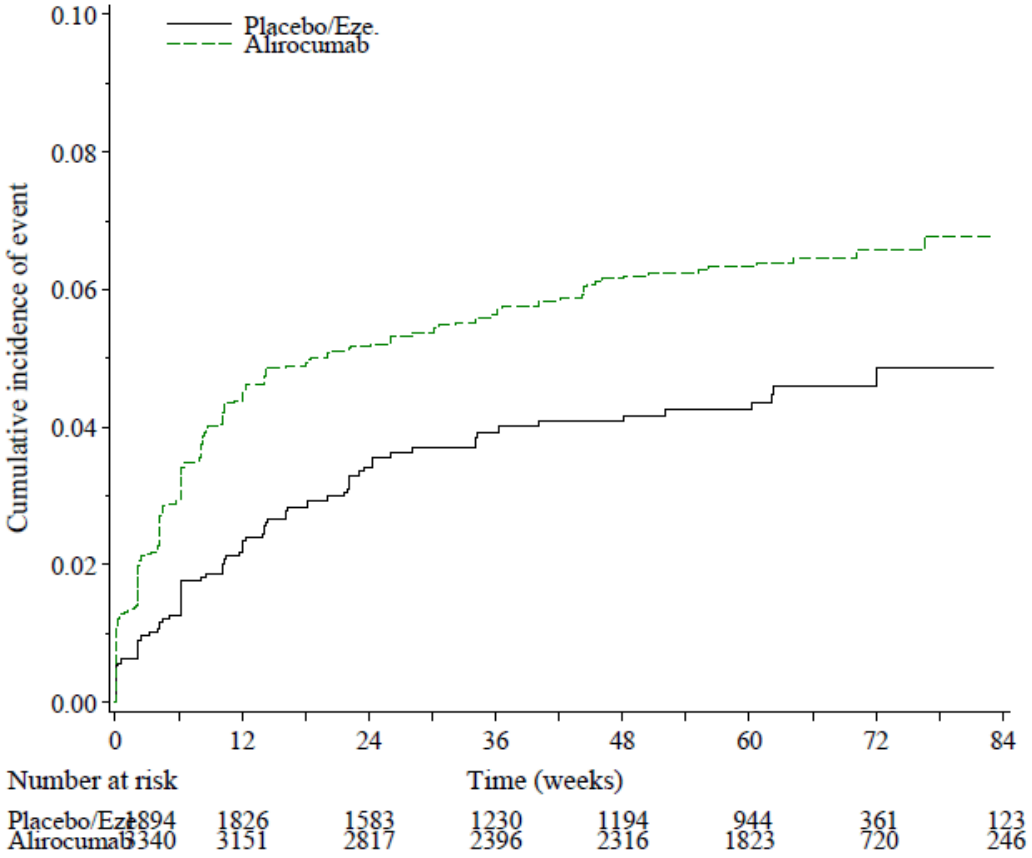
Table 87. Overview of local injection site reactions (safety population) – global pool

Local injection site reaction	Control N=1894 n (%)	Alirocumab N=3340 n (%)	HR[1] (95% CI)
TEAE	78 (4.1)	205 (6.1)	1.50 (1.15 -1.95)
SAE	0	0	
Treatment discontinuation due to TEAE	6 (0.3)	8 (0.2)	

Source: ISS appendix 1.4.1.1.5
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Calculated using a Cox model stratified on the study

The majority of the injection site reactions were mild, however a higher proportion of patients treated with alirocumab reported a moderate reaction (11.2%) compared to patients treated with placebo injections (7.7%). One alirocumab-treated patient reported a severe local injection site reaction. There were no serious local injection site reactions reported.

A higher proportion of alirocumab-treated patients compared to control-treated patients had greater than 1 injection site reaction (36.1% alirocumab versus 19.2% control). Patients treated with alirocumab were more likely to experience an injection site reaction after the first dose (22.0%) compared to control-treated patients (15.4%). The mean duration of local injection site reactions was 11.1 days in control-treated patients compared with 15.2 days in alirocumab-treated patients. Most injection site reactions occurred before 24 weeks of treatment in both groups, with the cumulative probability of an event by Week 24 of 5.2% in the alirocumab group and 3.4% in the control group. Cumulative incidences of injection site reactions at 12, 24, 52, and 78 weeks were higher in the alirocumab treatment group compared to the control group.



Placebo-controlled studies: phase 3 (LTS11717, 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)
Note: Patients are censored at the end of TEAE period (last injection of study treatment + 70 days)
The selection of PTs is based on pre-specified category on AE e-CRF form or HLT 'injection site reaction' depending on the study
Source: ISS Figure 3

Figure 32. Study-adjusted Kaplan-Meier cumulative incidence curve for time to Local injection site reaction events during TEAE period (safety population) – global pool

Symptoms associated with the injection site reaction in the alirocumab and control treated patients in the global pool of phase 3 studies included pain (1.9% alirocumab, 1.3% control), tenderness (1.6% alirocumab; 0.8% control); erythema/redness (3.0% alirocumab, 1.4% control), swelling (2.3% alirocumab, 0.9% control), and itching (2.4% alirocumab, 0.6% control).

There were 14 patients (8 [0.2%] alirocumab, 6 [0.3%] control) who experienced local injection site reactions leading to permanent treatment discontinuation. With one exception where the outcome is unknown, all symptoms associated with the injection reaction resolved.

Among the 147 patients in phase 3 studies with positive treatment-emergent ADA in the alirocumab group local injection site reactions occurred in 10.2% patients compared to 5.9% in patients without treatment-emergent ADA (n = 2886).

Allergic events

In all phase 2 and 3 studies, general allergic events were selected using the standardized MedDRA query "hypersensitivity" (broad + narrow) and excluding preferred terms linked to local injection site reactions such as "injection site dermatitis".

Table 88 summarizes the treatment-emergent general allergic events in the placebo-controlled and ezetimibe-controlled pools. Further description of these categories follows.

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)
Ezetim be-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

Table 89. Number (%) of patients with General allergic TEAEs by CMQ and PT (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
General allergic TEAE				
n (%)	99 (7.8)	213 (8.6)	33 (5.3)	59 (6.8)
# of pts with an event per 100 pt-yrs[1]	7.2	7.9	7.3	8.4
95% CI	5.8 to 8.7	6.9 to 9.0	5.0 to 10.3	6.4 to 10.8
HR (95% CI)[2]	1.10 (0.87 to 1.40)		1.31 (0.85 to 2.02)	

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Hypersensitivity CMQ, n (%)	**99 (7.8)**	**213 (8.6)**	**33 (5.3)**	**59 (6.8)**
Rash	17 (1.3)	30 (1.2)	6 (1.0)	12 (1.4)
Pruritus	5 (0.4)	28 (1.1)	3 (0.5)	7 (0.8)
Seasonal allergy	6 (0.5)	21 (0.8)	3 (0.5)	2 (0.2)
Conjunctivitis	10 (0.8)	20 (0.8)	1 (0.2)	1 (0.1)
Asthma	10 (0.8)	19 (0.8)	1 (0.2)	3 (0.3)
Eczema	8 (0.6)	15 (0.6)	3 (0.5)	5 (0.6)
Dermatitis contact	3 (0.2)	9 (0.4)	1 (0.2)	4 (0.5)
Drug hypersensitivity	1 (<0.1)	8 (0.3)	0	0
Pruritus generalized	4 (0.3)	7 (0.3)	0	2 (0.2)
Rhinitis allergic	7 (0.5)	7 (0.3)	4 (0.6)	4 (0.5)
Urticaria	1 (<0.1)	7 (0.3)	2 (0.3)	3 (0.3)
Conjunctivitis allergic	2 (0.2)	5 (0.2)	0	0
Hypersensitivity	1 (<0.1)	5 (0.2)	1 (0.2)	3 (0.3)
Dermatitis allergic	0	4 (0.2)	1 (0.2)	1 (0.1)
Drug eruption	2 (0.2)	4 (0.2)	0	0
Erythema	4 (0.3)	4 (0.2)	0	1 (0.1)
Flushing	2 (0.2)	4 (0.2)	2 (0.3)	2 (0.3)
Swelling face	0	4 (0.2)	0	0
Pruritus allergic	1 (<0.1)	3 (0.1)	1 (0.2)	0
Sneezing	0	3 (0.1)	0	1 (0.1)
Stomatitis	1 (<0.1)	3 (0.1)	0	0
Angioedema	0	2 (<0.1)	0	1 (0.1)
Bronchospasm	1 (<0.1)	2 (<0.1)	0	1 (0.1)
Dermatitis	4 (0.3)	2 (<0.1)	0	3 (0.3)
Eye swelling	1 (<0.1)	2 (<0.1)	0	0
Photosensitivity reaction	0	2 (<0.1)	0	0
Rash erythematous	0	2 (<0.1)	0	1 (0.1)
Rash generalized	0	2 (<0.1)	0	0
Rash maculo-papular	0	2 (<0.1)	0	0
Wheezing	0	2 (<0.1)	0	1 (0.1)
Allergic bronchitis	0	1 (<0.1)	0	0
Blister	0	1 (<0.1)	0	0
Dermatitis atopic	0	1 (<0.1)	0	1 (0.1)
Eczema nummular	0	1 (<0.1)	0	0
Eyelid edema	0	1 (<0.1)	0	0
Generalized edema	0	1 (<0.1)	1 (0.2)	1 (0.1)
Hand dermatitis	0	1 (<0.1)	0	0
Interstitial lung disease	0	1 (<0.1)	0	0
Laryngospasm	0	1 (<0.1)	0	0
Mouth ulceration	0	1 (<0.1)	0	0
Periorbital edema	0	1 (<0.1)	0	0
Rash macular	1 (<0.1)	1 (<0.1)	0	0
Rash pruritic	4 (0.3)	1 (<0.1)	0	0
Rash pustular	2 (0.2)	1 (<0.1)	0	1 (0.1)
Skin exfoliation	1 (<0.1)	1 (<0.1)	1 (0.2)	0
Skin swelling	0	1 (<0.1)	0	0
Acute respiratory failure	1 (<0.1)	0	1 (0.2)	0
Allergic transfusion reaction	0	0	1 (0.2)	0

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Allergy to chemicals	1 (<0.1)	0	0	0
Anaphylactic reaction	1 (<0.1)	0	0	0
Bronchial hyperreactivity	0	0	0	2 (0.2)
Cytokine release syndrome	1 (<0.1)	0	0	0
Eosinophilia	1 (<0.1)	0	0	0
Hypersensitivity vasculitis	0	0	0	1 (0.1)
Lip edema	1 (<0.1)	0	0	0
Lip swelling	1 (<0.1)	0	1 (0.2)	0
Rhinitis perennial	1 (<0.1)	0	0	0

Source: ISS Table 21
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-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 as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study

Treatment-emergent general allergic (Hypersensitivity CMQ) events

A higher proportion of alirocumab-treated patients (8.6%) compared to placebo-treated patients (7.8%) reported a treatment-emergent allergic event. In the ezetimibe-controlled pool, allergic TEAEs were reported in 59 (6.8%) patients in the alirocumab group and 33 (5.3%) patients in the ezetimibe group.

The most commonly reported preferred term which occurred in more alirocumab-treated patients compared to placebo-treated patients was pruritus at 1.1% and 0.4%, respectively. Other preferred terms occurring at a higher incidence in the alirocumab group than the placebo group (and in ≥0.2% patients) were seasonal allergy, contact dermatitis, drug hypersensitivity, urticaria, hypersensitivity, allergic dermatitis, and face swelling. TEAEs reported with a higher incidence in the alirocumab group compared to the ezetimibe group were rash (1.4% in the alirocumab group versus 1.0% in the ezetimibe group), pruritus (0.8% versus 0.5%), asthma (0.3% versus 0.2%), eczema (0.6% versus 0.5%), hypersensitivity (0.3% versus 0.2%), dermatitis contact (0.5% versus 0.2%), and dermatitis (0.3% versus 0%).

In the pool of placebo-controlled studies, pruritus (not associated with the injection site) was the adverse event with the greatest between-group difference noted [HR: 2.84 (1.10 to 7.36)]. In the 28 alirocumab-treated patients reporting pruritus, none of the events were serious and with the exception of 3 patients, dosing continued. First onset of pruritus was more frequently reported in the first 24 weeks of treatment with alirocumab compared to placebo.

Drug hypersensitivity occurred in 8 (0.3%) alirocumab-treated patients and 1 placebo-treated patient (<0.1%). In all of the events, an allergic reaction to a non-study drug

(mostly antibiotics) was reported and dosing with study drug continued. Only 1 event was classified as serious and is reported below.

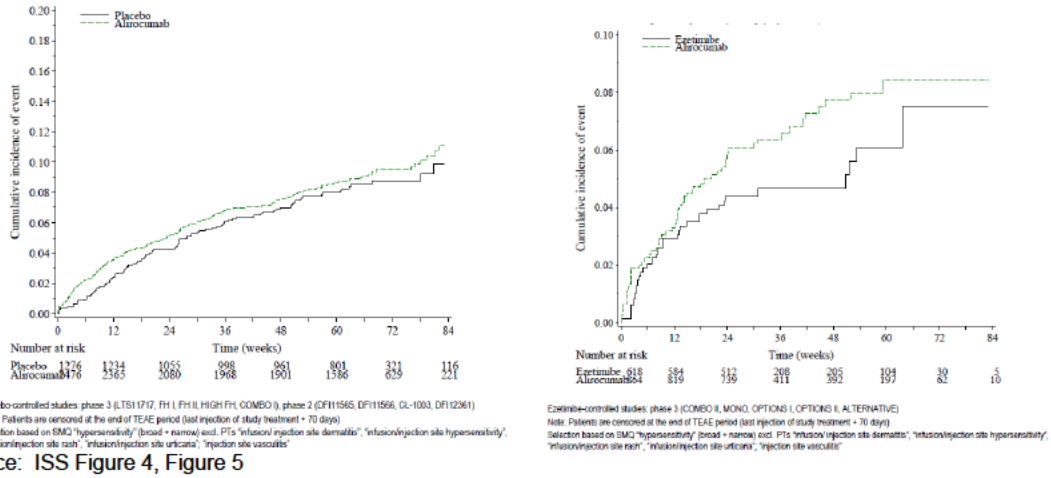
Adverse events coded to the preferred term "hypersensitivity" were reported in 5 (0.2%) and 1 (<0.1%) patient(s) in the alirocumab and the placebo groups, respectively, and 3 (0.3%) and 2 (0.2%) patients in the alirocumab and the ezetimibe groups, respectively. Of the 8 hypersensitivity events in alirocumab-treated patients, 2 were serious events which resulted in treatment discontinuation (patient ID 011717-484-002-003, 011569-208-905-010). Narratives of these events are described below. Two patients with non-serious hypersensitivity events also discontinued treatment with alirocumab (patient ID 011566-840-603-002, 001118-484-850-002).

Angioedema occurred in 3 alirocumab-treated patients and no placebo or ezetimibe-treated patients (see brief summaries below). A fourth case of angioedema associated with hypersensitivity vasculitis occurred in a patient reported in the 4 month safety update report and is described in the section summarizing serious allergic events (patient ID 11717-840-209-003).

- 001119-840-982-001/alirocumab/angioedema: 61 year-old man with a history of food and drug allergies, experienced angioedema on Day 143 while he was hospitalized for a work-up of atrial fibrillation. After ingesting blueberry jam and dosing with sotalol, the patient reported rash, urticaria, and angioedema. Symptoms resolved with treatment (oxygen, Benadryl, steroids). Treatment with alirocumab had been discontinued with his hospitalization for atrial fibrillation. This patient had a positive ADA response on Day 87 (titer 30). No further ADA levels drawn, so it is unknown what the levels were at the time of the event.
- 001112-528-201-008/alirocumab/angioedema: According to the Investigator. "Patient suffered from angioedema, last episode occurred years before participation in the study. After starting IP [investigational product alirocumab] patient had several episodes of spontaneous swelling of different body parts (tongue, lips, feet), swelling resolved spontaneously after several hours, speed of recovery did not seem to be affected by antihistamine use. After discontinuation of IP no more episodes". In total the patient experienced 6 episodes of angioedema, 2 were reported as severe, 1 moderate, 3 mild in intensity. Corrective treatment included desloratidine. The events occurred on Day 2 (right foot), Day 3 (left-sided tongue swelling), Day 7 (right-sided tongue swelling), Day 8 (left foot), Day 9 (right wrist), Day 48 (tongue). The last event, which triggered discontinuation, occurred 3 days after the alirocumab administration. Patient was ADA negative.
- 011717-276-014-006/alirocumab/angioedema: 68 year old man with no personal or family history of allergy, on ramipril since 2005, on day 302 of the study, reported left cheek angioedema of moderate intensity. The patient was treated in the office with dexamethasone and had "very good response to the treatment, with fast relief of his symptoms". No action was taken with alirocumab and the patient recovered without sequelae. Patient was ADA negative.

There were no significant differences in the outcome of general allergic events between treatment groups. The majority of events (80%) recovered.

Cumulative incidences of allergic reactions were higher at 12, 24, 52, and 78 weeks in the alirocumab treatment group compared to the placebo group and ezetimibe group.



Source: ISS Figure 4, Figure 5

Figure 33. Study-adjusted Kaplan-Meier cumulative incidence curve for time to first general allergic event during TEAE period (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

In the pool of placebo-controlled studies, a significant interaction between the treatment groups and the following baseline characteristics/demographics were noted for allergic reactions: medical history of allergy, region, and age. The hazard ratios of the comparison of alirocumab to placebo were higher in patients with a medical history of allergy, aged <65 years or residing in North America (Table 90). There were no interactions noted in the ezetimibe-controlled pool. Any significant treatment interactions in subgroups should be considered hypothesis generating and interpreted with caution.

Table 90. General allergic reactions: HR versus control by baseline characteristics (safety population) – pool of placebo-controlled studies

	Placebo n/N (%)	Alirocumab n/N (%)	HR versus control[1] (95% CI)	Interaction p-value
Age				0.0233
<65 years	55/878 (6.3%)	143/1671 (8.6%)	1.35 (0.99 to 1.85)	
≥65 to 75 years	34/322 (10.6%)	62/642 (9.7%)	0.92 (0.61 to 1.40)	
≥75 years	10/76 (13.2%)	8/163 (4.9%)	0.39 (0.15 to 0.99)	
Medical history of allergy[2]				0.0211
Yes	51/544 (9.4%)	117/914 (12.8%)	1.39 (1.00 to 1.93)	
No	48/630 (7.6%)	85/1404 (6.1%)	0.79 (0.55 to 1.12)	
Region				0.0134
North America	21/426 (4.9%)	81/795 (10.2%)	1.99 (1.23 to 3.23)	
Western Europe	51/467 (10.9%)	86/929 (9.3%)	0.86 (0.61 to 1.22)	
Eastern Europe	13/200 (6.5%)	15/403 (3.7%)	0.59 (0.28 to 1.25)	

	Placebo n/N (%)	Alirocumab n/N (%)	HR versus control[1] (95% CI)	Interaction p-value
Rest of World	14/183 (7.7%)	31/349 (8.9%)	1.14 (0.61 to 2.15)	

Source: ISS Appendix 1.4.1.2.23
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)

1. Hazard ratio calculated using a Cox model stratified on the study in each subgroup. The interaction is tested in a separate Cox model including the study, the subgroup factor term, the treatment and the treatment-by-subgroup interaction
2. Only for phase 3 studies

Serious adverse events –Allergic treatment-emergent adverse events
In the placebo-controlled pool, 9 (0.4%) patients in the alirocumab group and 5 (0.4%) in the placebo group reported serious allergic TEAEs. None of these events led to death.

In the ezetimibe-controlled pool, 1 (0.1%) patient in the alirocumab group and 2 (0.3%) in the placebo group reported a treatment-emergent allergic SAE. One of the ezetimibe-treated patients experienced cytokine release syndrome, secondary to chemotherapy and leukemia, resulting in multi-organ failure and death (patient ID 11717-826-001-010).

The majority of patients experiencing a serious allergic event had a history of allergies or asthma. Four of the alirocumab-treated patients experienced the allergic event within 1 to 9 days of drug administration; 3 of these patients were positive for ADA. Two patients treated with a sham injection experienced an event within hours to 8 days after drug administration. None of the placebo or ezetimibe treated patients were positive for ADA.

During the four-month safety update report (SUR) period, there was one serious report of anaphylaxis requiring intubation in an alirocumab-treated patient at a dose of 300 mg Q4W (patient ID 001308-840-174-018), 1 year and 6 months after the first dose and 11 days after the last dose prior to this event. This patient was rechallenged with a single dose of alirocumab after recovery from the event and did not have signs and symptoms, but treatment was discontinued after this dose. Please note the patient was enrolled in CHOICE I, a study not included in the phase 2/3 studies that contribute to the safety review, but this event is included due to its serious nature. Further details of this event are included in the selected narratives. Also reported in the 4 month SUR, were 5 serious general allergic events from the LONG TERM study in 3 patients treated with alirocumab: 1 patient with leukocytoclastic vasculitis and angioedema, 1 patient with laryngeal edema and rash, and 1 patient with asthma. No serious general allergic event was reported in the placebo group during the 4-month SUR period. These 4 patients are not included in the table below but the events of anaphylaxis (patient ID 001308-840-174-018), laryngeal edema (patient ID 11717-840-190-006), and hypersensitivity vasculitis (patient ID 11717-840-209-003) are included in the selected SAE narratives.

Table 91. Summary of serious allergic treatment emergent adverse events (safety population)

Pt ID	Age/ Sex	Allergy/ Asthma hx	ADA (treatment emergent)	Onset[1] (Study day)	Verbatim term PREFERRED TERM	Outcome
Alirocumab-treated						
11569-208-905-010 COMBO II Alirocumab 75 mg Q2W	60 M	Y	Y	3	Allergic reaction HYPERSENSITIVITY	Hospitalized, corrective treatment – IV methylprednisolone, inhaled epi, antihist, steroids, study tx DC, recovered. Treatment-emergent ADA Day 14 (titer 480). ADA negative by Day 85
12492-710-403-004 FH I Alirocumab 75 mg Q2W	62 F	Y	N	1	Numular exczema NUMMULAR EXCZEMA	Corrective treatment, study tx DC after event became serious on approximately Day 156 , recovered with sequelae (post inflammatory hyperpigmentation)
11568-840-857-005 COMBO I Alirocumab 150 mg Q2W	62 F	N	N	185	Interstitial lung disease INTERSTITIAL LUNG DISEASE	Corrective treatment, study tx DC, not recovered, also diagnosed with rheumatoid arthritis (rheumatoid factor and CCP antibodies positive)
11568-840-853-012 COMBO I Alirocumab 75 mg Q2W	74 M	N	N	152	Asthmatic bronchitis ASTHMA	Hospitalized, corrective treatment, recovered, IMP continued
11568-840-857-010 COMBO I Alirocumab 75 mg Q2W	62 F	Y	N	38	Asthma aggravation ASTHMA	Hospitalized, corrective treatment, recovered, IMP continued
11717-484-002-003 LONG TERM Alirocumab 150 mg Q2W	55 F	Y	Y	1	Upper respiratory tract hypersensitivity reaction – site unspecified HYPERSENSITIVITY	No corrective tx, study tx DC after first dose, recovered within minutes. No respiratory compromise. Treatment emergent ADA Day 34 and 90 (titer 60), negative by Day 174
11717-616-007-032 LONG TERM Alirocumab 150 mg Q2W	63 M	Y	N	194	Allergy to suxamethonium chloride DRUG HYPERSENSITIVITY	No corrective tx, recovered Hospitalized for allergy testing b/c of previous bronchospastic reaction with general anesthesia. Diagnosed with suxamethonium (muscle relaxant) allergy
11717-616-010-024 LONG TERM Alirocumab 150 mg Q2W	63 M	N	N	164	Asthma ASTHMA	Smoker, history of chronic bronchitis, hospitalized for bronchiectasis/ dyspnea. Corrective treatment, recovered
11717-616-013-008 LONG TERM Alirocumab 150 mg Q2W	76 F	N	N	84	Allergic dermatitis-petechiae on lower legs DERMATITIS ALLERGIC	On same day, had moderate grade 2 weakness, hypotonia, fainting episodes, sore throat, generalized itch, flushing, rash with petechiae on lower legs. On Day 99, hospitalized had derm consult for erythema 1 week, swelling face, maculopapular rash. CRP >206 mg/L, tx with steroids, recovered, study tx DC (patient decision)
11717-840-040-009 LONG TERM Alirocumab 150 mg Q2W	49 M	Y	N	144	Asthma exacerbation ASTHMA	History of asthma, hospitalized Corrective treatment, recovered, IMP continued
11565-840-529-013 DFI1165 Alirocumab 300 mg Q4W	57 M	N	Y	9	Leukocytoclastic vasculitis purpura HYPERSENSITIVITY VASCULITIS	Corrective treatment, study tx DC after first dose, recovered Treatment emergent ADA at Week

Pt ID	Age/ Sex	Allergy/ Asthma hx	ADA (treatment emergent)	Onset[1] (Study day)	Verbatim term PREFERRED TERM	Outcome
						20 (titer 30) 2.5 months after event. Negative retest after 6 months
Placebo-treated						
11717-826-001-010 LONG TERM Placebo	49 M	Y	N	337	Cytokine release syndrome CYTOKINE RELEASE SYNDROME	Fatal secondary to leukemia and chemotherapy
11717-840-073-001 LONG TERM Placebo	45 M	Y	N	182	Acute exacerabation of asthma ASTHMA	Corrective treatment, recovered
11717-840-113-013 LONG TERM Placebo	56 F	N	N	548	acute respiratory insufficiency secondary to metabolic acidosis non allergic etiology ACUTE RESPIRATORY FAILURE	Associated with diabetic ketoacidosis, UTI, acute renal failure, Corrective treatment, recovered
12492-840-408-002 FH I Placebo	57 F	Y	N	399	Asthma exacerbation ASTHMA	Corrective treatment, recovered, study drug continued
12732-840-702-002 HIGH FH Placebo	64 M	Y	N	183 (2 hours after last dose)	Anaphylactic reaction to excipient of placebo ANAPHYLACTIC REACTION	Corrective treatment, study drug DC, recovered
Ezetimibe-treated						
001119-376-934-006 ALTERNATIVE Ezetimibe	56 F	Y	N	129	Acute pulmonary sensitivity HYPERSENSITIVITY	Pt had been treated with azithromycin for bronchitis, nitrofurantoin for UTI prior to events. Hospitalized, Corrective treatment, recovered
11569-208-907-011 COMBO II Ezetimibe	50 M	Y	N	23	Urticaria URTICARIA	Corrective treatment (diphenhydramine), Not hospitalized, study tx DC, recovered

Source: ISS, CSR narratives
1. Onset relative to first dose of IMP

Selected SAE narratives

Alirocumab-treated

- 11565-840-529-013/Alirocumab 300 mg Q4W/Hypersensitivity vasculitis: A 57-year-old male patient with medical history of seborrheic keratosis, basal cell carcinoma, without recent vaccinations/illness experienced on Day 9 an episode of diarrhea followed on the same evening by a non-pruritic rash of arms, legs and abdomen without fever. Purpura, petechieae and rash worsened within 24 hours. Oral steroids were started. A biopsy showed on sections of small vessels fibrin in the vessel walls, perivascular neutrophils, neutrophil fragments, red blood cell extravasation. Immunofluorescence staining showed positive fibrinogen staining with negative IgG, IgM, IgA and C3 resulting in diagnosis of leukocytoclastic vasculitis. Recovery occurred on steroid treatment. Immunological / immunohistochemical assessments were performed 6 months later on banked blood samples and additional samples provided by the patient included IgM, IgG, IgE, complement levels, antinuclear antibody (ANA), double - stranded DNA, CRP, and tryptase; all were unremarkable. The event was considered to be related to the IMP by the Investigator. Patient was ADA negative at baseline and at the time of the treatment discontinuation but had a low ADA titer (30) on Week 20 only.

- 11569-208-905-010/Alirocumab/Hypersensitivity: A 60-year-old male patient, with a history of rhinitis allergic, asthma, house dust, food and seasonal allergies, experienced an allergic reaction of moderate intensity on Day 3. The patient was admitted to hospital with erythema, swelling, and itching, with generalized itching and swelling of the hands. Corrective treatment was given and included clemastine fumarate, IV methylprednisolone, inhaled epinephrine, antihistamines, and steroids. The investigational medicinal product (IMP) was permanently discontinued due to this event. The patient recovered on Day 4. Fourteen days after the first and last study injection, the patient's ADA status was found to be positive, ADA concentration was 480 which was considered to be high (>= 240). On Day 85 (b) (6), the patient's ADA status had converted back to negative.
- 11717-484-002-003/Alirocumab/Hypersensitivity: A 55-year old female patient with a medical history of drug hypersensitivity and house dust allergy experienced upper respiratory tract hypersensitivity reaction - site unspecified of mild intensity on Day 1. The patient had an episode of a burning sensation in her trachea immediately after the IMP administration, followed by a feeling of tracheal obstruction, which reached its maximum within 1 minute. The event was considered as a general allergic reaction to the study treatment. No corrective treatment was given. Study treatment was permanently discontinued due to the event, and the patient recovered without sequelae on the same day. No additional follow-up data was available. The Investigator considered the event to be related to the IMP (alirocumab). Preexisting ADA status was negative; a transient ADA positive response was measured at Week 4 (titer: 60) and Week 12 (titer: 60)
- 12492-710-403-004/Alirocumab/Nummular Eczema: On Day 1 of the study (b) (6)), the patient had a new adverse event of moderate intensity, reported as nummular eczema, which became serious Day 160. At the time of the first administration of study drug on Day 1, the patient was noted to have general allergic skin reaction. The patient had generalized itching, flushing, and hives. The Investigator described the eczema as 'raised erythematous patches on the face, waist, and legs, and as a raised puritic rash on the back'. On Day 160, four days after last study drug administration, she was referred to a dermatologist. Examination showed scattered papules on scalp, large scattered nummular plaques on her upper back, no oral or mucosal lesions, large patch on her left cheek, and post inflammatory lesions on her leg and feet. A skin biopsy was not performed. Corrective treatment was given (Chlorphenamine maleate, Topical clobetasol, Topical iralfaris, Glycerin bar, and Acetyl alcohol/propylene glycol/stearyl alcohol). Study treatment was permanently discontinued due to this event. The patient recovered from the event with sequelae (residual post inflammatory hyperpigmentation) on 20-AUG-2013.
- 11717-840-190-006/Alirocumab/Laryngeal edema: A 56-year-old female patient with a history of coronary artery disease, peripheral artery disease, presumed chronic obstructive pulmonary disease, pulmonary hypertension experienced laryngeal edema about 1 year and 3 months (Day 460) after the first IMP administration. The patient presented to the emergency room with choking, swallowing difficulties and stridor and was in acute respiratory distress. The patient thought that she was having a transient ischemic attack not confirmed on the neurological examination and CT (computed tomography)-scan of the brain without contrast. The patient was also diagnosed with non-serious laryngeal edema of non-allergic etiology. CT-scan of the neck without contrast revealed very prominent vascular calcifications and stenosis of the right carotid. On Day 462, magnetic resonance imaging of the head revealed hypoplastic left A1 segment, short segment, stenosis of the A2 segment. Magnetic resonance imaging of the brain and stem was also normal. Antibiotics were administered and steroid dose was tapered as corrective treatment to the patient. The IMP was continued as planned. On Day 511, the event of laryngeal edema - non allergic etiology became serious and the patient presented to the hospital with worsening of choking, swallowing difficulty and stridor. A CT angiogram of neck revealed asymmetric thickening and slight deviation of the aryepiglottic folds that significantly narrowed and nearly occluded the subglottic airway at that level. The patient was admitted to the intensive care unit with subglottic edema. The patient was started on antibiotics (moxifloxacin) and corticosteroids as corrective treatment for the event. On Day 512, laryngoscopy showed erythema of the hypopharynx. Two days later a bronchoscopy revealed normal airways and no

subglottic stenosis or edema. The recommendation was to continue moxifloxacin and prednisone taper for a few days. No action was taken with the IMP. The patient recovered from the event without sequelae. The Investigator considered the event not to be related to the IMP. The patient received the last dose of IMP on Day 527. On Day 531, about 1 year and 6 months after the first IMP administration and 4 days after the final IMP administration, the patient had a new serious adverse event of moderate intensity, reported as abdominal rash non-allergic etiology (PT: rash). The patient had abdominal redness and itching (a 10 cm rash on the left lower quadrant of her abdomen not at the injection site). The rash had increased in size over the past 3 days. She had a temperature of 99.9°F the previous night and denied chills and night sweats. She also complained of one episode of diarrhea, which was resolved. No dermatologist consultation or biopsy was performed. It was confirmed that the rash was neither an allergic reaction to the study medication nor was associated with it. As a corrective measure, diphenhydramine hydrochloride cream was applied topically. On Day 561, the patient recovered from the event of abdominal rash non-allergic etiology. Patient had negative ADA response throughout the study, including before and after these events.

- 11717-840-209-003/alirocumab/hypersensitivity vasculitis: a 60-year-old male patient with a history of multiple allergies, hepatitis C, angioedema and who was receiving concomitant treatment with aspirin, valsartan, diclofenac, gabapentin and rosuvastatin experienced hypersensitivity vasculitis, and angioedema about 1.5 years after the start of alirocumab treatment and 12 days after the last injection (Week 76) protocol-specified. The patient presented with macular nonpruritic irregular rash spreading from the lower limbs to all over the body, associated with diarrhea, vomiting and slight lethargy. He was hospitalized and a diagnosis of leukocytoclastic vasculitis (PT: hypersensitivity vasculitis) was made. The patient was discharged home on the same day. The diagnosis of leukocytoclastic vasculitis was confirmed on skin biopsy 7 days after the onset of the event. The patient was rehospitalized on the same day for swollen tongue with facial angioedema (PT: angioedema) of severe intensity. Investigations (immune complexes, C1q binding, antinuclear antibody, angiotensin-converting enzyme, anticardiolopin, antimyeloperoxidase, antiphosphatidylserine, complement C3, C4, HBsAg were negative. Corrective treatment included methylprednisolone IV and diphenhydramine, then prednisolone 20 mg/day. The patient recovered from both events. Patient had negative ADA response throughout the study, including before and after these events.
- 001308-840-174-018/alirocumab 300 mg Q4W/anaphylactic reaction: 60 year-old female with a history of adhesive allergy since 1973 and drug allergies (not specified) since 2005, on Day 222 of the study (b) (6), the patient had a new serious adverse event of severe intensity, reported as angioedema (Angioedema) and a serious adverse event of moderate intensity, reported as anaphylaxis reaction (Anaphylactic Reaction). The patient awoke at 04:00 and noticed that half her tongue and the right side of her face was swollen; she took diphenhydramine and ibuprofen and went back to sleep. At 08:00, she awoke again and noticed that both sides of her face were swollen. She took another dose of diphenhydramine hydrochloride and ibuprofen and went to the hospital. She presented to the Emergency Room (ER) on (b) (6) with progressive shortness of breath and swelling. Within 20 minutes of admission, she was taken to the intensive care unit (ICU), immediately intubated for airway protection, and treated with IV methylprednisolone. She was later weaned from the ventilator and remained on bronchodilators (Combivent), steroids (methylprednisolone, prednisone), and antihistamines (cetirizine, diphenhydramine). The Investigator described the patient's symptoms as: 'generalized itch and flushing, swelling of the lips, face and tongue, pharyngeal signs and symptoms (hard to swallow) and laryngeal signs and symptoms (hoarseness and change in pitch of voice)'. Vital signs included a BP of 153/86 mmHg, respiratory rate of 20 breaths per minute, oxygen saturation of 99%, body temperature of 36.8°C, and heart rate in the 90s beats per minute range (normal range not provided). The patient also developed an erythematous maculopapular rash along the trunk. Allergy/immunology was consulted for further evaluation. There was a question of antigen-antibody complex disease/serum sickness. The patient was diagnosed with "angioedema likely secondary to ACE inhibitors (versus questionable unknown drug), anaphylactic reaction with

respiratory failure". Of note, there was no clear temporal relationship with the IMP since the event occurred 11 days after the last injection [redacted]. The patient was on benazepril since June 2012 and this medication was discontinued on [redacted] The patient was also discontinued from bisoprolol, which was started in May 2013; the patient was subsequently initiated on amlodipine and hydrochlorothiazide. The rash along her trunk was pleuritic, improved with cetirizine, and continued to improve during her hospital stay. The Investigator described the event as 'tongue and faced swollen, anaphylaxis, rash developed while in hospital [redacted] which is still present, currently being treated by allergist'. The patient was discharged on [redacted]. The patient recovered from the event without sequelae on [redacted] **The patient was re-challenged with IMP on 23-AUG-2014 without any associated signs or symptoms,** but the IMP was still permanently discontinued (last dose: 23-AUG-2014).

Placebo-treated

- 12732-840-702-002/Placebo/Anaphylactic reaction: A 64-year-old male patient with a medical history of drug (niacin) hypersensitivity, food allergy and rash, experienced an anaphylactic reaction to excipient of the study drug of severe intensity on Day 183. The symptoms began 2 hours after taking the last dose of study drug. The patient reported a feeling of itchiness, noted hives on the face quickly spreading to the trunk and ankles, and then developed nausea twice. The patient had syncope several times lasting approximately 1 minute each and each episode was followed by emesis. The patient reported feeling clammy, having shortness of breath with wheezing and his wife called Emergency Medical Service (EMS). Upon arrival of the EMS his oxygen saturation was less than 90%. In the emergency room the patient had cool and clammy skin with hot/sweaty episodes. He had no fever (36.4 degrees Celsius) and vital signs were normal. The patient returned to baseline quickly without residual deficits, no incontinence or injury. The patient was unblinded. Corrective treatment was given and included prednisone, oxygen supplementation, IV diphenhydramine, methylprednisolone, nebulizers, and IV fluids. The IMP was permanently discontinued. All symptoms except for general weakness and hot/sweaty episodes resolved on Day 184. The patient fully recovered from the event without sequelae on Day 201. The patient received corrective treatment and recovered. The event was considered by the Investigator to be related to the excipient.

Ezetimbe-treated

- 001119-376-934-006/Ezetimibe/hypersensitivity: 56-year-old female patient, with a history of drug allergies and allergy to vaccine, experienced acute pulmonary sensitivity reaction (PT: hypersensitivity) of severe intensity with ezetimibe on Day 129. The patient fully recovered with corrective treatment (antibiotics, diuretic). No action was taken with the IMP.
- 011569-208-907-011/Ezetimibe/Urticaria: A 50-year-old male patient, with a history of perfume and washing powder allergies, drug allergies, and family history of asthma, experienced urticaria of severe intensity on Day 23. The patient did not show any local signs or symptoms, but did develop cutaneous signs and symptoms (hives) on his entire body and respiratory signs and symptoms (cough). He was not seen by a dermatologist and was not hospitalized. Corrective treatment was given and included diphenhydramine hydrochloride. The IMP was permanently discontinued. The patient recovered from the event without sequelae on Day 32.

Discontinuations due to allergic events

A greater percentage of patients treated with alirocumab (n=21; 0.6%) permanently discontinued treatment due to an allergic event compared to patients treated with placebo or ezetimibe (n=4; 0.2%). Of the 14 (0.6%) alirocumab-treated patients in the placebo-controlled pool discontinuing treatment, 3 were reported as not recovered/resolved, and 1 was recovered with sequelae. Of the 7 patients (0.8%) treated with alirocumab in the ezetimibe-controlled pool, all patients had recovered or

were recovering from the event. All four control-treated patients recovered from the allergic event.

Table 92. Number (%) of patients with TEAE(s) leading to permanent treatment discontinuation (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
Primary System Organ Class Preferred Term n(%)	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any class	2 (0.2%)	14 (0.6%)	2 (0.3%)	7 (0.8%)
Infections and infestations	0	2 (<0.1%)	0	0
Conjunctivitis	0	2 (<0.1%)	0	0
Immune system disorders	2 (0.2%)	2 (<0.1%)	0	2 (0.2%)
Hypersensitivity	1 (<0.1%)	2 (<0.1%)	0	2 (0.2%)
Anaphylactic reaction	1 (<0.1%)	0	0	0
Vascular disorders	0	1 (<0.1%)	0	1 (0.1%)
Flushing	0	1 (<0.1%)	0	1 (0.1%)
Respiratory, thoracic and mediastinal disorders	0	1 (<0.1%)	0	1 (0.1%)
Interstitial lung disease	0	1 (<0.1%)	0	0
Sneezing	0	0	0	1 (0.1%)
Skin and subcutaneous tissue disorders	0	9 (0.4%)	2 (0.3%)	3 (0.3%)
Pruritus	0	3 (0.1%)	0	0
Angioedema	0	1 (<0.1%)	0	0
Drug eruption	0	1 (<0.1%)	0	0
Eczema nummular	0	1 (<0.1%)	0	0
Rash	0	1 (<0.1%)	1 (0.2%)	1 (0.1%)
Rash generalised	0	1 (<0.1%)	0	0
Rash maculo-papular	0	1 (<0.1%)	0	0
Dermatitis contact	0	0	0	1 (0.1%)
Hypersensitivity vasculitis	0	0	0	1 (0.1%)
Urticaria	0	0	1 (0.2%)	0

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 . n(%) = number and percentage of patients with at least one TEAE leading to permanent IMP injections and/or capsules discontinuation
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')

Source: Response to FDA IR dated 19 February 2015, submitted 4 March 2015 (SD 14)

Neurologic events and neurocognitive disorders

Neurologic events of interest
In all phase 2 and 3 studies, neurologic events potentially related to myelin-sheath disorders and neuropathies were assessed. Events were screened for using the standardized MedDRA query of "Demyelination" (broad + narrow), "Peripheral neuropathy" (broad + narrow), and "Guillain-Barre syndrome" (broad + narrow) excluding the following PTs of "acute respiratory distress syndrome", "asthenia", "respiratory arrest", and "respiratory failure".

Table 93 summarizes the treatment-emergent neurologic events of interest in the placebo and ezetimibe controlled pools. Further description of these categories follows.

Table 93. Overview of TEAE neurologic events of interest (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Neurologic TEAE	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	45 (3.5)	86 (3.5)	0.98 (0.68 -1.41)	15 (2.4)	29 (3.4)	1.43 (0.76 - 2.69)
Treatment emergent SAE	1 (<0.1)	5 (0.2)		1 (0.2)	2 (0.2)	
TEAE leading to death	0	0		0	0	
TEAE leading to discontinuation	2 (0.2)	5 (0.2)		3 (0.5)	4 (0.5)	

Source: ISS Table 23, ISS appendix 1.4.1.6.4
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Calculated using a Cox model stratified on the study

Placebo-controlled pool – neurological events of interest
Overall, the same proportion of neurological events of interest: 3.5%, with HR (95% CI): 0.98 (0.68 to 1.41) was reported in patients in both the alirocumab and placebo groups.

- SMQ Demyelination: Four (0.2%) alirocumab-treated patients versus no placebo-treated patients reported TEAEs within the SMQ Demyelination. Alirocumab-treated patients reported the following events: trigeminal neuralgia (2 patients), demyelination, optic neuritis.

- SMQ Guillain-Barre syndrome: The proportion of patients reporting an event within this SMQ was similar between the alirocumab (3.2%) and placebo (3.1%) groups. The preferred terms of paresthesia and dysarthria occurred in at least 3 patients and with a higher incidence in alirocumab versus placebo-treated

patients. Within this SMQ, the SAE of Miller-Fisher syndrome was reported in an alirocumab-treated patient and is described below.

- SMQ Peripheral neuropathy: A smaller proportion of alirocumab-treated patients versus placebo-treated patients reported a TEAE within this SMQ. Only paresthesia occurred with higher incidence and in at least 3 patients in the alirocumab versus placebo group. None of the paresthesia events were reported as serious.

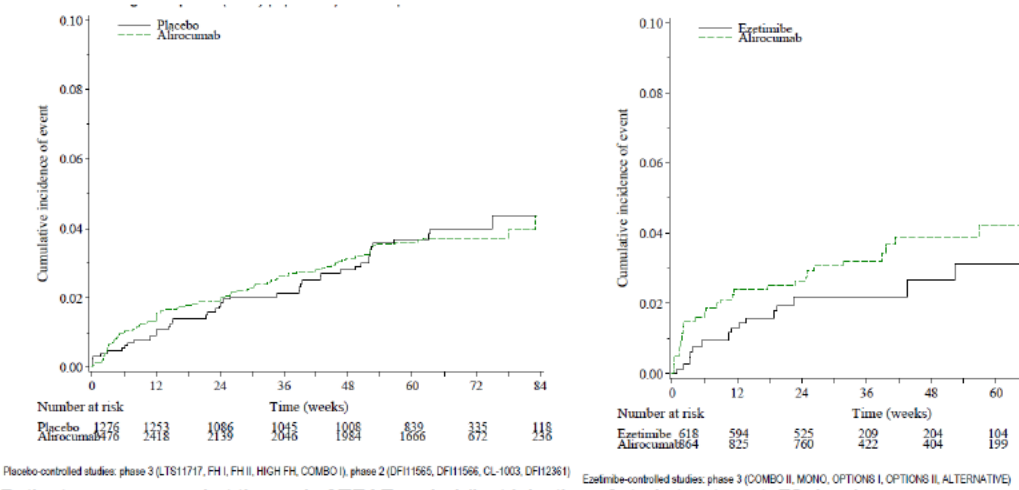
Ezetimibe-controlled pool – neurological events of interest
In the smaller ezetimibe-controlled pool, neurologic events of interest occurred in 3.4% of alirocumab-treated and 2.4% of ezetimibe-treated patients, with a HR of 1.43 (0.76 to 2.69).

- SMQ Demyelination: Only 1 patient experienced a SMQ defined demyelination event – transverse myelitis reported as a SAE in an alirocumab-treated patient. See below for a further description of this event.

- SMQ Guillain-Barre: TEAEs within this SMQ were reported in 24 (2.8%) of alirocumab-treated patients versus 14 (2.3%) of ezetimibe-treated patients. TEAE reported with a higher incidence in the alirocumab than the ezetimibe group (incidence rate ≥0.2% in any treatment group) were paresthesia (6 [0.7%] in the alirocumab versus 2 [0.3%] in the ezetimibe group), dysphagia (5 [0.6%] in the alirocumab group versus none in the ezetimibe group), and hypoaesthesia (4 [0.5%] in the alirocumab group versus 2 [0.3%] in the ezetimibe group).

- SMQ Peripheral neuropathy: TEAEs within this SMQ were reported in 20 (2.3%) of alirocumab-treated patients versus 13 (2.1%) of eztimibe-treated patients. Many of the preferred terms within this SMQ overlap with the SMQ for Guillain-Barre, so as seen with the SMQ Guillain-Barre, paresthesia and hypoesthesia were reported with higher incidence (≥0.2%) in the alirocumab-treated group compared to the ezetimibe-treated group.

Cumulative incidences of neurologic events over the TEAE period were slightly higher in the alirocumab group, with a higher cumulative incidence during the first 12 weeks overall. Similar to the placebo-controlled pool, cumulative incidences of neurologic events in the pool of ezetimibe-controlled studies appeared to be higher in the alirocumab-treated group not only in the first 12 weeks but at all timepoints.



Patients are censored at the end of TEAE period (last injection of study treatment+70 days)

Figure 34. Study-adjusted Kaplan-Meier cumulative incidence curve for time to first Neurologic events of interest during TEAE period (safety population) – Pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Table 94. Number (%) of patients with Neurologic TEAEs of interest by SMQ and PT (safety population) – pool of placebo and ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Neurologic TEAE of special interest				
n (%)	45 (3.5)	86 (3.5)	15 (2.4)	29 (3.4)
# of pts with an event per 100 pt-yrs[1]	3.2	3.1	3.3	4.0
95% CI	2.3 to 4.2	2.5 to 3.8	1.8 to 5.4	2.7 to 5.8
HR (95% CI)[2]	0.98 (0.68 to 1.41)		1.43 (0.76 to 2.69)	
Demyelination SMQ, n (%)	**0**	**4 (0.2)**	**0**	**1 (0.1)**
Trigeminal neuralgia	0	2 (<0.1)	0	0
Demyelination	0	1 (<0.1)	0	0
Optic neuritis	0	1 (<0.1)	0	0
Myelitis transverse	0	0	0	1 (0.1)
Guillain-Barre SMQ, n (%)	**39 (3.1)**	**78 (3.2)**	**14 (2.3)**	**24 (2.8)**
Paresthesia	9 (0.7)	25 (1.0)	2 (0.3)	6 (0.7)
Hypoesthesia	10 (0.8)	18 (0.7)	2 (0.3)	4 (0.5)
Decreased vibratory sense	7 (0.5)	7 (0.3)	0	0
Muscular weakness	4 (0.3)	6 (0.2)	5 (0.8)	3 (0.3)
Dysarthria	0	3 (0.1)	1 (0.2)	0
Dysphagia	0	2 (<0.1)	0	5 (0.6)
Neuropathy peripheral	5 (0.4)	2 (<0.1)	2 (0.3)	3 (0.3)
Paresthesia oral	0	2 (<0.1)	0	0
Polyneuropathy	0	2 (<0.1)	0	0
Ataxia	0	1 (<0.1)	0	0
Balance disorder	1 (<0.1)	1 (<0.1)	1 (0.2)	0

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Demyelination	0	1 (<0.1)	0	0
Extensor plantar response	0	1 (<0.1)	0	0
Facial paresis	0	1 (<0.1)	0	1 (0.1)
Gait disturbance	2 (0.2)	1 (<0.1)	1 (0.2)	0
Hypoesthesia oral	2 (0.2)	1 (<0.1)	0	0
Hyporeflexia	1 (<0.1)	1 (<0.1)	0	0
Hypotonia	0	1 (<0.1)	0	0
Miller Fisher syndrome	0	1 (<0.1)	0	0
Peripheral nerve palsy	0	1 (<0.1)	0	0
Polyneuropathy idiopathic progressive	0	1 (<0.1)	0	0
Quadriparesis	0	1 (<0.1)	0	0
Radiculopathy	0	1 (<0.1)	0	0
Aphasia	0	0	0	1 (0.1)
Areflexia	1 (<0.1)	0	0	0
Paresis	0	0	0	1 (0.1)
Sensory disturbance	0	0	0	1 (0.1)
Sensory loss	1 (<0.1)	0	0	0
Peripheral neuropathy SMQ, n (%)	**42 (3.3)**	**70 (2.8)**	**13 (2.1)**	**20 (2.3)**
Paresthesia	9 (0.7)	25 (1.0)	2 (0.3)	6 (0.7)
Hypoesthesia	10 (0.8)	18 (0.7)	2 (0.3)	4 (0.5)
Decreased vibratory sense	7 (0.5)	7 (0.3)	0	0
Muscular weakness	4 (0.3)	6 (0.2)	5 (0.8)	3 (0.3)
Burning sensation	2 (0.2)	4 (0.2)	0	1 (0.1)
Neuralgia	2 (0.2)	3 (0.1)	1 (0.2)	1 (0.1)
Neuropathy peripheral	5 (0.4)	2 (<0.1)	2 (0.3)	3 (0.3)
Polyneuropathy	0	2 (<0.1)	0	0
Gait disturbance	2 (0.2)	1 (<0.1)	1 (0.2)	0
Hyporeflexia	1 (<0.1)	1 (<0.1)	0	0
Hypotonia	0	1 (<0.1)	0	0
Miller Fisher syndrome	0	1 (<0.1)	0	0
Peripheral nerve palsy	0	1 (<0.1)	0	0
Polyneuropathy idiopathic progressive	0	1 (<0.1)	0	0
Areflexia	1 (<0.1)	0	0	0
Mononeuritis	0	0	0	1 (0.1)
Sensory disturbance	0	0	0	1 (0.1)
Sensory loss	1 (<0.1)	0	0	0
Skin burning sensation	1 (<0.1)	0	0	1 (0.1)

Source: ISS Table 23
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
[a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
[b] Calculated using a Cox model stratified on the study

SAEs – neurologic events

Seven alirocumab-treated and 2 control-treated patients (1 placebo, 1 ezetimibe) experienced serious neurologic events. No fatal case resulting from a neurological event as defined above was reported. Of these serious events, there were 4, all

occurring in alirocumab-treated patients, that are notable [optic neuritis, Miller-Fisher syndrome, demyelination (suspicious of multiple sclerosis), and transverse myelitis]. All 9 neurologic SAEs are summarized in Table 95 below.

An internal neurology consult was sought regarding these neurological events of interest In brief, based on review of the neurological cases of interest and analysis of adverse event data files, there did not appear to be any imbalances in either individual or groups of adverse events that would be suggestive of a disorder of peripheral myelin (peripheral neuropathy or polyradiculopathy). Regarding the specific serious neurological adverse events of interest, the consultant concluded that Miller Fisher syndrome and transverse myelitis are so rare that a single case of either is unexpected in this clinical trial population. However none of the cases were considered definitive, each lacking important supportive clinical or laboratory findings, and there appeared to be no evidence supporting a particular biological pathway that would give alirocumab a propensity to cause such side effects.

Table 95. Tabular summary of serious neurologic events of interest (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Alirocumab-treated							
Optic neuritis	011717-840-202-001 LONG TERM Alirocumab 150 mg Q2W	66 M	36 mg/dL (Wk4) 30 mg/dL (Wk8)	No (had pre-existing positive ADA titer 120) Titer remained 60 to 120	normal	D/C tx Resolved post steroid tx	History of severe vasculitis affecting the skin of right upper arm , blurred vision x 2 years On atorva 40 mg x 5 months prior to study, fenofibrate 135 mg 4 yrs prior to study. Day 34, diagnosed with retrobu bar optic neuritis of right eye. Retinal Nerve F ber Layer/ Optic Nerve Head revealed optic nerve cupping which appeared non-glaucomatous in both eyes. MRI of the brain showed enhancement of right optic nerve and the surrounding fat consistent with optic neuritis, right maxillary sinusitis, and was said to rule out tumor, cerebrovascular accident, and multiple sclerosis. Alirocumab was discontinued and after 1 month of prednisolone (20 mg 3 times daily) treatment, an 85% to 90% improvement was observed. Full recovery was reported 2 months later. An academic neuro-ophthalmologist consultant to the applicant considered the case to be optic-perineuritis, which is commonly due to vasculitis and a more consistent diagnosis with the described MRI findings in patients of this age

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Miller-Fisher syndrome	011717-826-010-268 LONG TERM Alirocumab 150 mg Q2W	47 M	1.5 mg/dL (Wk24/Day 168)	positive ADA response (titer: 480) at Week 4, not associated with neutralizing activity. ADA negative responses were observed at all other evaluated time points.	normal	D/C tx Resolved post gamma-globulin treatment	On simvastatin 40 mg/day for 6 years. Reported diplopia on Day 190. Had been preceded by nausea and diarrhea and "some weight loss". Condition continued to deteriorate leading to hospitalization on Day 197. On admission, mild distal weakness, areflexia (upper and lower extremities) and 6th cranial nerve palsy (external ophthalmoplegia, subtle ptosis of right eyelid) were noted. CT and MRI of the brain were normal. Miller-Fisher syndrome was diagnosed. The patient received gammaglobulin treatment. Cerebrospinal fluid revealed normal glucose, protein and cells. Antibodies to GQ1b were not detected. Multiple tests, including complete blood count, C-reactive protein, renal and liver tests, serum angiotensin converting enzyme (ACE), anti-neutrophil cytoplasmic antibody (ANCA) screen, Lyme serology, syphilis, human immunodeficiency virus (HIV) serology, anti-myelin-associated glycoprotein (MAG) ant bodies, anti-gangliozide antibodies, serum immunoglobulins were all normal, with the exception of slight transitory lymphocytosis.

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Demyelination	011717-380-002-004 LONG-TERM Alirocumab 150 mg Q2W	57 F	44 mg/dL (Wk4)	Neg ADA	Normal	Given high dose steroid Recovered with sequelae (myalgia of lower limbs)	A 57-year-old female patient with anxiety and depression, treated with rosuvastatin 5 mg/day for 8 months at alirocumab initiation, complained of walking difficulty, lower limb weakness and tingling in toes, persisting after rosuvastatin withdrawal, on Day 64. Electromyogram (EMG) was negative. The event was not diagnosed until neurological examination performed 11 months later, MRI of the brain showed multiple lesions of supratentorial and subtentorial white matter and cervical spine cord. Autoimmune screening was normal. Cerebrospinal fluid revealed presence of oligoclonal bands with intrathecal IgG synthesis. Reduced amplitude of the brainstem auditory-evoked response (BAER) and delayed and reduced potential of evoked somesthetic response (PESS) on the left side and the MRI findings led to the diagnosis of demyelinating disease of central nervous system, and suspicion of multiple sclerosis. High dose corticosteroid therapy for 3 days resulted in noticeable improvement. The patient recovered with sequelae, reported as ongoing constant myalgia of the lower limbs. No action was taken with the IMP. Long-term immunomodulatory therapy and neurological check-up were planned.

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Transverse myelitis	011569-840-974-004 COMBO II Alirocumab 75 mg Q2W	75 F	44 mg/dL (Wk8)	Neg ADA at baseline, no other values available	Not measured	D/C tx	A 75-year-old female patient on simvastatin 40 mg/day for over 15 years and with relevant medical history of hypothyroidism, obesity, depression and arthritis, experienced myelitis transverse on Day 64. She was hospitalized for dizziness, impaired balance, left abdominal pain, left-sided numbness, left back pain and weakness of the left lower extremity. Initial diagnosis was stroke of the spinal cord. MRI of the thoracic spine showed increased spinal cord signal, and slight expansion at T6-T9 level, and was considered more consistent with a diagnosis of transverse myelitis. Cerebrospinal fluid by lumbar puncture was acellular with normal proteins and without oligoclonal bands. Pulse steroids led to rapid improvement and a discharge within 10 days. Alirocumab was discontinued. On consecutive evaluations up to 9 months after discharge left lower extremity spasticity was persisting with presence of MRI spine lesion at T6-T8 level. CT of the brain did not show an active process at the time of event. The patient used a wa ker and received baclofen 10 mg 3 times a day and valium. The event was considered not to be related to the IMP, to statin, or to other LMT. Two brain MRI findings were available at 6 and 7 months post-event onset, respectively. The first MRI concluded generalized cerebral volume loss and mild degree of chronic small vessel ischemic disease, while the second was said to show several small areas of white matter involvement around the corpus callosum posteriorly and one such area in the splenium of the corpus callosum. This case is still under investigation and efforts are being made to obtain the original MRI images.

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Sensory disturbance	011569-208-914-009 COMBO II Alirocumab 75 mg Q2W	57 M	25 mg/dL (W4)	Negative	Not measured	None Recovered	On Day 289 of the study (b) (6) the patient had a new serious adverse event of moderate intensity, reported as sensory disturbance in arms and legs (Sensory Disturbance). The patient was admitted to the hospital, he was tired, and had tingling feeling and felt as if water was running on the skin, but there was nothing wrong with hands and feet. All blood tests, including hematology, liver panel, and infection parameters, were normal. No findings in the neurological exam were seen and no other tests were done.
Ataxia	011717-124-006-008 LONG-TERM Alirocumab 150 mg Q2W	65 F	5 mg/dL (W52)	Negative	High	None Recovered	On Day 33 of the study (b) (6), the patient had a new serious adverse event of severe intensity, reported as ataxia due to combination of dehydration and lyrica (Ataxia). On this day, the patient also had 3 other adverse events, reported as acute renal insufficiency (Renal Failure Acute) of moderate intensity, possible drug reaction related to pregabalin (adverse drug reaction) of moderate intensity, and confusional state due to combination of dehydration and lyrica (Confusional State) of mild intensity. Myoclonus and tremor resolved within 14 hours and the QT interval and eGFR returned to normal within 24 hours of receiving intravenous hydration. A neurologist's consultation letter stated that the events were probably due to pregabalin (Lyrica) and acute renal failure, while other ongoing medications such as aspirin, metformin, labetalol, hydrochlorothiazide, fenofibrate, esomeprazole, ubiquinone, amlodipine, and ramipril could also have contributed.

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Muscle weakness	11568-840-894-001 COMBO I Alirocumab 75 mg Q2W	70 M	46 mg/dL (W24)	Positive ADA when AE reported	Not measured	Recovered	On Day 242 of the study (07-JUL-2013), the patient had a new serious adverse event of mild intensity, reported as bilateral lower extremity profound weakness (Muscular Weakness). On (b) (6) the patient presented to the emergency room because he could not get out of his wheelchair to transfer into bed. Since he lived alone and was wheelchair bound, home health nurses suggested transfer back to emergency room. Nothing significant was found but he could not be triaged anywhere and did not want to go back to the extended care facility, therefore he was hospitalized. He again complained of aches and pains and cramps in both lower extremities but denied any chest pain or discomfort. On examination, there were chronic changes to both lower extremities and trace edema to bilateral lower extremities. Knees had chronic changes but nothing acute noted. Musculoskeletal status was grossly normal. The patient was able to move all four limbs. The patient could not get out of bed to see if he could bear weight or not and to check his balance. Impression was bilateral lower extremity chronic pain and profound weakness to a point where he was not able to transfer himself from wheelchair to bed, morbid exogenous obesity and osteoarthritis of multiple joints. Diagnostic conclusion for reported symptoms was muscular. On 01-AUG-2013, the patient was admitted to nursing home for rehabilitation.
Control-treated							

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Gait disturbance	012492-840-430-009 FH I Placebo	78 M	84 mg/dL (W64)	Negative	Not measured	Recovered	On Day 363 of the study (b) (6), the patient had a new serious adverse event of severe intensity, reported as gait disturbance (Gait Disturbance). The patient had recurrent and frequent falls due to increased gait disturbance, and showed acute-on-chronic confusion (patient with Alzheimer's mixed syndrome). The patient was transferred via ambulance to hospital. At physical examination, the patient had a good range of motion in all major joints, no tenderness to palpation or major deformities noted. He was alert and oriented, grossly normal motor function, good sensory function testing, no cog wheeling or rigidity, very slight resting tremor left hand, no focal deficits was noted. Mild fasciculations, tongue and hyperreflexia with mild to moderate weakness were observed. CXR, head CT, ECT, EEG, MRI no significant abnormalities. The patient underwent gait strengthening rehabilitation (Rehabilitation therapy) and was considered recovered from gait disturbance and discharged on (b) (6)

Preferred term	Pt. ID Study Treatment	Age (y)/ Sex/	Lowest LDL-C	Treatment emergent ADA	Vit E levels	Action taken & Outcome	Summary
Paresthesia	001118-826-860-003 OPTIONS II Ezetimibe	52 F	96 mg/dL (W16)	Negative	Not measured	Recovered	On Day 136 of the study (b) (6) the patient had a new serious adverse event of severe intensity, reported as paraesthesia of right arm unspecified cause no stroke (Paraesthesia), accompanied by right arm numbness and weakness, and chest pain. The patient underwent an ECG on Day 136 (b) (6) with no significant abnormalities detected. On (b) (6) the patient experienced mild chest discomfort and mild back pain (both non-serious events) associated with nausea but no vomiting. On the same day, the patient was hospitalized with right arm weakness and tingling of the arm. On (b) (6), the patient also experienced mild headache and mild hypertension (both non-serious events). No fever, shortness of breath, palpitation, or neck stiffness was noted. On examination, cranial nerves were normal, pupils were equal and constricting to light, there was no pronator drift, power was normal on all 4 limbs, there was no gaze palsy, and gait was normal. Laboratory results on (b) (6) included magnesium 0.97 mmol/L (normal range: 0.7-1 mmol/L), inorganic phosphate 0.96 mmol/L (normal range: 0.8-1.5 mmol/L), sodium 139 mmol/L (normal range: 133-146 mmol/L), and potassium 4.2 mmol/L (normal range: 3.5-5.3 mmol/L). A chest x-ray on Day 138 (b) (6) showed normal results. A CT scan of the head on the same day showed no evidence of major infarct mass or bleeds, but there were a few deep white matter changes lateral to the left caudate nucleus consistent with small vessel disease (non-serious adverse event), and small possible tiny infarct in the right superior parietal region. The patient was discharged on (b) (6) with improved condition. The patient underwent an x-ray of the cervical spine on Day 148 (b) (6) with no significant abnormalities detected ('xr cervical spine has a mild degenerative changes involing facet joints are noted.there is a slight reversal of cervical lordosis.no significant abnormally can be seen')

Discontinuations due to neurologic events of interest
In the placebo-controlled pool, the number of patients who experienced neurologic events leading to permanent treatment discontinuation was similar in the alirocumab and placebo groups (5 [0.2%] and 2 [0.2%], respectively). In 4 of these 7 patients, the event outcome was "recovered" while in 3 patients who were treated with alirocumab the events (hypoesthesia, Miller Fisher syndrome, polyneuropathy idiopathic progressive) were listed as "not recovered". The narrative for the patient reporting idiopathic progressive polyneuropathy is listed below.

- 011717-840-150-016/Alirocumab/Polyneuropathy idiopathic progressive: 75 year old white female on rosuvastatin 20 mg, on Day 32 of the study experienced left arm pain with mild tenderness and small bruise thought secondary to IP (investigational product) injection. IMP was discontinued due to this event. Seen by neurologist for evaluation of numbness, tingling, and paresthesia. The patient underwent neurological examination and laboratory tests the same day, results of which were abnormal for neuropathy indicating paresthesia in the hand along with bilateral and idiopathic progressive neuropathy. The pain was described as paresthesia, which had existed for 6 weeks prior to the initial visit. The patient stated that the problem was on both the left and right hands, which was exacerbated when using them. The frequency of the pain was same throughout the day but worsened during the night time. The patient reportedly had arthritis as well. The final impressions included median nerve sensory neuropathy with bilateral, paresthesia in the hand, bilateral and ulnar nerve entrapment at the elbow along with bilateral and idiopathic progressive polyneuropathy. The patient was finally diagnosed with idiopathic progressive polyneuropathy (moderate). The event was idiopathic with no underlying cause. The event was reported to have been stabilized. LDL-C levels at baseline were 108 mg/dL. On Study Day 32, LDL-C was 9 mg/dL and 12 mg/dL on Study Day 65. Patient was ADA negative.

The number of patients in the ezetimibe-controlled pool who experienced neurologic events leading to permanent treatment discontinuation was 4 (0.5%) in the alirocumab group (paresthesia, muscle weakness, neuralgia, myelitis transverse) and 3 (0.5%) in the ezetimibe group (all 3 were muscle weakness). In 6 of these 7 patients, the event outcome was "recovered" while in 1 patient the event of transverse myelitis was recovering at the time of last information received.

Neurologic events of interest – low LDL-C
Of the 796 alirocumab-treated patients who achieved two consecutive LDL-C values <25 mg/dL, 15 (1.9%) experienced a neurologic TEAE of interest. The preferred terms that occurred in 2 or more of these patients were paresthesia (n=3), decreased vibratory sense (n=2), and hypoesthesia (n=2). None of these events were serious.

Neurocognitive events
Neurocognitive events were assessed in all phase 2 and 3 studies using company selected MedDRA terms or company MedDRA Query (CMQ), based on the five following high level group terms (HLGTs); "Deliria (includes confusion)", "Cognitive and attention disorders and disturbances", "Dementia and amnestic conditions", "Disturbances in thinking and perception", "Mental impairment disorders". A second grouping based on the Division's recommendation was also evaluated in phase 2 and 3 studies (Appendix).

Overall, neurocognitive events were low in number and similar across treatment groups Table 96.

Table 96. Overview of TEAE neurocognitive events (safety population) – pool of placebo-controlled studies and pool of ezetimibe controlled studies

	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)
Neurocognitive TEAE (CMQ)	9 (0.7)	21 (0.8)	1.18 (0.54-2.58)	6 (1.0)	8 (0.9)	0.94 (0.32-2.74)
Neurocognitive SAE (CMQ)	2 (0.2)	3 (0.1)		1 (0.2)	1 (0.1)	
Neurocognitive TEAE leading to death (CMQ)	1 (<0.1)	0		0	0	
Neurocognitive TEAE leading to discontinuation (CMQ)	2 (0.2)	0		2 (0.3)	0	
Neurocognitive TEAE (FDA grouping)	11 (0.9)	21 (0.8)	0.96 (0.46-2.00)	6 (1.0)	7 (0.8)	0.80 (0.26-2.40)

Source: ISS appendix 1.4.1.7.4, 1.4.1.8.1, 1.4.1.8.4
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
MedDRA 17.0 . The selection of PTs is based on the HLGTs 'deliria (incl. confusion)', 'cognitive and attention disorders and disturbances', 'dementia and amnestic conditions', 'disturbances in thinking and perception', 'mental impairment disorders'
1. Calculated using a Cox model stratified on the study

Treatment-emergent neurocognitive adverse events
Neurocognitive events were reported in 21 (0.8%) patients in the alirocumab group and 9 (0.7%) patients in the placebo group. The preferred terms of confusional state and memory impairment occurred at a higher incidence in the alirocumab group (0.2% for both preferred terms) than in the placebo group (<0.1% for both preferred terms). The remaining preferred terms occurred in less than 2 alirocumab-treated patients or at a similar or lower incidence to placebo-treated patients.

The mean time-to-onset of a neurocognitive event from the beginning of study treatment was198 days (4 to 461 days) for patients in the alirocumab group and 85 days (27 to 364 days) for patients in the placebo group.

In the ezetimibe-controlled pool, 14 patients overall experienced a neurocognitive disorder: 6 (1.0%) in the ezetimibe group and 8 (0.9%) in the alirocumab group. The preferred term memory impairment occurred in 3 (0.3%) of alirocumab-treated patients and did not occur in any ezetimibe-treated patient. The remaining preferred terms

occurred in less than 2 alirocumab-treated patients or at a similar or lower incidence to placebo-treated patients.

The mean time-to-onset from the beginning of study treatment was 194 days for patients in the alirocumab group (9 to 448 days) and 155 days for patients in the ezetimibe group (7 to 336 days).

Table 97. Number (%) of patients with Neurocognitive TEAEs of interest by CMQ and PT (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Neurocognitive disorders				
n (%)	9 (0.7)	21 (0.8)	6 (1.0)	8 (0.9)
# of pts with an event per 100 pt-yrs[1]	0.6	0.7	1.3	1.1
95% CI	0.3 to 1.2	0.5 to 1.1	0.5 to 2.8	0.5 to 2.2
HR (95% CI)[2]	1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)	
Neurocognitive disorders (CMQ)	**9 (0.7)**	**21 (0.8)**	**6 (1.0)**	**8 (0.9)**
Confusional state	1 (<0.1)	6 (0.2)	2 (0.3)	2 (0.2)
Amnesia	2 (0.2)	5 (0.2)	2 (0.3)	1 (0.1)
Memory impairment	1 (<0.1)	5 (0.2)	0	3 (0.3)
Disturbance in attention	1 (<0.1)	2 (<0.1)	2 (0.3)	0
Confusion postoperative	0	1 (<0.1)	0	0
Dementia	2 (0.2)	1 (<0.1)	0	0
Disorientation	0	1 (<0.1)	0	0
Frontotemporal dementia	0	1 (<0.1)	1 (0.2)	0
Transient global amnesia	1 (<0.1)	1 (<0.1)	1 (0.2)	0
Aphasia	0	0	0	1 (0.1)
Delirium	1 (<0.1)	0	0	0
Dementia Alzheimer's type	1 (<0.1)	0	0	1 (0.1)
Hallucination	0	0	0	1 (0.1)

Source: ISS Table 24
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
MedDRA 17.0 . The selection of PTs is based on the HLGTs 'deliria (incl. confusion)', 'cognitive and attention disorders and disturbances', 'dementia and amnestic conditions', 'disturbances in thinking and perception', 'mental impairment disorders'

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study

The preferred term of "memory impairment" occurred in a higher proportion of alirocumab-treated patients compared to placebo-treated patients in the placebo-controlled pool and ezetimibe-treated patients in the ezetimibe-controlled pool. A summary of the 8 alirocumab-treated patients and 1 placebo-treated patient reporting this event is in the table below. None of the events were serious, 2 patients had symptoms associated with a stroke that were listed as "not recovered, stabilized." Three others recovered from mild events lasting 1 to 2 months. The remaining events

were listed as not recovered. The table below also lists patients with reports of confusional state and amnesia.

Table 98. Summary of events coded as 'memory impairment', 'confusional state', and 'amnesia' (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Pt ID	Age/Sex	PREFERRED TERM Verbatim term	Day of study event occurred[1]	Outcome	2 LDL-C <25 Last LDL-C before event	Comments
Alirocumab-treated						
001119-578-960-002	55 F	MEMORY IMPAIRMENT /Forgetful	9	Recovered	N 283 mg/dL	Duration 29 days Also reported tiredness, myalgia, and palpitations on same day
001119-840-939-005	68 M	MEMORY IMPAIRMENT /Forgotfulness	14	Not recovered	N 173 mg/dL	Listed as mild, non-serious event
011569-840-990-001	61 M	MEMORY IMPAIRMENT /Forgetfulness etiology unknown	344	Recovered	N 81 mg/dL	Duration 64 days Listed as mild, non-serious drug interrupted
011717-124-007-001	79 M	MEMORY IMPAIRMENT / Worsening of forgetfulness	54	Not recovered,	N 49 mg/dL	No narrative of event On amitriptlyline and lorazepam concomitantly Dose not changed
011717-578-003-016	82 M	MEMORY IMPAIRMENT /Reduced memory problem due to hemorrhagic stroke	96	Not recovered, stabilized	N 31 mg/dL	On same day as hospitalization for hemorrhagic stroke, non-serious mild memory impairment. IMP permanently discontinued. LDL-C on study day 82 was 31 mg/dL
011717-616-001-004	58 M	MEMORY IMPAIRMENT /Memory disorder	345	Recovered	N 21 mg/dL	Duration 52 days Associated with dizziness of unknown etiology while changing body position and twisting head. Diagnosed with insufficient posterior function of cerebral circulation. Corrective treatment nicergoline. All symptoms resolved. LDL-C on study day 260 21 mg/dL, 365 was 38 mg/dL and 36 mg/dL on study day 450
011717-616-009-028	78 M	MEMORY IMPAIRMENT /Memory disorder suspected as result of ischemic stroke	204	Not recovered, stabilized	Y 58 mg/dL	While hospitalized for ischemic stroke which occurred 5 days before the report of memory impairment, a cognitive function test revealed moderate memory disturbances. During hospitalization, IMP temporarily discontinued. Reinitiated treatment. LDL-C 58 mg/dL study day 171 LDL-C 17 mg/dL study day 253 LDL-C 23 mg/dL study day 365
011717-826-011-140	70 F	MEMORY IMPAIRMENT Worsening short term memory etiology	missing	Not recovered,	N	Memory impairment in medical history with diagnosis of early dementia prior to randomization Brain CT scan at time of the diagnosis: bilateral temporal cerebral involution may be within the range of normal age

Pt ID	Age/Sex	PREFERRED TERM Verbatim term	Day of study event occurred[1]	Outcome	2 LDL-C <25 Last LDL-C before event	Comments
		unknown				related. On mini mental status exam (2 months thereafter: lost marks on orientation and recall Family history: mother had Alzheimer's disease Nitazepam concomitantly
011566-840-615-016	61 M	CONFUSIONAL STATE/ Confusion	4	Recovered	N 115 mg/dL	Patient with medical history of depression, bipolar disorder, and alcohol use Desvenlafaxine, gabapentin, risperidone, temazepam concomitantly Reported on same day dizziness, syncope, and inner ear infection
011717-124-006-008	65 F	CONFUSIONAL STATE/ Confusion due to combination of dehydration and Lyrica	33	Recoved	N 26 mg/dL	Patient with anxiety, past ischemic stroke, past short term memory loss, and intermittent hallucinations. Patient on pregabalin, citalopram, trazodone, zopiclone concomitantly. Patient also reported ataxia (due to dehydration and pregabalin),
		AMNESIA/ Worsening short term memory loss etiology unknown	363	Recoved	N 54 mg/dL	Also reported syncope, hypomagnesemia, hypokalemia (caused by gastroenteritis) on the same day as the amnesia
011717-124-015-003	78 F	CONFUSIONAL STATE/ Confusion etiology unknown	94	Recovered	N 70 mg/dL	Patient with seizure disorder (1954), intermittent heaches, ischemic stroke (2011), episode of vertigo, cerebellar atrophy, possible old parietal lobe infarcts. On same day of event reported presyncope and dehydration which resolved
011717-208-005-007	62 M	CONFUSIONAL STATE/ Confusion, regarded related to stress	456	Recovered	N 96 mg/dL	Presyncope reported on Study Day 453 Morphine concomitantly
011717-710-009-013	55 F	AMNESIA/ Memory loss	110	Recovered	N 29 mg/dL	Dose not changed
011717-826-006-080	70 M	AMNESIA/ Memory loss	NA	Not recovered	N 51 mg/dL	IMP stopped about 2 months before onset of amnesia Relevant medical history includes ischemic stroke (1995)
011717-826-012-006	64 M	CONFUSIONAL STATE/ Intermittent confusion (etiology unknown)	461	Recovered	Y 11 mg/dL	Confusional state occurring the day after surgery for sigmoid colon cancer Flupentixol, sertraline concomitantly
011717-840-083-004	45 M	AMNESIA/ Short term memory loss – etiology unknown	45	Recovered	N 156 mg/dL	Relevant medical history included short term memory loss, anxiety (2011), depression (2011), insomnia (2011) Citalopram, alprazolam concomitantly
011717-840-204-002	63 M	AMNESIA/ Short term	NA	Not recovered	N 31 mg/dL	Dose not changed

Pt ID	Age/Sex	PREFERRED TERM Verbatim term	Day of study event occurred[1]	Outcome	2 LDL-C <25 Last LDL-C before event	Comments
		memory loss				
012492-710-401-007	76 F	CONFUSIONAL STATE/ Confusion	206	Recovered	N 29 mg/dL	UTI and weight loss also reported on the same day as confusional state
001118-840-488-002	85 M	CONFUSIONAL STATE/ Confusion	134	Recovered	N 54 mg/dL	Urospesis, viral infection reported on same day
011569-208-914-006	71 M	CONFUSIONAL STATE/ Temporary confusion	448	Recovered	N 26 mg/dL	Non serious Consultation with neurologists: no findings
011569-840-986-001	76 M	AMNESIA Worsening of memory loss	263	Not recovered	Y 9 mg/dL	Dose not changed Reported mild depression on the same day
Placebo-treated						
011717-276-019-002	71 F	MEMORY IMPAIRMENT Forgetfullness etiology unknown	80	Not recovered	N 101 mg/dL	No narrative of event No corrective treatment Dose not changed
011717-826-008-301	56 F	CONFUSIONAL STATE/ Confused	29	Recovered	N 124 mg/dL	Patient with depression (treatment with citalopram, gabapentin, tramadol) On same day reported feeling hot and sweating Dose not changed
012492-840-428-001	48 M	AMNESIA/ Memory loss (related to supraventricular tachycardia)	125	Recovered	N 114 mg/dL	Lorazepam concomitantly Dose not changed
12732-840-702-004	57 F	AMNESIA/ Memory loss	27	Recovered	N 279 mg/dL	Duloxetine, gabapentin, zolpidem concomitantly Same day reported asthenia (weakness related to Lisinopril), heart rate decreased, nausea and pain extremity
Ezetimibe-treated						
001118-840-487-001	62 M	CONFUSIONAL STATE/ Confused state before and after stroke	74	Not recovered	N 78 mg/dL	Concomitant to stroke CT scan: acute intraparenchymal hemorrhage in the superior right cerebellar hemisphere Brain MRI acite intra-axial hemorrhage centered in the right hemisphere with subarachnoid extension Lorazepam, venlafaxine, bupropion concomitantly
001119-840-919-012	81 F	AMNESIA/ Memory loss	47	Not recovered	N 184 mg/dL	Sertraline concomitantly
011569-840-914-001	64 F	AMNESIA/ Memory loss due to MVA	367	Recovered	N 48 mg/dL	Concomitant to road traffic accident Zolpidem concomitantly

Source: ADAE.xpt dataset, individual CSR narratives, Response to FDA IR dated 16 April 2015
1 Relative day to the start date of IMP

SAEs - Neurocognitive disorders

A total of 7 serious neurocognitive disorders defined by the applicant's CMQ of neurocognitive events were reported (4 in alirocumab treated and 3 in control treated patients) (Table 99). An additional 2 serious neurocognitive events with the preferred

term “mental status change” occurred in 2 placebo-treated patients, when using the FDA defined grouping of neurocognitive terms.

Table 99. Summary of serious neurocognitive events – CMQ and FDA definitions (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Patient ID Study name Treatment	Age/Sex	Preferred term Outcome	Summary
Alirocumab-treated			
11717-826-009-127 LONG TERM Alirocumab 150 mg Q2W	77 M	Dementia Not resolved	On baseline treatment with citalopram and amitriptyline, experienced confusion during an acute cardiac decompensation in the context of aggravation of his underlying ischemic cardiomyopathy and a hypotensive episode. Patient had discontinued treatment on Day 227 due to physician decision. He was found with moderate dementia on Day 278 after hospitalization for ischemic cardiomyopathy. CT scan of head showed small vessel disease of unknown clinical significance. The patient did not receive corrective treatment other than diuretics for cardiac decompensation. Dementia was persisting at the time of most recent follow-up report. Reached 2 values of LDL-C <25 mg/dL (Wk 4 and Wk 8). Lowest value 15.4 mg/dL at Week 8. LDL-C >25 mg/dL at all other assessments.
11717-840-204-015 LONG TERM Alirocumab 150 mg Q2W	57 M	Frontotemporal dementia Stabilized, not recovered	A 57-year-old male patient with relevant medical history of ischemic stroke, epilepsy and cannabis use, was hospitalized on Day 364 for moderate frontotemporal dementia with behavior disturbance, associated with bipolar disorder and antisocial personality features. Frontotemporal damage was attr buted to previous cerebrovascular accident. Frontotemporal dementia is a degenerative condition of unknown etiology. Corrective treatment included valproate, trazodone, lorazepam, and haloperidol. Alirocumab was continued. At the last report received the patient was considered stabilized. This patient experienced at least 2 consecutive values of LDL-C <25 mg/dL and the lowest value observed was 8 mg/dL at Week 24. LDL-C was <25 up to Day 254. LDL-C >25 mg/dL at Days 387 and 455.
11717-208-005-007 LONG TERM Alirocumab 150 mg Q2W	62 M	Confusional state Recovered	A 62-year-old male patient without psychiatric medical history experienced a confusional state on Day 456. He was found 8 km away from home without remembering how he got there. He also complained of headaches. Neurological work-up did not reveal a cause of the symptoms. The Investigator attributed the moderate confusional state lasting for 2 days to the patient’s stress due to the closure of his business, his wife facing deportation and a shoulder injury. This patient did not reach 2 consecutive values of LDL-C<25 mg/dL. His lowest LDL-C value was 33 mg/dL at Week 12
011569-208-907-009 COMBO II Alirocumab 75 mg Q2W	76 F	Dementia Alzheimer’s type	A 76-year-old female patient was diagnosed with dementia of Alzheimer’s type on Day 285, based on symptoms of decreased memory and brain CT findings. The event was of mild intensity. Treatment with alirocumab was continued. The patient did not tolerate donepezil or memantine given as corrective treatment and had not recovered at the date of the last received information. Symptoms of impaired memory may have been present over the last 2 to 3 years according to the patient’s husband. This patient did not reach 2 consecutive values of LDL-C<25 mg/dL. Her lowest value reached was a LDL-C of 11 mg/dL at Week 64.
Control-treated			
11568-840-898-010 COMBO I Placebo	78 M	Dementia Fatal	A 78-year-old male patient was diagnosed with dementia on Day 251. This was an aggravation of a preexisting condition, in the context of general health deterioration due to multiple traumas involving the face with consequent impossibility of regular food intake. This patient died due to his multiple morbidities, including dementia
11717-348-004-015	79 F	Dementia	A 79-year-old female patient was diagnosed with transitory

LONG TERM Placebo		Recovered	aggravation of forgetfulness on Day 33 during hospitalization for bronchitis.
11569-840-917-003 COMBO II Ezetim be	75 M	Transient global amnesia Confusional state	A 75-year-old male patient experienced transient global amnesia and confusion lasting for 1 hour only on Day 102
11717-840-077-009 LONG TERM Placebo	81 M	Mental status change Recovered	An 81-year-old male patient experienced a transient altered mental status leading to a hospitalization on Day 37. The event lasted for 2 days, after which the patient recovered
11717-840-113-013 LONG TERM Placebo	56 F	Mental status change Recovered	A 56-year-old female patient experienced altered mental status requiring hospitalization on Day 548. The etiology of the event remained "unknown". The patient fully recovered within 2 weeks

Source: ISS and corresponding CSR narratives

Neurocognitive disorders – low LDL-C
A total of 796 patients treated with alirocumab achieved 2 consecutive LDL-C values <25 mg/dL. Of these 4 (0.5%) patients reported a neurocognitive disorder: amnesia, confusional state, dementia, and frontotemporal dementia. Two of these were serious events and are described above.

Discontinuations due to neurocognitive events
No patients treated with alirocumab discontinued treatment due to a neurocognitive event.

ALT increase and hepatic disorders

The following analyses used the standardized MedDRA query for "hepatic disorders".

A higher proportion of alirocumab-treated patients reported treatment-emergent AEs, SAEs, and discontinuation due to AEs related to hepatic disorders compared to placebo-treated patients. All patients in the placebo-controlled pool were on maximally tolerated background statin therapy.

Within the ezetimibe-control pool, TEAEs did not occur at a higher incidence in the alirocumab-treated group compared to the ezetimibe-treated group. Only 1 patient experienced an SAE (alirocumab-treated) and a slightly higher percentage of alirocumab-treated patients discontinued treatment due to a hepatic disorder.

Table 100. Overview of treatment-emergent hepatic disorders (SMQ) (safety population) – placebo and ezetimibe-controlled studies

Hepatic disorder	Placebo-controlled			Ezetimibe-controlled		
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	HR* (95% CI)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)	HR* (95% CI)
TEAE	23 (1.8)	61 (2.5)	1.36 (0.84-2.20)	14 (2.3)	16 (1.9)	0.69 (0.34-1.43)
SAE	1 (<0.1)	8 (0.3)		0	1 (0.1)	
TEAE leading to death	0	0		0	0	
TEAE leading to discontinuation	2 (0.2)	9 (0.4)		1 (0.2)	4 (0.5)	

Source: ISS Appendix 1.4.1.5.4
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
The selection of PTs is based on the standardized MedDRA SMQ 'hepatic disorder'

Hepatic disorders – Treatment emergent AE

The preferred terms which comprise the events in the hepatic disorder SMQ were mostly related to laboratory abnormalities, among which, "ALT increased", was the most frequently reported [(placebo-controlled pool: placebo 0.7%, alirocumab 1.1%); (ezetimibe-controlled pool: ezetimibe 0.8%, alirocumab 0.6%)].

Table 101. Number (%) of TEAE hepatic disorders by SMQ and PT (safety population) – pool of placebo-controlled studies and ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Hepatic disorders				
n (%)	23 (1.8)	61 (2.5)	14 (2.3)	16 (1.9)
# of pts with an event per 100 pt-yrs[1]	1.6	2.2	3.1	2.2
95% CI	1.0 to 2.4	1.7 to 2.8	1.7 to 5.1	1.3 to 3.6
HR (95% CI)[2]	1.36 (0.84 to 2.20)		0.69 (0.34 to 1.43)	
Hepatic disorders (SMQ)	**23 (1.8)**	**61 (2.5)**	**14 (2.3)**	**16 (1.9)**
Alanine aminotransferase increased	9 (0.7)	28 (1.1)	5 (0.8)	5 (0.6)
Gamma-glutamyltransferase increased	3 (0.2)	10 (0.4)	2 (0.3)	1 (0.1)
Hepatic enzyme increased	1 (<0.1)	7 (0.3)	1 (0.2)	1 (0.1)
Aspartate aminotransferase increased	0	5 (0.2)	1 (0.2)	2 (0.2)
Hepatic steatosis	4 (0.3)	4 (0.2)	4 (0.6)	0
International normalized ratio increased	1 (<0.1)	3 (0.1)	0	1 (0.1)
Non-alcoholic steatohepatitis	0	3 (0.1)	0	0
Drug-induced liver injury	1 (<0.1)	2 (<0.1)	0	0
Hepatitis alcoholic	0	2 (<0.1)	0	0
Ascites	1 (<0.1)	1 (<0.1)	0	0
Blood alkaline phosphatase increased	0	1 (<0.1)	0	0
Hemangioma of liver	0	1 (<0.1)	0	0
Hepatitis A	0	1 (<0.1)	0	0
Hepatocellular injury	0	1 (<0.1)	0	0

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Hepatomegaly	0	1 (<0.1)	0	0
Ocular icterus	0	1 (<0.1)	0	0
Prothrombin level decreased	0	1 (<0.1)	0	0
Transaminases increased	0	1 (<0.1)	1 (0.2)	2 (0.2)
Ammonia increased	1 (<0.1)	0	0	0
Blood bilirubin increased	0	0	2 (0.3)	2 (0.3)
Hepatic cyst	1 (<0.1)	0	1 (0.2)	2 (0.2)
Hepatic lesion	0	0	0	1 (0.1)
Hepatitis C virus test positive	1 (<0.1)	0	0	0
Hepatitis E	0	0	0	1 (0.1)

Source: ISS Appendix 1.4.1.5.1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-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 SMQ 'hepatic disorder'

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length
2. Calculated using a Cox model stratified on the study

As of the cut-off date, the majority of patients reporting events recovered in the placebo and ezetimibe pools, respectively. One alirocumab-treated patient recovered with sequelae (ALT not completely into normal ranges).

Analysis of the intrinsic and extrinsic factors identified a single interaction, based on a 10% significance level, between the treatment groups in the placebo-controlled pool. A higher hazard ratio was obtained for the comparison of alirocumab over the placebo group, in patients with 'Not diabetes' status at baseline [HR 2.73 (1.34 to 5.58)], compared to patients with Diabetes at baseline [HR 0.53 (0.25 to 1.13)] (interaction p-value 0.0014). There was no significant treatment interaction by baseline dose of statin treatment (p=0.36). No treatment interactions were noted in the ezetimibe-control pool.

In the placebo-controlled safety pool, cumulative incidences of hepatic disorders were higher in the alirocumab-treated group compared to placebo-treated group throughout the study. The incidence of the preferred term ALT increased was higher in the first 24 weeks and after 52 weeks in the alirocumab versus placebo group. However, this pattern was not observed in the ezetimibe-controlled safety pool.

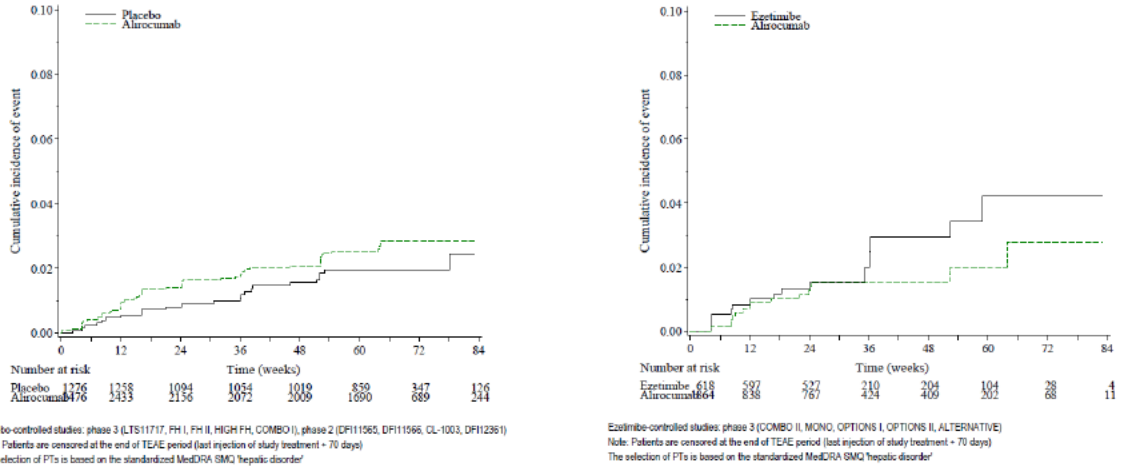


Figure 35. Study-adjusted Kaplan-Meier cumulative incidence curve for time to first TEAE related to hepatic disorders events during TEAE period (safety population) – pool of placebo and ezetimibe-controlled studies

Hepatic disorders – SAEs

Within the placebo-controlled pool, 8 (0.3%) of alirocumab-treated patients compared with 1 (<0.1%) placebo-treated patient experienced a hepatic disorder SAE. An additional alirocumab-treated patient in the ezetimibe-controlled pool experienced an SAE versus no ezetimibe-treated patients. All of the patients, with the exception of one recovered from the serious event. Three of these events resulted in permanent study treatment discontinuation. Two patients (11717-710-005-031 "ALT increased" and 012492-840-415-006 "INR increased", the latter being the result of warfarin and not liver dysfunction) recovered from the event while continuing on alirocumab treatment. The remaining patients temporarily discontinued alirocumab treatment - in 3 of these cases there were no further elevations in ALT after reinitiation of alirocumab, in the remaining case (11717-380-001-003) the patient experienced additional episodes of increased ALT after restarting alirocumab but continued treatment. Further details regarding these patients are summarized below.

Table 102. Summary of hepatic disorders SAEs (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

Patient ID Study name Treatment	Age/Sex/BMI	Statin therapy	Day of onset	Preferred term Outcome	Summary
Alirocumab-treated					
11717-208-005-007 LONG TERM Alirocumab 150 mg Q2W	62 M 27.5	Atorva 80	448	ALT increased **Study tx DC** Not resolved	Peak ALT 182 IU/L (4.2x ULN) Peak AST 140 IU/L (3.9 ULN) Normal bilirubin Reported reason listed as alcohol (5 drinks in 7 days prior to event)
11717-380-001-003 LONG TERM	36 M 24.2	Simva 10	132	ALT increased Study tx	Peak ALT 233 IU/L (5.4 ULN) Peak AST 162 IU/L (4.5 ULN)

Alirocumab 150 mg Q2W				temporarily discontinued, simva and eze continued resolved	Normal bilirubin
11717-710-005-031 LONG TERM Alirocumab 150 mg Q2W	53 M 33.6	Atorva 80	450	ALT increased No corrective tx Recovered	Peak ALT 138 IU/L (3.2 ULN) Peak AST 76 IU/L (2.1 ULN) Normal bilirubin Alirocumab continued Atorvastatin 80 mg continued
12492-203-405-001 FH I Alirocumab 75 mg Q2W	67 F 29.6	Rosuva 40	169	Hepatic enzyme increased **Study tx DC** Recovered	Peak ALT 539 IU/L (15.85 ULN) Peak AST 438 IU/L (12.88 ULN) Peak alkaline phosphatase 813 IU/L (6.61 ULN) Peak total bilirubin 24 µmol/L Peak GGT 528 IU/L (10.56 ULN) Viral serologies negative
11717-250-009-007 LONG TERM Alirocumab 150 mg Q2W	60 F 27.6	Rosuva 40	29	Hepatocellular injury Alirocumab temporarily DC Recovered	Peak ALT 280 IU/L (8.2 ULN) Peak AST 168 IU/L (4.9 ULN) Normal bilirubin Alirocumab interrupted from Week 6 to Week 14, then restarted without ALT increase. No change to rosuvastatin treatment throughout event
1112-528-202-003 FH II Alirocumab 75 mg Q2W	50 M 30.2	Atorva 80	1	Hepatitis A Alirocumab temporarily DC Atorvastatin 80 temporarily discontinued Recovered	Peak ALT 2094 IU/L (48.7 ULN) Peak AST 889 IU/L (24.7 ULN) Peak bilirubin 7.38 ULN Both alirocumab (no injections from Wk 6 to Wk 34 and atorvastatin interrupted Alirocumab restarted once patient recovered on Week 34 with no further increase in ALT. Atorvastatin was restarted 3 months before alirocumab
12492-250-401-003 FH I Alirocumab 75 mg Q2W	42 M 27.5	Rosuva 20	89	Hepatitis alcoholic **Study tx DC** Recovered	Peak ALT 75 IU/L Peak AST 154 IU/L History of alcoholism, elevation in LFTs following 20 drinks within 1 week. Associated with asthenia, nausea, abdominal pain, vomiting. Hospitalized, received blood transfusion for moderate anemia
12492-840-415-006 FH I Alirocumab 75 mg Q2W	69 M 32.7	Atorva 80	107	INR increased No change to alirocumab Recovered	Recent total knee arthroplasty, on warfarin Not considered a hepatic disorder.
11569-643-904-027 COMBO II Alirocumab 75 mg Q2W	75 M 27.8	Atorva 20	365	Hepatitis E Alirocumab temporarily DC Recovered	Peak ALT 763 (21.8 ULN)
Placebo-treated					
11717-276-005-024 LONG TERM Placebo	50 F 38.5	Simva 20	84	Hepatic steatosis Placebo temporarily DC Recovered Hepatic steatosis on Day 388 (mild), placebo DC permanently	Peak ALT 1285 IU/L (37.8 ULN) Peak AST 1294 IU/L (37.8 ULN) Normal bilirbuin

Source: ISS, CSR narratives

Selected SAE narratives

- 011717-380-001-003/Alirocumab/ALT increase: 36 year old white man with fatty liver and previous history of ALT increase several years prior to this study. The patient experienced a mild ALT increase 28 days after receiving first alirocumab injection which progressed to a peak ALT of 233 (5.4x ULN) and AST 162 (4.5x ULN), alkaline phosphatase and bilirubin were within normal limits. Viral serologies were negative. Liver ultrasound confirmed fatty liver infiltration. Alirocumab was temporarily interrupted and liver function tests returned to baseline. Simvastatin and ezetimibe as background therapy were continued throughout this event. After reintroduction of alirocumab, this patient had five additional episodes of increased ALT, no further action regarding the study drug was taken, and the patient completed the study. Since submission of the BLA, the serious event was downgraded to non-serious by the Investigator.
- 011717-250-009-007/Alirocumab/Hepatocellular injury: A 60-year-old female patient (baseline BMI 27.6 kg/m2), with a relevant medical history of coronary artery disease including acute MI, no hepatic disorders or alcohol consumption, experienced hepatic cytolysis on Day 29. ALT and AST increased up to 8.2 ULN (280 IU/L) and 4.9 ULN (168 IU/L), respectively. Bilirubin levels were normal. Alirocumab was temporarily interrupted. The patient recovered without corrective treatment and alirocumab was resumed without recurrence of ALT increase. The patient received ciprofloxacin up to 3 weeks before randomization and the combination of tiliquinol/ tilbriquinol in the month before and in the first week after randomization for the treatment of acute sigmoiditis that started about two months prior to randomization. These drugs are listed to have a risk of liver toxicity and may represent potential alternative cause for the transaminase increases. The ALT values at screening and at baseline were moderately high, 1.8 ULN and 2.6 ULN, respectively as well as an aspartate aminotransferase (AST) value of 1.7ULN at baseline (Day 1).
- 012492-203-405-001/Alirocumab/hepatic enzyme increased: A 67-year-old female patient (baseline BMI 29.6 kg/m2), with a relevant medical history of hypertension and peripheral arterial occlusive disease, experienced hepatic enzyme increased of severe intensity on Day 169 following a viral infection. Liver function tests (LFTs) on Day 169 showed elevated ALT at 129 IU/L (3.8 ULN) with high AST at 133 IU/L (3.91 ULN) and normal total bilirubin; baseline ALT was 54 IU/L (1.59 ULN). On Day 171 ALT values increased to 313 IU/L with high AST at 229 IU/L (6.74 ULN) and high total bilirubin at 24 µmol/L. On Day 176, ALT values increased to 539 IU/L (15.85 ULN) with AST at 438 IU/L (12.88 ULN), elevated alkaline phosphatase (ALP) 813 IU/L (6.61 ULN), and gamma-glutamyl transferase (GGT) 528 IU/L (10.56 ULN). Ultrasonography showed mild nonserious cholesterolosis of the gallbladder. Serology results were negative for hepatitis B, C, and A. No specific corrective treatment was required but paracetamol, ibuprofen, rosuvastatin and ezetimibe were interrupted. The IMP was permanently discontinued, with the last administration on 15-MAY-2013. The patient recovered from the event without sequelae on 06-JUN-2013. On that date, alkaline phosphatase was 275 U/L (2.24 ULN), AST was 23 U/L (0.68 ULN), and ALT was 31 U/L (0.91 ULN). On 07-AUG-2013, approximately one month after rosuvastatin and ezetimibe were re-started, ALT, AST, and alkaline phosphate were all within normal range.

Discontinuations due to hepatic disorders

A higher percentage of patients treated with alirocumab discontinued treatment due to a treatment-emergent event related to a hepatic disorder. Of the 9 alirocumab-treated patients who discontinued due to a hepatic disorder event, 8 discontinued due to abnormal hepatic laboratory values.

One discontinuation is an example of a positive rechallenge in a 42-year-old female patient (baseline BMI 36.3 kg/m^2) with a medical history of obesity experienced ALT

increased of mild intensity on Day 68. Alirocumab was temporarily discontinued due to this elevation and ALT returned to baseline. However, when the patient was re-challenged, the ALT started to rise again increasing to a peak of 3.6 x ULN (124 IU/L) on Day 97. This led to permanent discontinuation of alirocumab.

Hepatic-related laboratory evaluation

Overall, the number of patients with elevations in liver enzymes was low; however for some categorical elevations in ALT, a slightly higher proportion of patients treated with alirocumab compared to placebo or ezetimibe-treated patients met the criteria..

Table 103. Hepatic biochemistry: Categorical increase in liver enzymes (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

	Placebo-controlled				Ezetimibe-controlled			
	Placebo N=1276		Alirocumab N=2476		Ezetimibe N=618		Alirocumab N=864	
	n/N1	%	n/N1	%	n/N1	%	n/N1	%
ALT elevation								
≥3x ULN (if BL ALT < ULN) or ≥2x baseline (if BL ALT ≥ULN)	13/1266	1.0	34/2453	1.4	1/612	0.2	10/850	1.2
>3x ULN	18/1266	1.4	41/2455	1.7	1/612	0.2	9/850	1.1
>5X ULN	7/1266	0.6	8/2455	0.3	0	0	5/850	0.6
>10X ULN	3/1266	0.2	2/2455	<0.1	0	0	1/850	0.1
>20x ULN	1/1266	<0.1	1/2455	<0.1	0	0	1/850	0.1
AST elevation								
>3x ULN	18/1266	1.4	28/2455	1.1	0	0	10/849	1.2
>5X ULN	5/1266	0.4	7/2455	0.3	0	0	4/849	0.5
>10X ULN	3/1266	0.2	3/2455	0.1	0	0	1/849	0.1
>20x ULN	1/1266	<0.1	1/2455	<0.1	0	0	0	0
Alkaline phosphatase elevation								
>1.5x ULN	13/1266	1.0	11/2455	0.4	6/612	1.0	7/850	0.8
Bilirubin elevation								
>2x ULN	6/1266	0.5	13/2456	0.5	2/612	0.3	5/850	0.6
ALT >3x ULN and Bili >2x ULN	2/1266	0.2	1/2455	<0.1	0	0	0	0

Source: ISS Table 34
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during treatment. The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period
Classification is performed on the worst value

Evidence for potential severe hepatotoxicity may be signaled by a set of findings called Hy's Law. These findings consist of an increased rate of transaminase elevations, no

significant evidence of obstruction, and a rise in bilirubin to 2x ULN in the absence of concurrent hepatic infection, hepatotoxic drugs, or injury.

There were 3 incidences of elevated transaminase levels with total bilirubin elevated 2x ULN (1 alirocumab-treated, 2 placebo-treated), which are summarized below. These cases of concomitant increases in liver transaminases and bilirubin do not qualify as Hy's Law cases based on the alternative etiologies of hepatitis A, cholangitis, or acute cholecystitis.

Alirocumab-treated

- 001112-528-202-003: A 50-year-old male patient (baseline BMI 30.2 kg/m2), with a history of type 2 diabetes mellitus and daily consumption of alcohol, experienced ALT increase on Day 1 due to hepatitis A (PT: hepatitis A) of mild intensity. IMP was temporarily discontinued. AST reached peak levels on Day 41 at 30.03 x ULN, ALT reached peak levels on Day 50 at 48.7 x ULN, and bilirubin reached peak levels on Day 46 at 7.38 x ULN. The patient was diagnosed with hepatitis A, reported as a treatment-emergent SAE and leading to a temporary drug withdrawal. The patient recovered from the event without sequelae.

Placebo-treated

- 12492-840-428-001: A 48-year-old male patient had increased ALT (12.36 ULN), AST (17.9 ULN), and total bilirubin (3 ULN) on Day 144. The patient was diagnosed with acute cholecystitis and possible choledocholithiasis reported as a treatment-emergent SAE
- 11717-124-008-007: A 68-year-old female patient, with a history of cholelithiasis and cholecystectomy, had increased total bilirubin (2.78 ULN) on Day 75, and then increased ALT (8.75 ULN) and AST (6.38 ULN) on Day 136. The patient was diagnosed with a cholangitis reported as a treatment-emergent SAE. Corrective treatment included piperacillin/tazobactam. The IMP (placebo) was temporarily interrupted due to the event of cholangitis. The patient recovered.

One additional case meeting the biochemical requirements for Hy's Law was submitted as a MedWatch 15 day safety report under alirocumab's IND 105574 regarding a 48 year old woman with HeFH participating in the open label extension study (LTS13463), and initially enrolled in the parent study FH I where she received alirocumab for 18 months. During the parent study and OLE study, the patient was treated concomitantly with simvastatin 40 mg and ezetimibe 10 mg. Nine months after entry into the OLE study and 4 days after the most recent alirocumab injection, the patient developed jaundice, nausea, and malaise. Liver function tests revealed an ALT 66.2 ULN, AST 52.9 ULN, GGT 16.6 ULN, and total bilirubin 4.1 ULN. Workup included serologies for hepatitis A, B, C, Herpes virus, and EBV, copper and cerulosplasmin, search for autoimmune hepatitis and abdominal echography. The results were all negative. The patient was seen secondarily by a hepatologist who considered the "hepatitis" as possibly induced by the IMP, although the time to onset occurring more than 2 years after the start of the exposure did not strongly support this initially suggested causal relationship. **Hepatitis E IgM were tested and detected on 05 March 2015**, however these results were not provided to the applicant until June 12. Results on IgM titers were received by the applicant on 2 July 2015 and showed an index for HEV IgM of

7.83 (threshold for detection for any value >0.255). The patient was negative for ADA antibodies.

The Division requested that the applicant query the entire safety database again to look in all unblinded trials, ongoing open-label trials and blinded clinical trials for additional cases of Hy's Law and elevations in liver enzymes defined as ALT ≥5x ULN in association with SAE or interruption of therapy. No confirmed Hy's Law cases were found.

The following studies were queried.

The unblinded studies included:

- The pool of placebo-controlled studies as presented in the integrated safety summary (ISS): phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361). All the phase 3 studies are now completed and the database lock for the second-step analysis has been done.
- The pool of ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). Only the COMBO II study is still ongoing (second-step analysis as planned at the end of the study).
- The studies evaluating 2 once monthly dosing regimens, 300 mg Q4W and 150 mg Q4W, in 2 phase 3 studies CHOICE I (first-step analysis) (b) (4) .
- Study EFC13672 (first-step analysis) conducted in Japan

The ongoing open-label extension studies/periods included:

- For phase 2 studies: CL-1032 (extension of CL-1003 phase 2 study in heFH patients), and CL-1018 (extension of the double-blind period).
- For phase 3 studies: ALTERNATIVE (extension of the double-blind period), LTS13463 (OLE; includes patients from FH I, FH II, HIGH FH, and the heFH stratum of LTS11717), (b) (4)).

The ongoing double-blind phase 3 studies included:

- COMBO II study (remaining blinded period after the first step analysis), CHOICE I study (remaining blinded period after the first step analysis), and the OUTCOMES study

ALT≥3X ULN and bilirubin ≥2x ULN: No new cases were found in the unblinded studies. In the open-label studies, the applicant stated that two patients in open-label extension studies met biochemical criteria, however 1 patient was subsequently diagnosed with Hepatitis E and in the other patient (01003-840-309-002), after 20 months on treatment had elevated transminases (ALT 7X ULN, AST 8X ULN), but total bilirubin and alkaline phosphatase remained normal (which does not meet the biochemical definition). This patient's laboratory values returned to normal with continued treatment of alirocumab.

In the ongoing double-blind studies, there were 3 patients meeting these biochemical criteria among the 14,987 patients that were queried (0.02%). One patient was unblinded and was on placebo, another had diagnosis of Hepatitis C, and the third patient (11570-804-001-022) had elevated ALT 4.5x ULN, AST 2.9x ULN, total bilirubin 1.9x ULN 4 months after initiation with IMP (patient blinded). The patient was asymptomatic, ultrasound showed hepatomegaly and cholestasis. A hepatologist was not consulted, Hepatitis C was negative and other serology results were not reported. The diagnostic conclusion was increased ALT values due to cholestasis. The IMP was temporarily discontinued while no action was taken with background rosuvastatin therapy. The patient recovered with normalization of LFT values within 2 weeks. There is no information whether the IMP has been resumed.

ALT ≥5x ULN in association with SAE or interruption of therapy: In unblinded studies with either first step or second step analyses an equal proportion (0.3%) of patients treated with alirocumab or control (placebo, ezetimibe, and titration of statin or statin switch) had a serum ALT ≥ 5X ULN in association with a serious event or leading to interruption in therapy. In ongoing double-blind trials, 21 (0.1%) patients have had a serum ALT ≥ 5X ULN with a serious event or leading to interruption of therapy. The applicant provided short narratives of these 21 patients. Conclusions from these narratives are limited as several of the narratives have incomplete information regarding the work-up of these patients (e.g. results of serologies have not yet been reported), or if a rechallenge of the IMP was done. However, many of them have potential alternative etiologies such as diagnoses with Hepatitis E, Hepatitis C, pancreatitis, and concomitant medications. At least one patient had a negative rechallenge with the IMP. For the majority of patients, liver enzymes normalized with either discontinuation of IMP and/or statin therapy.

Please note, upon review of the initial MedWatch report which did not have information regarding the patient's Hepatitis E status, the Division requested an internal review of the case by the Associate Director for Science (Hepatology), Office of Pharmacoviligiance and Epidemology (OPE), Dr. John Senior. Dr. Senior reviewed the case as well as the additional requested information regarding elevations in liver enzymes submitted by the applicant. The consult review confirms that the case prompting the consult was probably not induced by alirocumab but by acute hepatitis E. Regarding the additional information submitted, the consult aligns with this reviewer's assessment of the cases that a causal association with alirocumab cannot be made at this time.

(b) (4)

Ophthalmologic adverse events

Selection of ophthalmologic TEAEs for analysis was based on SMQs "optic nerve disorders" (broad and narrow), "retinal disorders" (narrow), and "corneal disorders" (narrow).

A slightly higher percentage of alirocumab-treated patients experienced a treatment-emergent ophthalmologic adverse event of interest, serious ophthalmological adverse event, and discontinuations due to ophthalmologic AEs compared to placebo-treated patients. There were no fatalities associated with these events. A smaller proportion of patients in the ezetimibe-controlled group experienced a TEAE, however, more occurred with alirocumab treatment. It is possible the higher number of ophthalmologic events in the placebo-controlled pool versus the ezetimibe-controlled pool is a result of testing color vision in all patients in the placebo-controlled LONG TERM study as well as additional testing performed in the ophthalmologic sub-study.

Table 104. Overview of treatment emergent ophthalmological adverse events (SMQ) (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

Ophthalmologic disorders (SMQ)	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	18 (1.4)	44 (1.8)	1.24 (0.72-2.15)	3 (0.5)	7 (0.8)	1.36 (0.35-5.31)
SAE	3 (0.2)	7 (0.3)		0	1 (0.1)	
TEAE leading to death	0	0		0	0	
TEAE leading to discontinuation	0	2 (<0.1)		0	0	

Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-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): 'optic nerve disorders' (broad + narrow), 'retinal disorders' (narrow) and 'corneal disorders' (narrow)
1. Calculated using a Cox model stratified on the study

Optic nerve disorders (SMQ) occurred in 17 (0.7%) and 3 (0.2%) patients in the alirocumab and placebo groups, respectively, and retinal disorders (SMQ) were reported in 35 (1.4%) and 13 (1.0%) patients, respectively. The only preferred term in the optic nerve disorder SMQ reported in both the alirocumab and placebo treated group was visual acuity reduced (0.2% in each group). Events that occurred in at least 2 patients and with higher frequency in the alirocumab treated group were visual impairment, color vision tests abnormal, and optic nerve cupping. In the retinal disorders SMQ, the most reported events occurred with equal frequency between the two groups (diabetic retinopathy, vitreous floaters, visual acuity reduced). Events that occurred in at least 2 patients and with higher frequency in the alirocumab treated group were vitreous detachment, visual impairment, color vision tests abnormal, retinal detachment, retinal hemorrhage.

Table 105. Number and frequency of opthalmological disorders by SMQ and PT (safety population) – pool of placebo-controlled studies and ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Ophthalmologic disorders				
n (%)	18 (1.4)	44 (1.8)	3 (0.5)	7 (0.8)
# of pts with an event per 100 pt-yrs[1]	1.2	1.6	0.6	1.0
95% CI	0.7 to 2.0	1.1 to 2.1	0.1 to 1.9	0.4 to 2.0
HR (95% CI)[2]	1.24 (0.72 to 2.15)		1.36 (0.35 to 5.31)	
Ophthalmologic disorders, n (%)	**18 (1.4)**	**44 (1.8)**	**3 (0.5)**	**7 (0.8)**
Corneal disorders (SMQ)	**5 (0.4)**	**2 (<0.1)**	**0**	**1 (0.1)**
Corneal abrasion	2 (0.2)	1 (<0.1)	0	0
Ophthalmological examination abnormal	0	1 (<0.1)	0	0
Corneal scar	0	0	0	1 (0.1)
Injury corneal	1 (<0.1)	0	0	0
Keratitis	1 (<0.1)	0	0	0
Keratoconus	1 (<0.1)	0	0	0
Optic nerve disorders (SMQ)	**3 (0.2)**	**17 (0.7)**	**0**	**0**
Visual acuity reduced	2 (0.2)	4 (0.2)	0	0
Color vision tests abnormal	0	2 (<0.1)	0	0
Optic nerve cupping	0	2 (<0.1)	0	0
Amblyopia	0	1 (<0.1)	0	0
Arteritis	0	1 (<0.1)	0	0
Color blindness acquired	0	1 (<0.1)	0	0
Demyelination	0	1 (<0.1)	0	0
Ophthalmological examination abnormal	0	1 (<0.1)	0	0
Optic atrophy	0	1 (<0.1)	0	0
Optic neuritis	0	1 (<0.1)	0	0
Retinal disorders (SMQ)	13 (1.0)	35 (1.4)	3 (0.5)	6 (0.7)
Diabetic retinopathy	2 (0.2)	5 (0.2)	0	1 (0.1)
Vitreous floaters	2 (0.2)	5 (0.2)	0	1 (0.1)
Visual acuity reduced	2 (0.2)	4 (0.2)	0	0
Vitreous detachment	1 (<0.1)	4 (0.2)	1 (0.2)	0
Visual impairment	1 (<0.1)	3 (0.1)	0	0
Color vision tests abnormal	0	2 (<0.1)	0	0
Macular degeneration	1 (<0.1)	2 (<0.1)	0	1 (0.1)
Retinal detachment	0	2 (<0.1)	1 (0.2)	1 (0.1)
Retinal hemorrhage	0	2 (<0.1)	0	0
Age-related macular degeneration	1 (<0.1)	1 (<0.1)	0	0
Chorioretinopathy	0	1 (<0.1)	0	0
Color blindness acquired	0	1 (<0.1)	0	0
Detachment of retinal pigment epithelium	0	1 (<0.1)	0	0
Diabetic retinal edema	0	1 (<0.1)	0	0

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Macular fibrosis	2 (0.2)	1 (<0.1)	0	0
Retinal artery embolism	0	1 (<0.1)	0	0
Retinal tear	0	1 (<0.1)	0	0
Retinal vein thrombosis	0	1 (<0.1)	0	0
Retinopathy hypertensive	0	1 (<0.1)	1 (0.2)	0
Arteriosclerotic retinopathy	0	0	0	1 (0.1)
Retinal vein occlusion	3 (0.2)	0	0	1 (0.1)

Source: ISS Table 27
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-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): 'optic nerve disorders' (broad + narrow), 'retinal disorders' (narrow) and 'corneal disorders' (narrow)

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study

Serious adverse events - ophthalmological disorders

There were a total of 8 alirocumab-treated patients and 3 placebo-treated patients reporting a SAE. The SAE of "demyelination" is a preferred term included in the optic nerve SMQ but this case does not include an ophthalmic disorder. This SAE is discussed in the section of neurological adverse events. The SAE of "optic neuritis" is also discussed in the neurological adverse events section. A summary of the remaining events is provided below. Most of the events occurred in patients with a medical history of ophthalmological or other conditions (ischemic heart disease) which could have contributed to the occurrence of these events.

Table 106. Summary of ophthalmological disorder (SMQ) SAEs

Patient ID Study name Treatment	Age/Sex	Day of onset	Preferred term Outcome	Comments
Alirocumab-treated				
11568-840-846-002 COMBO I	64 F	38	Retinal detachment Recovered	Medical history of cataract/cataract surgery Had corrective treatment No action taken with IMP
11717-616-009-027 LONG TERM Alirocumab 150 mg Q2W	73 M	294	Visual impairment Recovered	Medical history of transient vision disturbances No corrective treatment, pt recovered No action taken with IMP
11717-616-013-018 LONG TERM Alirocumab 150 mg Q2W	71 F	167	Retinal hemorrhage Not recovered	Medical history of cataract surgery and retinal detachment 6 months earlier No corrective treatment No action taken with IMP
11717-826-008-149 LONG TERM Alirocumab 150 mg Q2W	69 M	447	Retinal vein thrombosis Recovering Vitreous detachment Not recovered	Medical history of ischemic heart disease, atrial f brillation, MI No action taken with IMP
12492-840-429-001 FH I	36 M	337	Retinal artery embolism Resolving (residual field defects and	Medical history CAD, MI, HTN, obesity, T2DM, intracardiac thrombus Corrective treatment with warfarin

			blurred vision)	
11569-208-914-003 COMBO II	67 M	283	Retinal detachment Recovered	Medical history of retinal detachment Received corrective treatment No action taken with IMP
Placebo-treated				
11717-710-008-017 LONG TERM Placebo	60 M	31	Retinal vein occlusion Recovered with sequelae (reduced vision right eye)	Sudden onset blindness in right eye to cilio retinal artery occlusion. No action taken with IMP
11717-826-008-067 LONG TERM Placebo	83 F	286	Retinal vein occlusion Not recovered	Medical history T2DM, MI, HTN Received corrective treatment No action taken with IMP
11717-840-075-018 LONG TERM Placebo	56 F	58	Retinal vein occlusion Not recovered	Medical history T2DM, HTN Received corrective treatment No action taken with IMP

Source: ISS and individual CSR narratives

Discontinuations due to ophthalmological disorders

A total of 2 alirocumab-treated patients (1 due to optic neuritis which is discussed in the section regarding neurological events) and no placebo or ezetimibe treated patients discontinued treatment due to a TEAE. The alirocumab-treated patient who discontinued treatment was a 76 year-old female patient with a medical history of bilateral intraocular lens implants and caratact and reduced visual acuity, who experienced floaters in both eyes of mild intensity (PT: vitreous floaters) at an undetermined date after the first administration of alirocumab. Alirocumab was discontinued. The patient did not receive corrective treatment and had not recovered at the time of alirocumab BLA submission to Division.

Ophthalmologic sub-study

An ophthalmologic sub-study within the LONG TERM study was conducted at selected sites and enrolled 139 patients [55 (6.5%) placebo, 88 (5.7%) alirocumab). Randomization in patients participating in the ophthalmologic sub-study was also stratified by diabetes status. Ophthalmologic assessments (including color vision testing, best corrected visual acuity, slit lamp ophthalmoscopy, intraocular pressure assessment, dilated lens and fundus examination, or optic disc and fundus photographs) were performed periodically throughout the study as per the usual practice of the ophthalmologist/optometrist involved in this sub-study. It was recommended that the same ophthalmologist/optometrist performed the evaluations. Abnormalities identified during ophthalmologic assessments were to be reported as AEs.

Mean treatment exposure was similar between treatment groups, 60.6 weeks in the alirocumab group and 60.9 weeks in the placebo group. In the sub-study, 73 patients in the alirocumab group and 42 patients in the placebo group were exposed to study treatment for ≥52 weeks, and 17 patients [19.3%] in the alirocumab group and 9 patients [17.6%] in the placebo group were exposed to study treatment for ≥76 weeks.

Diabetes status was similarly distributed between treatment groups – approximately 30% of alirocumab and placebo-treated patients participating in the sub-study reported a history of diabetes.

Among the 139 patients participating in the ophthalmological sub-study, 6 patients had an ophthalmological TEAE by SMQ (4 patients [4.5%] in the alirocumab group and 2 patients [3.9%] in the placebo group). In the four alirocumab-treated patients, the events reported in 1 patient each were age-related macular degeneration, demyelination, detachment of the retinal pigment epithelium, retinal hemorrhage, and retinal tear. The case of "demyelination" did not involve an ophthalmic disorder and based on the narrative is a case of probably multiple sclerosis which is discussed in this document under neurologic events. In the placebo group, 1 patient each had diabetic neuropathy and macular degeneration.

Results of the ophthalmological sub-study did not demonstrate a specific ophthalmologic safety signal.

Diabetes mellitus

The following table describes the baseline diabetic status of patients in the phase 2 and phase 3 trials included in the placebo and ezetimibe safety pools. Approximately 70% of patients had either impaired fasting glucose or diabetes at baseline as per medical history and/or laboratory values.

Table 107. Diabetes status at baseline (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

Baseline diabetes status	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Normal	**418 (32.8)**	**803 (32.4)**	**174 (28.2)**	**223 (25.8)**
Impaired glucose control	**455 (35.7)**	**919 (37.1)**	**243 (39.3)**	**333 (38.5)**
As per medical history	30 (2.4)	62 (2.5)	19 (3.1)	29 (3.4)
As per laboratory data only	425 (33.3)	857 (34.6)	224 (36.2)	304 (35.2)
Diabetes	**403 (31.6)**	**754 (30.5)**	**201 (32.5)**	**308 (35.6)**
As per medical history	367 (28.8)	710 (28.7)	190 (30.7)	282 (32.6)
As per laboratory data only	36 (2.8)	44 (1.8)	11 (1.8)	26 (3.0

Source: ISS appendix 1.3.7.14
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Impaired glucose control was defined as: specific terms reported in the medical history as "impaired glucose control", or baseline HbA1c ≥5.7% and <6.5%, or 2 FPG at screening and randomization ≥100 mg/dL but no more than 1 ≥126 mg/dL
Diabetes defined as type 1 or 2 diabetes reported in the medical history, or baseline HbA1c ≥6.5%, or 2 values of FPG at screening and randomization ≥126 mg/dL

The incidence of diabetes mellitus or complications of diabetes mellitus related events in phase 2 and phase 3 studies was assessed using a CMQ based on the primary and

secondary high level group term (HLGT) 'diabetes complications', high level term (HLT) 'diabetes mellitus', and HLT 'carbohydrate tolerance analyses (incl diabetes)' with the exception of the PT 'blood glucose decreased', PT 'hyperglycemia' included in this analysis.

The analyses of the events are presented in the following ways: (1) using the prespecified analyses in the safety population as a whole regardless of baseline diabetes status, (2) by baseline diabetes status as defined by medical history reported on the CRF, (3) exploratory analyses based on medical history and/or laboratory values at baseline.

Analyses of adverse events reported as diabetes mellitus and diabetes complications regardless of baseline diabetes status

In the placebo-control safety pool there was a slightly higher percentage of alirocumab-treated patients (4.2%) compared to placebo-treated patients (3.8%) reporting a TEAE related to diabetes or its complications. This pattern was not observed in the ezetimibe-control safety pool where a slightly lower percentage of alirocumab-treated patients (2.9%) versus ezetimibe-treated patients (3.6%) reported an event. Serious adverse events were confined to the placebo-controlled studies and were low and similar between treatment groups. There were no fatalities as a result of these TEAEs. Two patients (both alirocumab-treated) discontinued due to a diabetes-related TEAE.

Table 108. Overview of treatment emergent diabetes mellitus (CMQ) (safety population) – pool of placebo-controlled studies and pool of ezetimibe controlled studies

Diabetes mellitus (CMQ)	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	49 (3.8)	103 (4.2)	1.07 (0.76 -1.50)	22 (3.6)	25 (2.9)	0.71 (0.40-1.26)
SAE	5 (0.4)	6 (0.2)		0	0	
TEAE leading to death	0	0		0	0	
TEAE leading to discontinuation	0	2 (<0.1)		0	0	

Source: NDA 125559 ISS addendum Table 1.1.1.4 submitted 1 April 2015, SD #25
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
The selection of PTs is based on the primary and secondary HLGT 'diabetes complications', HLT 'diabetes mellitus' and HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased', includes PT 'hyperglycemia'
1. Calculated with Cox model stratified on the study

In the placebo-controlled safety pool, the preferred terms that occurred in more than 2 patients and in a higher proportion of alirocumab-treated patients were "diabetes mellitus" and "type 2 diabetes mellitus". In the ezetimibe-controlled safety pool, the

preferred terms that occurred in more than 2 patients and in a higher proportion of alirocumab-treated patients were “type 2 diabetes mellitus” and “diabetes mellitus inadequate control”.

Table 109. Number (%) of patients with diabetes mellitus or diabetic complications TEAEs by CMQ (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Diabetes mellitus or diabetic complications				
n (%)	49 (3.8)	103 (4.2)	22 (3.6)	25 (2.9)
# of pts with an event per 100 pt-yrs[1]	3.4	3.7	4.8	3.5
95% CI	2.5 to 4.5	3.0 to 4.5	3.0 to 7.3	2.2 to 5.1
HR (95% CI)[2]	1.07 (0.76 to 1.50)		0.71 (0.40 to 1.26)	
Diabetes mellitus or diabetic complications (CMQ)	**49 (3.8)**	**103 (4.2)**	**22 (3.6)**	**25 (2.9)**
Diabetes mellitus	14 (1.1)	32 (1.3)	10 (1.6)	7 (0.8)
Type 2 diabetes mellitus	12 (0.9)	31 (1.3)	2 (0.3)	5 (0.6)
Diabetes mellitus inadequate control	7 (0.5)	12 (0.5)	1 (0.2)	3 (0.3)
Hyperglycemia	6 (0.5)	9 (0.4)	3 (0.5)	3 (0.3)
Diabetic neuropathy	1 (<0.1)	6 (0.2)	1 (0.2)	3 (0.3)
Blood glucose increased	4 (0.3)	5 (0.2)	5 (0.8)	1 (0.1)
Diabetic retinopathy	2 (0.2)	5 (0.2)	0	1 (0.1)
Glycosylated hemoglobin increased	2 (0.2)	5 (0.2)	0	1 (0.1)
Diabetic foot	0	2 (<0.1)	0	1 (0.1)
Diabetic nephropathy	0	2 (<0.1)	1 (0.2)	1 (0.1)
Blood glucose abnormal	0	1 (<0.1)	0	0
Diabetic retinal edema	0	1 (<0.1)	0	0
Glucose tolerance decreased	0	1 (<0.1)	0	0
Microalbuminuria	0	1 (<0.1)	0	0
Diabetic autonomic neuropathy	1 (<0.1)	0	0	0
Diabetic ketoacidosis	1 (<0.1)	0	0	0

Source: Source: NDA 125559 ISS addendum Table 1.1.1.1 submitted 1 April 2015, SD #25
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
MedDRA 17.0 . The selection of PTs is based on the primary and secondary HLGT 'diabetes complications', HLT 'diabetes mellitus' and HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased'

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study

Most of the events were ongoing at the cut-off date of the studies: among those with one of the above events, a total of 66 (64.1%) patients in the alirocumab group and 38 (77.6%) patients in the placebo group had TEAEs related to diabetes mellitus or diabetes complications that were classified as “ongoing”. A recovering outcome was reported in 6 (5.8%) of patients in the alirocumab group versus 2 (4.1%) patients in the placebo group. Similar to the placebo-controlled pool, “not recovered” was the most frequent outcome for diabetes mellitus or diabetes complications TEAEs, reported in 17

(68.0%) patients in the alirocumab group and 12 (54.5 %) patients in the ezetimibe group.

There did not appear to be consistent differences between treatment groups for either the placebo or ezetimibe-controlled studies in the timing of a CMQ defined diabetes-related TEAE (Figure 36).

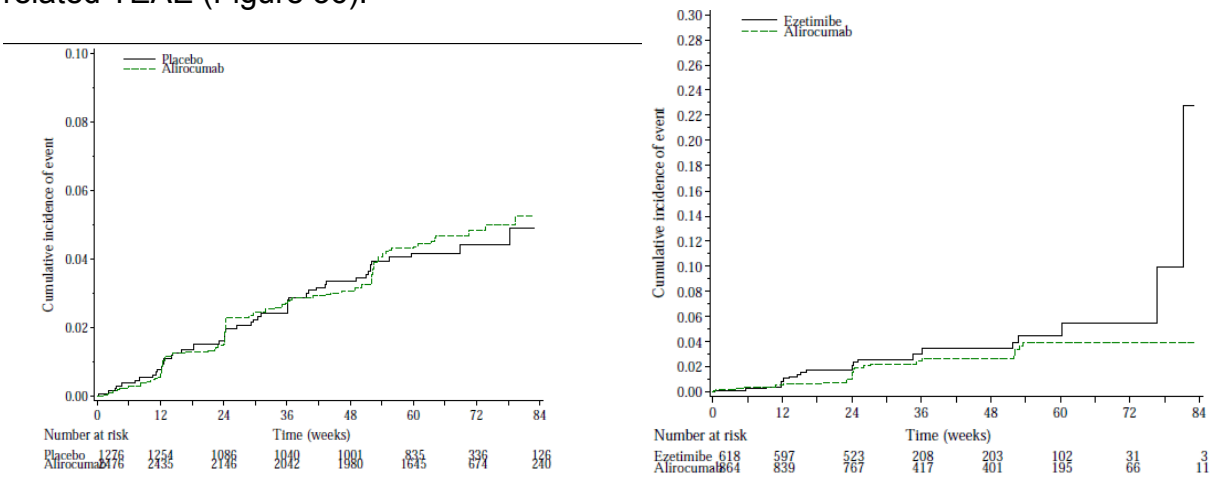


Figure 36. Study-adjusted Kaplan-Meier cumulative incidence curve for time to first diabetes mellitus or diabetic complications event during TEAE period (Safety population) – pool of placebo-controlled studies (left panel) and pool of ezetimibe-controlled studies (right panel)

Serious adverse events – Diabetes mellitus and diabetic complications (CMQ)

All patients with a serious diabetes mellitus event had reported a medical history of diabetes at baseline with the exception of one alirocumab-treated patient summarized below.

- 11717-100-005-028/**alirocumab**/**diabetes mellitus**: The event was reported in a 68-year-old female patient with history of stable angina pectoris and hypertension, and elevated baseline HbA1c of 7.7% and glucose of 214 mg/dL (no reported history of diabetes mellitus). The patient had a blood glucose level of 556 mg/dL and HbA1c of 15.6% (normal range: <6.5%) on Day 99, and an SAE of type 2 diabetes mellitus was reported on Day 100. The patient was hospitalized on Day 119 with typical symptoms of hyperglycemia and report of weight reduction of 10 kg over the prior 3 to 4 months. Corrective treatment included insulin and metformin.

Of the 11 SAEs reported, 2 patients (2 alirocumab, 2 placebo) had not recovered at the time of the submission cut-off date. Brief narratives of the "not recovered" SAE are included here.

- 11717-100-005-028/**alirocumab/type 2 diabetes mellitus**: See narrative above.
- 11717-100-013-002/**alirocumab/diabetes mellitus**: A 54-year-old male patient with a medical history of chronic renal failure, diabetic neuropathy, diabetic retinopathy, obesity, hypertension, and type 2 diabetes mellitus treated with Novomix and acarbose, experienced decompensated diabetes mellitus of moderate intensity, on Day 386. Alirocumab was permanently discontinued due to this event. The patient received corrective treatment with insulin. The patient had not recovered at the date of the last received information.
- 11717-826-010-175/**placebo/diabetes mellitus**: A 66-year-old female patient with a medical history of diabetic retinopathy, microalbuminuria, hypertension, menopause, and type 1 diabetes mellitus treated with insulin lispro, experienced worsening diabetes of moderate intensity, associated with urinary tract infection, on Day 361. No action was taken with the study drug. The patient did not receive corrective treatment. She had not recovered at the date of the last received information.
- 11717-840-075-018/**placebo/diabetic retinopathy**: A 56-year-old-female patient with a medical history of type 2 diabetes mellitus treated with metformin, hypertension, experienced a new serious adverse event of moderate intensity reported as diabetic retinopathy on Day 185. The event was diagnosed on optical coherence tomography. The patient was asymptomatic. No corrective treatment was given. No action was taken with the IMP. The patient had not recovered but the event has stabilized.

Discontinuations due to Diabetes mellitus and diabetes complications (CMQ)

There were 2 discontinuations due to a diabetes mellitus and diabetes complications adverse event, both occurring in alirocumab-treated patients. One was a serious event which was defined above (11717-100-013-002) and the other occurred in a 56-year old male patient with a relevant medical history of hypertension and type 2 diabetes mellitus treated with insulin detemir, metformin, saxagliptin, experienced worsening diabetes of mild intensity on Day 21. Alirocumab was permanently discontinued and the patient received corrective treatment with insulin lispro and metformin. He recovered from the event (11568-840-853-005).

Analyses of diabetes mellitus and diabetes complications (CMQ) by baseline diabetes status as per medical history

Table 110 below provides an overview of diabetes mellitus and diabetes complications (CMQ) divided by baseline diabetes status per medical history as recorded on the case

report forms. In patients at baseline with diabetes per medical history, a higher percentage of alirocumab-treated patients (10.6%) had an adverse event compared to placebo-treated patients (8.4%). The most commonly reported preferred term in patients with diabetes at baseline was “diabetes mellitus” (3.7% of alirocumab-treated patients and 2.5% of placebo-treated patients). In the ezetimibe-controlled group, 6.8% of ezetimibe-treated patients had a diabetes-related adverse event versus 5.7% of alirocumab-treated patients.

In patients without diabetes as per medical history, patients treated with alirocumab reported a lower incidence of CMQ defined diabetes mellitus and diabetes complications TEAEs compared to patients treated with placebo or ezetimibe.

Table 110. Number of patients with at least one diabetes mellitus or diabetic complications (CMQ) TEAE (safety population) – pool of placebo-controlled and pool of ezetimibe controlled studies

Diabetes mellitus (CMQ)	Diabetes at Baseline[1]				Without Diabetes at Baseline			
	Placebo-controlled		Ezetimibe-controlled		Placebo-controlled		Ezetimibe-controlled	
	Placebo N=367 n (%)	Alirocumab N=710 n (%)	Ezetimibe N=190 n (%)	Alirocumab N=282 n (%)	Placebo N=909 n (%)	Alirocumab N=1766 n (%)	Ezetimibe N=428 n (%)	Alirocumab N=582 n (%)
TEAE	31 (8.4)	75 (10.6)	13 (6.8)	16 (5.7)	18 (2.0)	28 (1.6)	9 (2.1)	9 (1.5)
SAE	5 (1.4)	5 (0.7)	0	0	0	1 (<0.1)	0	0
TEAE leading to death	0	0	0	0	0	0	0	0
TEAE leading to discontinuation	0	2 (0.3)	0	0	0	0	0	0

Source: ISS Addendum appendix Table 1.1.1.24, ISS Addendum appendix 1.1.1.26 Submitted 1 April 2015 SD#25
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
The selection of PTs is based on the primary and secondary HLGT 'diabetes complications', HLT 'diabetes mellitus' and HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased', and includes PT ‘hyperglycemia’
[1]Patient with term from “Type 1 or type 2 diabetes” CMQ recorded in medical history

Glucose-related laboratory values

Evaluation of mean change from baseline in fasting plasma glucose and HbA1c in the phase 3 placebo-controlled pool and ezetimibe-controlled pools did not demonstrate consistent meaningful changes over time including up to Week 52 (up to Week 24 for ezetimibe-controlled pool), last, or highest on-treatment value in the overall population (Table 111) or by baseline glucose control status (Table 112, Table 113).

Table 111. Change in glucose and HbA1c (safety population) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies

Parameter	Placebo-controlled pool				Ezetimibe-controlled pool			
	n	Placebo	n	Alirocumab	n	Ezetimibe	n	Alirocumab
Fasting plasma glucose (mg/dL)								
Baseline (BL)	117	110.8 (34.2)	2316	109.5 (31.2)	618	108.8 (27.0)	864	112.3 (28.2)
Mean change (SD) from BL to								
Last on-treatment[1]	1136	4.3 (31.3)	2238	3.8 (30.3)	589	3.2 (28.8)	820	2.6 (24.6)
Worst (highest) on-treatment[2]	1136	16.8 (35.4)	2238	17.0 (35.7)	589	10.0 (28.8)	820	11.9 (26.6)
Week 52 (pbo)/ Week 24 (eze)	969	2.4 (29.6)	1930	2.8 (27.3)	496	2.9 (24.4)	727	1.5 (23.0)
HbA1c (%)								
Baseline (BL)	1169	6.06 (0.95)	2310	6.04 (0.93)	618	5.99 (0.78)	860	6.05 (0.80)
Mean change (SD) from BL to								
Last on-treatment[1]	1126	0.08 (0.57)	2215	0.09 (0.65)	565	0.12 (0.49)	802	0.10 (0.56)
Worst (highest) on-treatment[2]	1126	0.25 (0.56)	2215	0.29 (0.67)	565	0.20 (0.50)	802	0.19 (0.54)
Week 52 (pbo)/ Week 24 (eze)	976	0.07 (0.54)	1950	0.10 (0.66)	497	0.14 (0.47)	733	0.08 (0.44)

Source: ISS appendix 1.5.2.1.2; ISS Table 43
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Defined as the last value collected up to 21 days after the last double-blind IMP injection.
2. Defined as the nadir and/or the peak value according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
Patients who had parameter assessed at baseline and/or post-baseline are included. Only central laboratory values are taken into account.

Table 112. Change in glucose and HbA1c by baseline glucose control status (safety population) – pool of phase 3 placebo-controlled studies

Parameter	Normal				Impaired fasting glucose				Diabetes mellitus			
	n	Placebo	n	Alirocumab	n	Placebo	n	Alirocumab	n	Placebo	n	Alirocumab
Fasting plasma glucose (mg/dL)												
Baseline (BL)	364	92.3 (9.7)	716	92.4 (9.5)	419	102.1 (11.5)	865	102.1 (11.4)	389	137.5 (46.8)	735	134.8 (43.0)
Mean change (SD) from BL												
Last on-treatment[1]	358	1.2 (9.3)	694	1.5 (10.0)	407	2.4 (11.8)	837	2.2 (12.2)	371	9.2 (52.2)	707	8.1 (51.0)
Worst (highest) on-treatment[2]	358	7.5 (10.1)	694	7.7 (9.9)	407	9.6 (12.7)	837	9.2 (12.2)	371	33.5 (56.1)	707	35.4 (57.2)
Week 52 (pbo)	308	0.6 (8.8)	589	0.9 (9.5)	355	0.2 (10.6)	742	1.5 (11.1)	307	6.8 (50.3)	599	6.4 (46.4)
HbA1c (%)												
Baseline (BL)	361	5.35 (0.22)	711	5.34 (0.22)	419	5.83 (0.27)	864	5.83 (0.28)	389	6.96 (1.12)	735	6.95 (1.10)
Mean change (SD) from BL												
Last on-treatment[1]	352	0.08 (0.24)	679	0.09 (0.25)	403	0.02 (0.28)	832	0.01 (0.31)	371	0.16 (0.93)	705	0.20 (1.06)
Worst (highest) on-treatment[2]	352	0.19 (0.21)	678	0.21 (0.23)	403	0.13 (0.26)	832	0.13 (0.29)	371	0.43 (0.89)	705	0.57 (1.08)
Week 52 (pbo)	308	0.09 (0.24)	591	0.10 (0.25)	356	0.01 (0.27)	746	-0.00 (0.30)	312	0.12 (0.88)	613	0.22 (1.09)

Source: ISS appendix 1.5.2.2.2.3; 1.5.2.2.10
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)

1. Defined as the last value collected up to 21 days after the last double-blind IMP injection.
2. Defined as the nadir and/or the peak value according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list

Patients who had parameter assessed at baseline and/or post-baseline are included. Only central laboratory values are taken into account.
Impaired glucose control and diabetes at baseline are defined using specific terms reported in the Medical history, baseline HbA1c, and fasting blood glucose at screening and randomization

Table 113. Change in glucose and HbA1c by baseline glucose control status (safety population) – pool of ezetimibe-controlled studies

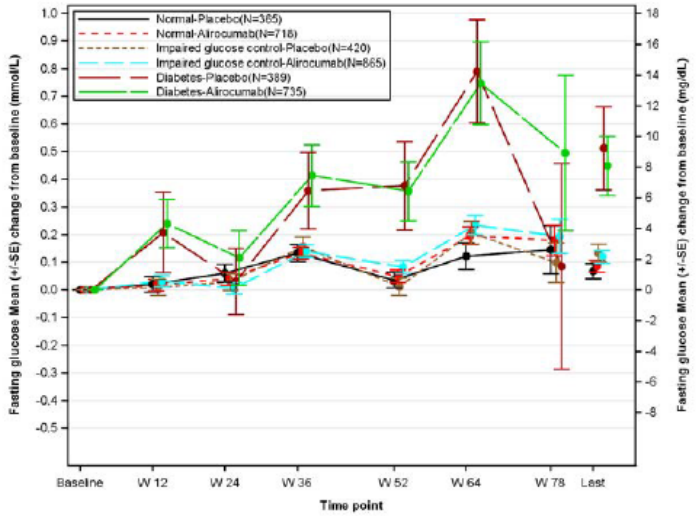
Parameter	Normal				Impaired fasting glucose				Diabetes mellitus			
	n	Ezetimibe	n	Alirocumab	n	Ezetimibe	n	Alirocumab	n	Ezetimibe	n	Alirocumab
Fasting plasma glucose (mg/dL)												
Baseline (BL)	174	92.6 (8.3)	223	94.2 (9.2)	243	102.8 (12.7)	333	105.3 (14.4)	201	130.0 (35.6)	308	133.1 (34.9)
Mean change (SD) from BL												
Last on-treatment[1]	165	2.7 (10.1)	213	1.6 (9.8)	234	-0.3 (13.7)	318	0.3 (13.8)	190	7.9 (47.1)	289	5.8 (37.7)
Worst (highest) on-treatment[2]	165	6.2 (10.1)	213	6.0 (10.5)	234	5.3 (13.5)	318	7.3 (17.7)	190	19.0 (45.1)	289	21.4 (38.0)
Week 24 (eze)	139	1.8 (9.3)	186	3.0 (9.7)	201	-0.1 (12.7)	282	-0.0 (16.4)	156	7.9 (39.7)	259	2.1 (33.5)
HbA1c (%)												
Baseline (BL)	174	5.35 (0.25)	221	5.37 (0.20)	243	5.81 (0.29)	333	5.81 (0.28)	201	6.77 (0.85)	306	6.81 (0.83)

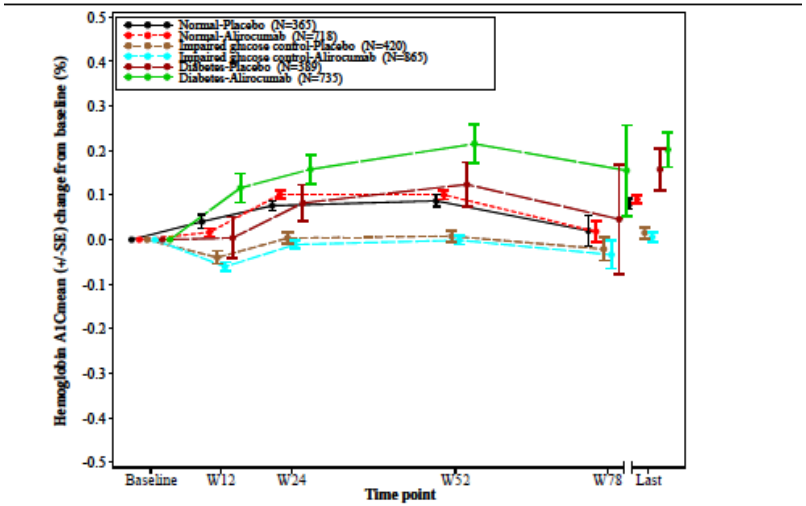
Parameter	Normal				Impaired fasting glucose				Diabetes mellitus			
	n	Ezetimibe	n	Alirocumab	n	Ezetimibe	n	Alirocumab	n	Ezetimibe	n	Alirocumab
Mean change (SD) from BL												
Last on-treatment[1]	159	0.09 (0.28)	207	0.05 (0.23)	226	0.04 (0.26)	313	0.01 (0.38)	180	0.23 (0.76)	282	0.23 (0.82)
Worst (highest) on-treatment[2]	159	0.14 (0.28)	207	0.11 (0.22)	226	0.10 (0.24)	313	0.11 (0.36)	180	0.38 (0.78)	282	0.35 (0.79)
Week 24 (eze)	139	0.10 (0.26)	188	0.06 (0.23)	203	0.05 (0.23)	286	0.02 (0.28)	155	0.27 (0.75)	259	0.16 (0.65)

Source: ISS Appendix 1.5.2.2.7; 1.5.2.2.13
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

1. Defined as the last value collected up to 21 days after the last double-blind IMP injection.
2. Defined as the nadir and/or the peak value according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list

Patients who had parameter assessed at baseline and/or post-baseline are included. Only central laboratory values are taken into account.
Impaired glucose control and diabetes at baseline are defined using specific terms reported in the Medical history, baseline HbA1c, and fasting blood glucose at screening and randomization





Source: ISS appendix 1.5.2.2.4, 1.5.2.2.11
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
The last on-treatment value is defined as the last value collected up to 21 days after the last double-blind IMP injection
Patients who had that parameter assessed at baseline and / or post-baseline are included.
Impaired glucose control and diabetes at baseline are defined using specific terms reported in the Medical history, baseline HbA1c, and fasting blood glucose at screening and randomization

Figure 37. Mean change (SE) change from baseline in fasting plasma glucose (left panel) and HbA1c (right panel) by baseline glucose control category (safety population) – pool of phase 3 placebo-controlled studies

Shifts in diabetic status

Exploratory analyses were conducted examining the shifts in diabetes status (normal, impaired fasting glucose, and diabetes) in patients from the phase 3 placebo-controlled pool and ezetimibe-controlled pool (phase 2 placebo trials excluded).

The following criteria were used to define baseline glucose control categories based on medical history and laboratory values.

- Diabetes
  - Type 1 or 2 diabetes reported in the medical history; or
  - Baseline HbA1c ≥ 6.5%; or
  - Two values of fasting plasma glucose (FPG) (at screening and randomization ≥126 mg/dL
- Impaired fasting glucose
  - Specific terms reported in the medical history; or
  - Baseline HbA1c ≥ 5.7% and <6.5%; or
  - Two values of FPG (at screening and randomization) ≥ 100 mg/dL but no more than one ≥ 126 mg/dL
- Normal was defined as not fulfilling the above criteria

As shown in Table 114 below, a greater percentage of alirocumab-treated patients experienced a worsening shift in diabetes status compared to placebo (17.3% alirocumab vs. 14.5% placebo) or ezetimibe-treated patients (13.1% alirocumab versus 11.9% ezetimibe).

A total of three patients shifted from normal glucose control to diabetes (2 alirocumab-treated patients and 1 placebo-treated patient). However, for these patients the shift to the diabetic category was based on transient changes in fasting plasma glucose not associated with change in HbA1c values. No patient required the prescription of an anti-diabetic agent.

- Patient ID. 011569-840-991-002 (alirocumab), the change in fasting glucose was apparently isolated and not associated with a change in HbA1c value or the reporting of a concomitant adverse event.
- Patient ID. 011717-056-001-006 (alirocumab), the high fasting glucose values were concomitant to the development of a B-cell lymphoma.
- Patient ID. 11717-840-111-001 (placebo), the shift to the diabetes category was determined on high fasting glucose values measured at the local laboratory of the hospital where the patient was admitted for severe pleuropericarditis and pleural effusion on Week 40, treated with high doses of corticosteroids, in particular intravenous (IV) methylprednisolone at the initiation of treatment. The high fasting glucose values were concomitant to the IV steroid injections.

Of the patients with normal glucose control at baseline in the placebo-controlled pool, 31.2% of alirocumab-treated patients and 26.6% of placebo-treated patients shifted to impaired fasting glucose. In the ezetimibe-controlled pool, 26.5% of alirocumab-treated patients versus 24.1% of ezetimibe-treated patients shifted from normal to impaired fasting glucose. All of these shifts were identified by laboratory data only.

A shift from impaired fasting glucose to diabetes was observed with greater incidence in alirocumab-treated patients in the placebo-controlled safety pool [alirocumab group (5.7%); placebo group (3.8%)] and ezetimibe-controlled safety pool [alirocumab group (3.9%); ezetimibe group (3.3%)]. Most of these shifts were identified by laboratory data only.

Of note, in the placebo-controlled safety pool of the 1285 patients with impaired fasting glucose at baseline and post-baseline measurements available for analyses, a higher percentage of alirocumab-treated patients (20.6%) demonstrated an improvement in glucose control status compared to placebo-treated patients (18.1%). This pattern was not replicated in the ezetimibe-controlled safety pool.

Table 114. Shifts in glucose control category during TEAE period (safety population) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1174 n/N1 (%)	Alirocumab N=2318 n/N1 (%)	Ezetimibe N=618 n/N1 (%)	Alirocumab N=864 n/N1 (%)
Total individuals with shift to worse glycemic category	**114/785 (14.5%)**	**274/1583 (17.3%)**	**50/417 (11.9%)**	**73/556 (13.1%)**
Normal to Impaired	97/365 (26.6%)	224/718 (31.2%)	42/174 (24.1%)	59/223 (26.5%)
Normal to Diabetes	1/365 (0.3%)	1/718 (0.1%)	0	1/223 (0.4%)
Impaired to Diabetes	16/420 (3.8%)	49/865 (5.7%)	8/243 (3.3%)	13/333 (3.9%)
Total individuals with shift to improved glycemic category	**76/1174 (6.5%)**	**178/2318 (7.7%)**	**77/618 (12.5%)**	**94/864 (10.9%)**
Impaired to normal	76/420 (18.1%)	178/865 (20.6%)	77/243 (31.7%)	94/333 (28.2%)

Source: ISS Appendix Table 1.5.2.2.1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period, by baseline glucose control status

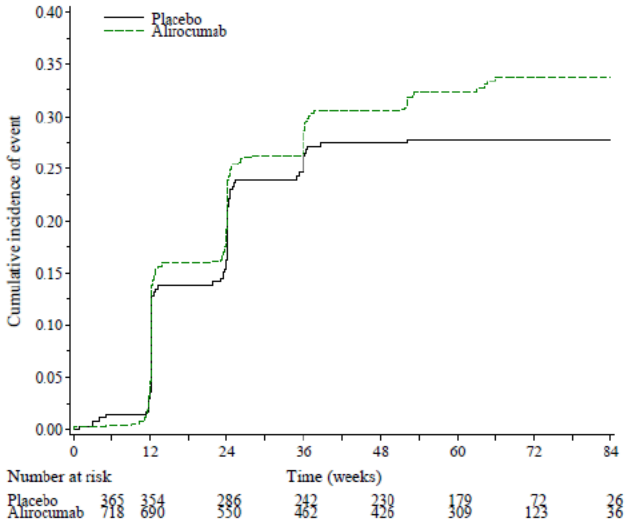
The following table gives a summary of the number of patients with normal glucose control at baseline who met the impaired fasting glucose criteria at least once as defined by adverse events, HbA1c and fasting plasma glucose values. A higher proportion of alirocumab-treated patients (31.2%) developed impaired fasting glucose compared to placebo-treated patients (26.6%); HR 1.21 (0.95 to 1.54). The corresponding study-adjusted Kaplan-Meier curve for the placebo-controlled pool is presented in Figure 38.

Table 115. Number (%) of patients shift from normal glucose category at baseline to impaired fasting glucose during TEAE period (safety population) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=365	Alirocumab N=718	Ezetimibe N=174	Alirocumab N=223
Any impaired fasting glucose during the TEAE period				
n (%)	97 (26.6)	224 (31.2)	42 (24.1)	59 (26.5)
# of pts with an event per 100 pt-yrs[1]	27.7	34.1	45.2	42.9
95% CI	22.5 to 33.8	29.8 to 38.8	32.6 to 61.1	32.6 to 55.3
HR (95% CI)[2]	1.21 (0.95 to 1.54)		0.88 (0.59 to 1.32)	

Source: Response to FDA 15 March 2015 IR: Submitted 16 April 2015, SD #32 Table 3
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
n(%) = number and percentage of patients with impaired glucose control during the TEAE period
Impaired fasting glucose: defined using specific AE terms reported, raw values in HbA1c, and fasting blood glucose during the TEAE period

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study



Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Note: Patients are censored at the end of TEAE period (last injection of study treatment + 70 days)
Impaired glucose control: defined using specific TEAE terms reported, raw values in HbA_{1c}, and fasting blood glucose during the TEAE period

Figure 38. Study-adjusted Kaplan-Meier cumulative incidence curve for time to onset of impaired fasting glucose during the TEAE period (safety population – patient in normal glucose control category at baseline) – pool of phase 3 placebo-controlled studies

Source: Response to FDA 15 March 2015 IR: Submitted 16 April 2015, SD #32, Figure 4

The number and proportion of patients from the Normal or Impaired fasting glucose categories at baseline who met the criteria for the Diabetes category during the TEAE period are presented in Table 116 for the phase 3 placebo-controlled pool and the ezetimibe-controlled pool. The corresponding study-adjusted Kaplan-Meier curve for the placebo-controlled pool is presented in Figure 39. Most of the patients who met the Diabetes criteria during the TEAEs period were identified using laboratory values.

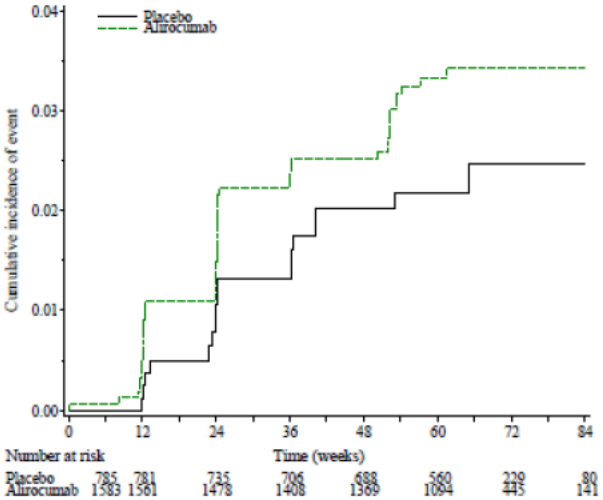
Table 116. Number (%) of patients shift from normal or impaired fasting glucose category at baseline to diabetes during TEAE period (safety population) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=785	Alirocumab N=1583	Ezetimibe N=417	Alirocumab N=556
Any onset of diabetes (AE or lab)				
n (%)	17 (2.2)	50 (3.2)	8 (1.9)	14 (2.5)
# of pts with an event per 100 pt-yrs[1]	1.8	2.7	2.6	3.0
95% CI	1.1 to 2.9	2.0 to 3.5	1.1 to 5.2	1.6 to 5.0
HR (95% CI)[2]	1.49 (0.86 to 2.59)		0.99 (0.41 to 2.38)	

Source: Response to FDA 15 March 2015 IR: Submitted 16 April 2015, SD #32 Table 7
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
n(%) = number and percentage of patients with impaired fasting glucose during the TEAE period
Diabetes: defined using specific AE terms reported, raw values in HbA1c, and fasting blood glucose during the TEAE Period

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study

Note: Due to the small number of patients, the scales used in this figure enlarges the differences between treatment groups.



Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Note: Patients are censored at the end of TEAE period (last injection of study treatment + 70 days)
Diabetes: defined using specific AE terms reported, raw values in HbA_{1c}, and fasting blood glucose during the TEAE period

Figure 39. Study-adjusted Kaplan-Meier cumulative incidence curve for time to onset of diabetes during the TEAE period (safety population – patient in normal glucose control category at baseline) – pool of phase 3 placebo-controlled studies

Source: Response to FDA 15 March 2015 IR: Submitted 16 April 2015, SD #32, Figure 10

Glucose control category shifts by level of LDL-C achieved

The following analysis looks at change in glucose control status in alirocumab-treated patients by levels of LDL-C achieved.

Table 117 presents the number and proportion of alirocumab-treated patients with normal glucose control at baseline who met the criteria for impaired fasting glucose by LDL-C achieved. Table 118 presents the number and proportion of alirocumab-treated patients with normal or impaired fasting glucose at baseline who met the criteria for diabetes across subgroups defined by LDL-C achieved. These analyses should be interpreted with caution as these analyses compare post-randomization subgroups.

In a small sub-population of patients with normal glucose control at baseline and two consecutive LDL-C values <25 mg/dL in the phase 3 placebo-controlled pool and ezetimibe-controlled pool, a higher proportion of patients met the criteria for impaired fasting glucose compared to alirocumab-treated patients with LDL-C levels >25 mg/dL.

Table 117. Number (%) of patients with impaired fasting glucose during the TEAE period according to LDL-C achieved (safety population of alirocumab-treated patients with normal glucose control at baseline) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies [Unadjusted]

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Alirocumab LDL-C≥25 N=581	Alirocumab 2 LDL-C<25 N=137	Alirocumab LDL-C≥25 N=198	Alirocumab 2 LDL-C<25 N=25
Any impaired fasting glucose during TEAE period	**161 (27.7)**	**49 (35.8)**	**49 (24.7)**	**8 (32.0)**

Source: Response to FDA 15 March 2015 IR: Submitted 16 April 2015, SD #32 Table 5
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Impaired fasting glucose: defined using specific AE terms reported, raw values in HbA1c, and fasting blood glucose during the TEAE period
Only event that occurred the day or after the first of the 2 consecutive LDL-C<25 mg/dL (<0.65 mmol/L) are considered for alirocumab 2 LDL-C < 25 mg/dL group. 2 consecutive values are considered if spaced out by at least 21 days.
1 Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of TEAE period. For patients in alirocumab<25mg/dL, number of patient years is calculated from the date of the first LDL-C<25mg/dL
2 Calculated using a Cox model stratified on the study
Alirocumab LDL-C>=25mg/dL group: alirocumab patients without 2 consecutive LDL-C<25mg/dL

In the small sub-population of patients from the normal or impaired fasting glucose categories at baseline and two consecutive LDL-C values <25 mg/dL, a similar

proportion of patients met the criteria for the Diabetes category in the different safety pools compared to alirocumab-treated patients with LDL-C levels >25 mg/dL.

Table 118. Number (%) of patients with shift into diabetes category (by AE or lab) during the TEAE period according to LDL-C achieved (safety population of alirocumab-treated patients with normal or impaired fasting glucose at baseline) – pool of phase 3 placebo-controlled studies and pool of ezetimibe-controlled studies [Unadjusted]

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Alirocumab LDL-C≥25 N=1204	Alirocumab 2 LDL-C<25 N=379	Alirocumab LDL-C≥25 N=476	Alirocumab 2 LDL-C<25 N=80
Any onset of diabetes (by AE or lab) during TEAE period	**36 (3.0)**	**13 (3.4)**	**11 (2.3)**	**2 (2.5)**

Source: Response to FDA 15 March 2015 IR: Submitted 16 April 2015, SD #32 Table 9
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Diabetes: defined using specific AE terms reported, raw values in HbA1c, and fasting blood glucose during the TEAE period
Only event that occurred the day or after the first of the 2 consecutive LDL-C<25 mg/dL (<0.65 mmol/L) are considered for alirocumab 2 LDL-C < 25 mg/dL group. 2 consecutive values are considered if spaced out by at least 21 days.
1 Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event; for patients without event, it corresponds to the length of TEAE period. For patients in alirocumab<25mg/dL, number of patient years is calculated from the date of the first LDL-C<25mg/dL
2 Calculated using a Cox model stratified on the study
Alirocumab LDL-C>=25mg/dL group: alirocumab patients without 2 consecutive LDL-C<25mg/dL

In reviewing these data it should be noted a higher proportion of patients with Normal glucose control at baseline and with two consecutive LDL-C values <25 mg/dL in the phase 3 placebo pool had at least 3 risk factors for diabetes at baseline: 27.9 % as compared to 13.7% for those in the LDL-C >25 mg/dL group. In addition, the subgroup of patients with two LDL-C values <25 mg/dL and change in glycemic control category was small which limits definitive conclusions regarding an association between low LDL-C levels and worsening glucose control.

The applicant has provided the following caveats in interpreting these results (1) many patients had values at baseline close to the thresholds between categories, so small changes between baseline and "worse value during TEAE period" could lead to a category change (2) HbA1c was infrequently measured, and (3) changes in drugs and other factors that can affect glucose control/levels are not accounted for. While these are reasonable considerations in the interpretation of these results, the following must be kept in mind, the mean baseline glucose and HbA1c values were well matched across glucose control categories and treatment groups. Therefore, both the alirocumab and control treated groups at baseline were probably equally likely to cross diabetes thresholds by chance. In addition, mean changes only incorporate scheduled visits and therefore may not capture all laboratory assessments, unlike shift table analysis which should include all laboratory values collected during the treatment period. This reviewer agrees that post-randomization changes in diabetes medications

are confounding factors as there was no standardized algorithm for managing glucose values and therefore conclusions regarding the contribution of medication changes in the overall pattern of diabetes TEAE are limited. While there was a higher incidence of unfavorable categorical shifts in glucose control categories in patients with two consecutive LDL-C levels less than 25 mg/dL, this type of analysis is limited by within group comparisons which do not account for other characteristics (both known and unknown) which differ between the two groups other than level of LDL-C achieved and severely restricts conclusions regarding an association with low levels of LDL-C, alirocumab, and glucose control; residual confounding is likely to be present even in "adjusted" analyses.

Finally, for the majority of patients, glucose control remained stable and serious diabetes TEAE were few. The potential for worsening glycemic control with alirocumab treatment is a monitorable and treatable event and must be considered in light of alirocumab's efficacy.

Musculoskeletal-related adverse events

Musculoskeletal-related events evaluated in the following analyses were identified by use of a company MedDRA query (CMQ). These terms were selected to reflect preferred terms most commonly associated with musculoskeletal-related events in statin intolerant patients (See Appendix for individual terms). These terms were selected prior to database lock and the analysis was performed on the ALTERNATIVE trial, which enrolled patients considered statin intolerant, and the placebo-controlled pool only.

In addition, muscle-related AEs within the system organ class Musculoskeletal and connective tissue disorders, which encompass overlapping terms with the CMQ analysis but also unique preferred terms was reviewed. This analysis was conducted in both the placebo and ezetimibe-controlled safety pools.

Placebo-controlled pool
In the placebo-controlled safety pool, 15.1% patients in the alirocumab group versus 15.4% patients in the placebo group experienced a musculoskeletal-related CMQ defined TEAE. Four (0.2%) alirocumab-treated patients versus 1 (<0.1) placebo-treated patients reported a SAE. None of these SAEs resulted in a fatal event.

Table 119. Overview of musculoskeletal (CMQ) TEAE (safety population) – pool of placebo-controlled studies

Musculoskeletal disorders (CMQ)	Placebo-controlled	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)
TEAE	197 (15.4)	373 (15.1)
SAE	1 (<0.1)	4 (0.2)

Musculoskeletal disorders (CMQ)	Placebo-controlled	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)
TEAE leading to death	0	0
TEAE leading to discontinuation	6 (0.5)	10 (0.4)

Source: ISS Appendix Table 1.4.1.11.1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)

CMQ-defined musculoskeletal TEAEs reported in a higher proportion of patients in the alirocumab group compared to the placebo group (incidence ≥2.0% in the alirocumab group and difference ≥0.5%) included: myalgia (4.2% alirocumab versus 3.4% placebo), muscle spasms (3.1% versus 2.4%), and musculoskeletal pain (2.1% versus 1.6%).

Table 120. Number (%) of patients with a musculoskeletal (CMQ) TEAE (safety population) – pool of placebo-controlled studies

Musculoskeletal disorders CMQ	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)
Total	**197(15.4)**	**373 (15.1)**
Back pain	61 (4.8)	108 (4.4)
Myalgia	44 (3.4)	104 (4.2)
Muscle spasms	30 (2.4)	77 (3.1)
Pain in extremity	53 (4.2)	65 (2.6)
Musculoskeletal pain	20 (1.6)	53 (2.1)
Musculoskeletal stiffness	7 (0.5)	14 (0.6)
Muscular weakness	4 (0.3)	6 (0.2)
Muscle fatigue	2 (0.2)	5 (0.2)
Muscle contracture	1 (<0.1)	3 (0.1)
Musculoskeletal discomfort	1 (<0.1)	3 (0.1)
Muscle twitching	0	1 (<0.1)
Muscle contractions involuntary	1 (<0.1)	0
Muscle tightness	2 (0.2)	0

Source: ISS Appendix 1.4.1.11.2
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)

Serious adverse events – musculoskeletal-related (CMQ) TEAE

There were 4 alirocumab-treated patients versus 1 placebo-treated patient with a SAE within the musculoskeletal CMQ. In the 4 SAEs occurring in the alirocumab group, all of the patients had a medical history or immediate circumstances (fall, moving furniture) that provide a possible alternative etiology. In all cases, no changes were made to alirocumab treatment. In 1 case, the event had not resolved, following spinal fusion surgery due to worsening back pain.

Table 121. Summary of musculoskeletal SAE (CMQ) – placebo controlled pool

Patient ID Study name Treatment	Age/Sex	Statin therapy	Day of onset	Preferred term Outcome	Comments
Alirocumab-treated					
11568-840-898-005 COMBO I Alirocumab 75 mg Q2W	68 M	Atorva 80	273	Muscle spasms Recovered	Developed acute onset of low back pain after moving furniture Alirocumab continued
11568-840-894-001 COMBO I Alirocumab 75 mg Q2W	70 M	Simva 40	242	Pain in extremity/muscular weakness Recovered	Developed symptoms after accidental fall Alirocumab continued
11717-826-010-122 LONG TERM Alirocumab 150 mg Q2W	46 M	Atorva 20	545	Muscle spasms Not resolved	History of ongoing leg muscle spasms. Developed muscle spasms – left L5 nerve root decompression (nonserious) at an unspecified date. Corrective surgery for nerve root compression Alirocumab continued
11717-826-011-146 LONG TERM Alirocumab 150 mg Q2W	69 M	Simva 40 switched to Atorva Day 22	423	Back pain Not resolved	Medical history back pain, muscle spasms Reported severe back pain on Day 32 which became serious. Patient had spinal fusion surgery Alirocumab continued
Placebo-treated					
11568-840-809-007 COMBO I Placebo	74 M	Rosuva 40	95	Pain in extremity Recovered	Hospitalized on Day 95 for rapid heart rate. Patient developed right lower leg pain. Ultrasound negative for DVT. Event resolved and patient discharged

Source: ISS or individual CSR narratives

ALTERNATIVE study

The ALTERNATIVE study was designed to enroll and treat patients with primary hypercholesterolemia (heFH and Non-FH) who were considered intolerant to statins.

Statin intolerance was defined as the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), and another statin at any dose, due to skeletal muscle-related symptoms (other than those due to strain or trauma), such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued. Only patients willing to be rechallenged with atorvastatin 20 mg were included in the study.

Patients not receiving a daily regimen of a statin (eg, 1 to 3 times weekly) were also considered not able to tolerate a daily dose and were eligible to enroll in the study if they could not tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size, and if the criteria outlined above were also met.

Patients who met all inclusion criteria, met none of the exclusion criteria, and had successfully completed the placebo-run-in period were randomized in a ratio of 2:2:1 to receive 1 of the following 3 regimens:

- Alirocumab 75 mg Q2W + placebo for ezetimibe/atorvastatin QD
- Ezetimibe 10 mg QD + placebo for alirocumab Q2W
- Atorvastatin 20 mg QD + placebo for alirocumab Q2W

Overall, patients treated with alirocumab reported a lower proportion of musculoskeletal TEAEs as defined by the CMQ compared to patients treated with atorvastatin or ezetimibe (alirocumab 32.5%; ezetimibe 41.1%; atorvastatin 46.0%). The most commonly reported preferred term was myalgia which occurred in 24.6%, 23.4%, and 27.0% of patients treated with alirocumab, ezetimibe, and atorvastatin, respectively. There were no events within this CMQ that met the criteria for a SAE.

A total of 23 (18.3%) alirocumab-treated patients reported a TEAE leading to discontinuation compared to 31 (25.0%) of ezetimibe-treated patients and 16 (25.4%) atorvastatin-treated patients. The majority of events in all treatment groups leading to discontinuation were musculoskeletal in nature.

A lower percentage of patients in the alirocumab treatment group (15.9%) experienced a skeletal muscle-related TEAE that led to treatment discontinuation than patients in the atorvastatin treatment group (22.2%) and ezetimibe treatment group (28.3%).

Table 122. Number (%) of musculoskeletal TEAE by CMQ and PT & discontinuations due musculoskeletal CMQ (safety population) - ALTERNATIVE

	Atorvastatin N=63 n (%)	Ezetimibe N=124 n (%)	Alirocumab N=126 n (%)
Musculoskeletal TEAE (CMQ)	**29 (46.0)**	**51 (41.1)**	**41 (32.5)**
Myalgia	17 (27.0)	29 (23.4)	31 (24.6)
Back pain	5 (7.9)	7 (5.6)	5 (4.0)
Muscle spasms	7 (11.1)	9 (7.3)	5 (4.0)
Pain in extremity	0	4 (3.2)	5 (4.0)
Musculoskeletal discomfort	0	3 (2.4)	2 (1.6)
Musculoskeletal pain	2 (3.2)	0	2 (1.6)
Muscular weakness	4 (6.3)	2 (1.6)	1 (0.8)
Musculoskeletal stiffness	1 (1.6)	1 (0.8)	1 (0.8)
Muscle fatigue	0	1 (0.8)	0
Musculoskeletal TEAE leading to treatment discontinuation	**14 (22.2)**	**25 (20.2)**	**20 (15.9)**
Myalgia	13 (20.6)	20 (16.1)	18 (14.3)
Pain in extremity	0	1 (0.8)	2 (1.6)
Muscle spasms	0	2 (1.6)	1 (0.8)
Muscular weakness	0	2 (1.6)	1 (0.8)
Musculoskeletal discomfort	0	1 (0.8)	0
Musculoskeletal pain	1 (1.6)	0	0

Source: ALTERNATIVE CSR Table 66, 68

Musculoskeletal and connective tissue disorders SOC

Within the musculoskeletal and connective tissue disorders SOC, which includes all of the preferred terms within the prespecified musculoskeletal CMQ along with other unique preferred terms, 24.8% and 26.1% of alirocumab and placebo-treated patients reported an event, respectively. In the ezetimibe-controlled safety pool, 22.3% and 23.5% of alirocumab and ezetimibe-treated patients reported an event, respectively.

Muscle TEAEs (PTs) occurring in ≥2.0% of patients in either group at a ≥0.5% higher frequency difference between groups are all captured in the CMQ described above. No other muscle TEAE met these criteria.

Events of interest include two patients in the alirocumab treatment group with reported rhabdomyolysis compared to no patients in the placebo or ezetimibe group. These events are summarized here.

- 11717-840-076-012/**alirocumab/rhabdomyolysis:** An 81-year-old male patient on atorvastatin 80 mg/day for over 3 years and with a history of chronic renal failure and hypertension experienced acute renal failure on Day 372, and was admitted to hospital with SAEs of rhabdomyolysis (mild intensity), pneumonia, atrial fibrillation, and troponin increased. This event occurred in the context of ground-level fall (the patient got up in the middle of the night, had a mechanical trip, fell on the floor and was too weak to get up again) on the previous day reported to be due to generalized weakness which was a manifestation of pneumonia. The local laboratory tests showed CK at 25 923 IU/L (normal 55-170 IU/L), CK-MB at 18.3 ng/mL (normal 0-6 ng/mL), blood urea nitrogen (BUN) at 39 mg/dL (normal range: 7-20 mg/dL) and creatinine at 1.9 mg/dL (normal range 0.7-1.3 mg/dL). The values at baseline were according to central laboratory BUN at19 mg/dL (normal range 4-34 mg/dL), creatinine at 1.3 mg/dL (normal range: 0.5- 1.6 mg/dL). The patient was treated and the event resolved on Day 374. Alirocumab was continued.
- 11717-840-181-005/**alirocumab/rhabdomyolysis**: A 54-year-old female patient on atorvastatin 80 mg/day for 2 years with a medical history significant for type 2 diabetes and hypertension was reported to have rhabdomyolysis of mild intensity on Day 422. CK was elevated at 5.1 x ULN (3.6 x baseline value) with normal CK-MB, troponin, creatinine, sodium, potassium, BUN, and eGFR of 72 mL/min. No organ damage was noted. Study treatment was withdrawn and the event resolved on Day 436. Note this event was later downgraded to myositis as the CK increase was mild and the patient was asymptomatic.

Muscle-related laboratory values

- Creatinine kinase

Overall, the percentages of patients with CK >3x ULN and CK >10x ULN were similar across treatment groups.

Table 123. Number (%) of patients with abnormalities in CK levels (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
CK >3x ULN	56/1254 (4.5%)	77/2423 (3.2%)	13/604 (2.2%)	19/842 (2.3%)
CK >10x ULN	8/1254 (0.6%)	12/2423 (0.5%)	2/604 (0.3%)	0/842 (0%)

Source: ISS appendix 1.5.2.1.7
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during TEAE period. The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period
PCSA classification is performed on the worst value

According to the applicant, of the 20 patients that had normal/missing CK values at baseline and increased to CK>10x ULN, 3 patients in the alirocumab group reported serious TEAEs and 1 patient in the placebo group reported a nonserious TEAE. The 3 SAEs in the alirocumab group were 1 case of rhabdomyolysis (patient ID 11717-840-076-012) described above, 1 case of suicide attempt by intentional overdose with propranolol, rosuvastatin, and ezetimibe (patient ID 11717-724-001-001), and a case of myositis leading to treatment discontinuation (summarized below). In the placebo group, the case of CK increased was reported as a nonserious event ("increase CK levels with no muscle symptoms") leading to treatment discontinuation (patient ID. 011717-840-047-012).

- 11717-840-209-001/**alirocumab/myositis**: A 54-year-old male patient on rosuvastatin 10 mg experienced an ALT increase due to myositis on Day 25, with ALT at 120 IU/L (normal range 6-43) and AST at 147 IU/L (normal range 11-36). On Day 30, CK was elevated to 15 957 IU/L (normal range 18-198), and LDH elevated to 708 IU/L (normal range 53-234), and ALT of 131 IU/L and AST of 269 IU/L. Patient was asymptomatic. On Day 37, the patient's blood myoglobin was 151 g/L (normal range: 15-70). The kidney function remained normal (creatinine throughout 1.0 mg/dL). Rosuvastatin and alirocumab was permanently discontinued due to this event. ALT, AST, and CK returned to normal or near normal range on Day 44, and the patient was considered recovered.

Cardiac disorders

This section first discusses all TEAEs regardless of adjudication occurring within the SOC of cardiac disorders. The analysis of adjudicated pre-specified cardiovascular events follows.

MedDRA SOC 'Cardiac Disorders'

In the placebo-controlled pool, 199 (8.0%) of alirocumab-treated patients and 115 (9.0%) of placebo-treated reported an event within the cardiac disorders SOC. Serious TEAEs in the cardiac disorders SOC were reported in 109 (4.4%) patients in the alirocumab group and in 58 (4.5%) patients in the placebo group. In the ezetimibe-controlled pool, TEAEs were reported in 76 (8.8%) patients in the alirocumab group and in 44 (7.1%) patients in the ezetimibe group. Serious TEAEs in the cardiac disorders SOC were reported in 48 (5.6%) patients in the alirocumab group and in 25 (4.0%) patients in the ezetimibe group, Table 125.

For both safety pools, the most frequent cardiac disorders by high level term (HLT) in any treatment group were 'ischemic coronary artery disorders'. In the placebo-controlled pool the incidence was lower in alirocumab-treated (3.9%) versus placebo-treated (4.5%) patients. Within the ezetimibe-controlled pool the incidence was higher in alirocumab-treated (4.4%) versus ezetimibe-treated (2.8%) patients.

In the placebo-controlled pool, a review of preferred terms within this HLT demonstrated the greatest difference between groups was 'unstable angina' with 30 (1.2%) alirocumab-treated patients reporting an event and 11 (0.9%) placebo-treated patients reporting an event. In the ezetimibe-controlled pool, a review of preferred terms within this HLT, showed the greatest difference in the PT 'acute myocardial infarction' and PT 'unstable angina'. For the PT 'acute myocardial infarction', the rate was 0.6 and 1.5 per 100 patient years in the ezetimibe and alirocumab-treated groups, respectively. For the PT 'unstable angina' the rate was 0.4 and 1.6 per 100 patient years in the ezetimibe and alirocumab-treated groups, respectively. The hazard ratio calculated using a Cox model stratified on the study versus ezetimibe for the PT 'unstable angina' was 3.78 with wide confidence intervals of 0.84 to 17.04. Further discussion of adjudicated cases of myocardial infarction and unstable angina requiring hospitalization occurs in this section.

The incidence of cardiac arrhythmias was similar between treatment groups in both the placebo and ezetimibe-controlled pools.

Table 124. Number (%) of patients with cardiac disorders TEAE by HLT (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

SOC HLT: Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Cardiac disorders	**115 (9.0)**	**199 (8.0)**	**44 (7.1)**	**76 (8.8)**
HLT: Cardiac conduction disorders	7 (0.5)	8 (0.3)	3 (0.5)	6 (0.7)
HLT: Rate and rhythm disorders NEC	6 (0.5)	16 (0.6)	3 (0.5)	5 (0.6)
HLT: Supraventricular arrhythmias	32 (2.5)	43 (1.7)	7 (1.1)	14 (1.6)
HLT: Ventricular arrhythmias and cardiac arrest	6 (0.5)	11 (0.4)	6 (1.0)	7 (0.8)
HLT: Cardiac disorders NEC	3 (0.2)	0	1 (0.2)	1 (0.1)
HLT: Cardiac signs and symptoms NEC	8 (0.6)	12 (0.5)	4 (0.6)	9 (1.0)
HLT: Aortic valvular disorders	3 (0.2)	4 (0.2)	2 (0.3)	0
HLT: Cardiac valve disorders NEC	1 (<0.1)	0	0	0
HLT: Mitral valvular disorders	3 (0.2)	3 (0.1)	1 (0.2)	0
HLT: Tricuspid valvular disorders	1 (<0.1)	0	0	0
HLT: Coronary artery disorders NEC	8 (0.6)	21 (0.8)	2 (0.3)	3 (0.3)
HLT: Ischemic coronary artery disorders[1]	57 (4.5)	96 (3.9)	17 (2.8)	38 (4.4)
Acute coronary syndrome	6 (0.5)	2 (<0.1)	0	0
Acute myocardial infarction	11 (0.9)	12 (0.5)	3 (0.5)	11 (1.3)
Angina pectoris	26 (2.0)	42 (1.7)	11 (1.8)	13 (1.5)
Angina unstable	11 (0.9)	30 (1.2)	2 (0.3)	12 (1.4)
Myocardial infarction	6 (0.5)	7 (0.3)	0	3 (0.3)
Myocardial ischemia	2 (0.2)	6 (0.2)	1 (0.2)	1 (0.1)
Silent myocardial infarction	0	1 (<0.1)	0	1 (0.1)
HLT: Heart failures NEC	12 (0.9)	22 (0.9)	2 (0.3)	5 (0.6)
HLT: Cardiomyopathies	2 (0.2)	3 (0.1)	0	1 (0.1)
HLT: Myocardial disorders NEC	5 (0.4)	2 (<0.1)	0	0
HLT: Noninfectious pericarditis	1 (<0.1)	1 (<0.1)	0	0

Source: ISS appendix 1.4.9.4
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Preferred terms listed for this HLT as the greatest number of patients reported an event within this HLT

Table 125. Number (%) of patients with cardiac disorders SAE by HLT (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

SOC HLT: Preferred term	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Cardiac disorders	**58 (4.5)**	**109 (4.4)**	**25 (4.0)**	**48 (5.6)**
HLT: Cardiac conduction disorders	0	3 (0.1)	2 (0.3)	2 (0.2)
HLT: Rate and rhythm disorders NEC	1 (<0.1)	3 (0.1)	0	1 (0.1)
HLT: Supraventricular arrhythmias	12 (0.9)	15 (0.6)	3 (0.5)	6 (0.7)
HLT: Ventricular arrhythmias and cardiac arrest	4 (0.3)	4 (0.2)	3 (0.5)	4 (0.5)
HLT: Cardiac disorders NEC	2 (0.2)	0	1 (0.2)	0
HLT: Aortic valvular disorders	1 (<0.1)	2 (<0.1)	1 (0.2)	0
HLT: Mitral valvular disorders	1 (<0.1)	0	0	0
HLT: Coronary artery disorders NEC	6 (0.5)	18 (0.7)	2 (0.3)	3 (0.3)
HLT: Ischemic coronary artery disorders[1]	36 (2.8)	63 (2.5)	12 (1.9)	33 (3.8)
Acute coronary syndrome	6 (0.5)	2 (<0.1)	0	0
Acute myocardial infarction	11 (0.9)	12 (0.5)	3 (0.5)	11 (1.3)
Angina pectoris	7 (0.5)	16 (0.6)	6 (1.0)	8 (0.9)
Angina unstable	9 (0.7)	25 (1.0)	2 (0.3)	12 (1.4)
Myocardial infarction	6 (0.5)	7 (0.3)	0	3 (0.3)
Myocardial ischemia	1 (<0.1)	3 (0.1)	1 (0.2)	0
Silent myocardial infarction	0	1 (<0.1)	0	1 (0.1)
HLT: Heart failures NEC	8 (0.6)	13 (0.5)	2 (0.3)	3 (0.3)
HLT: Cardiomyopathies	2 (0.2)	2 (<0.1)	0	1 (0.1)
HLT: Myocardial disorders NEC	1 (<0.1)	0	0	0
HLT: Noninfectious pericarditis	1 (<0.1)	0	0	0

Source: ISS appendix 1.4.10.1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Preferred terms listed for this HLT as the greatest number of patients reported an event within this HLT

Adjudicated CV events

Background

Cardiovascular events were evaluated for safety purposes in the phase 3 program; there are too few events to determine whether there is CV benefit with alirocumab at this time. A CV outcomes trial (OUTCOMES) is currently ongoing and will establish whether the changes observed in LDL-C (± other lipid parameters) translate to CV benefit in patients post-acute coronary syndrome. Target enrollment for OUTCOMES is 18,000 patients. As of 31 Oct 2014, 7992 patients (44.4%) have been randomized. Complete enrollment is projected to occur in Jan 2016. In addition, as of 29 Aug 2014, 186 patients are estimated to have had at least one primary efficacy endpoint (i.e., 11.5% of the total 1613 targeted number of events).

Table 126. Number of patients with at least one primary efficacy endpoint as of 29 August 2014, OUTCOMES study

	All (N=6528)
Patients with at least one primary efficacy endpoint confirmed by adjudication	156 (2.4%)
Patients with at least one primary efficacy endpoint reported but not yet adjudicated	47 (0.7%)
Estimated number of patients with at least one primary efficacy endpoint[a]	186 (2.8%)

[a] estimate obtained applying the confirmation rates observed to the events not yet adjudicated

Source: CVOT Status Update, Table 2

Methods

In the phase 3 trials, suspected CV events and all deaths that have occurred from time of randomization until the follow-up visit have been being adjudicated by the same clinical events committee (CEC) as used in the OUTCOMES trial. The CEC, managed by the Duke Clinical Research Institute (DCRI), is composed of experts in the field of cardiovascular diseases, independent from the sponsor and the investigators. Definitions of cardiovascular endpoints used by the CEC are located in the Appendix (section 9.2).

In this clinical program, MACE is defined as:

- coronary heart disease death
- nonfatal MI
- fatal or nonfatal ischemic stroke
- unstable angina requiring hospitalization

In addition to the above, the following events were sent to the CEC for adjudication:

- cerebrovascular events, including stroke, transient ischemic attack (TIA), intracranial bleeding, ischemia or bleeding of spine or retina
- congestive heart failure requiring an emergency room visit or requiring / prolonging hospitalization
- all coronary revascularization procedures (i.e., percutaneous coronary intervention and coronary artery bypass graft) [note that the phase 3 investigators were instructed not to report coronary revascularization procedures as AEs; rather, the investigators were asked to report the reason for the procedure as an AE term (e.g., unstable angina leading to PCI should be reported as 'unstable angina')]
- all deaths

The CEC also reviewed abnormal values of CK, CK-MB, and troponin I or T even if there was no investigator-reported MI.

The CEC could manually trigger an event. Manual triggers were created when the CEC, based on review of the clinical data, identified a possible endpoint event that had not been entered into the e-CRF by the site. After creating the manual trigger, a specific e-CRF was completed by the CEC. If the site agreed with the CEC, the site entered the relevant form into the e-CRF. If the site did not agree with CEC, the CEC adjudicated the case using the available data.

All events were adjudicated by two independent CEC physicians. If the adjudication was concordant, the event classification was complete. If they disagreed, an adjudication committee meeting, with at least three members, was organized and each case was adjudicated by consensus of the reviewers.

Members of the CEC committee were blinded to the study drug assignment and to the LDL-C results.

Preliminary Results

The sponsor presented the MACE results using an on-treatment (i.e., events that occurred within 70 days of the last dose) analysis. See Dr. McEvoy's review for intent-to-treat (on-study) analyses, which are consistent with the planned analyses described in the protocol for the OUTCOMES trial.

MACE occurred in 52 (1.6%) patients in the alirocumab group and in 33 (1.8%) patients in the control group, with HR 0.81 (95% CI 0.52 to 1.25). There were no significant study-by-treatment interactions or interactions between treatment groups and intrinsic and extrinsic factors were identified in the global pool for the MACE analysis.

Table 127. Positively adjudicated Major Adverse Cardiovascular Events, phase 3 studies combined

Category of adjudication	Control N=1792	Alirocumab N=3182
Any patients with treatment emergent MACE event, n (%)	**33 (1.8)**	**52 (1.6)**
Number of patients with an event per 100 patient year[1]	1.8	1.5
95% CI	1.2 to 2.5	1.1 to 1.9
Hazard ratio versus control (95% CI)[2]	0.81 (0.52 to 1.25)	
CHD death (including undetermined cause)	9 (0.5)	8 (0.3)
Non-fatal MI	23 (1.3)	30 (0.9)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	3 (0.2)	12 (0.4)
Unstable angina requiring hospitalization*	1 (<0.1)	2 (<0.1)

*The sponsor was asked to explain the discrepancy between the number of patients with positively adjudicated unstable angina requiring hospitalization (n=3) and those that had serious unstable angina events captured by the MedDRA PT 'angina unstable' (n=48, Table 125). The sponsor noted that only unstable angina meeting stringent criteria (unstable angina requiring hospitalization and with evidence of acute myocardial ischemia, as defined by new high-risk ECG findings consistent with ischemia or infarction, and definite contemporary evidence of angiographically significant coronary disease) would be counted in the composite endpoint. Therefore, a high number of investigator-reported unstable angina events requiring hospitalization were negatively adjudicated by the CEC. Additionally, some unstable angina events were adjudicated as MI. Furthermore, the MACE composite endpoint only includes first event (and therefore, if a patient had already had a previous MACE, additional events would be censored)

Source: NDA 125559 ISS Table 28
Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

1. Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
2. Calculated using a Cox model stratified on the study

.

Table 128. Positively adjudicated MACE, phase 3 studies by comparator

	Placebo-controlled pool		Ezetimibe-controlled pool	
Category of adjudication n(%)	Placebo (N=1174)	Alirocumab (N=2318)	Ezetimibe (N=618)	Alirocumab (N=864)
Any patients with treatment emergent MACE event				
n(%)	27 (2.3%)	35 (1.5%)	6 (1.0%)	17 (2.0%)
95% mid-p CI	1.6% to 3.3%	1.1% to 2.1%	0.4% to 2.0%	1.2% to 3.1%
Number of patients with an event per 100 patient year [a]	1.9	1.3	1.3	2.3
95% CI	1.3 to 2.8	0.9 to 1.7	0.5 to 2.8	1.4 to 3.7
Hazard ratio versus control (95% CI) [b]		0.65 (0.40 to 1.08)		1.51 (0.59 to 3.85)
CHD death (including undetermined cause)	7 (0.6%)	6 (0.3%)	2 (0.3%)	2 (0.2%)
Non-fatal MI	19 (1.6%)	17 (0.7%)	4 (0.6%)	13 (1.5%)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (0.2%)	11 (0.5%)	1 (0.2%)	1 (0.1%)
Unstable angina requiring hospitalization	1 (<0.1%)	1 (<0.1%)	0	1 (0.1%)

Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)

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

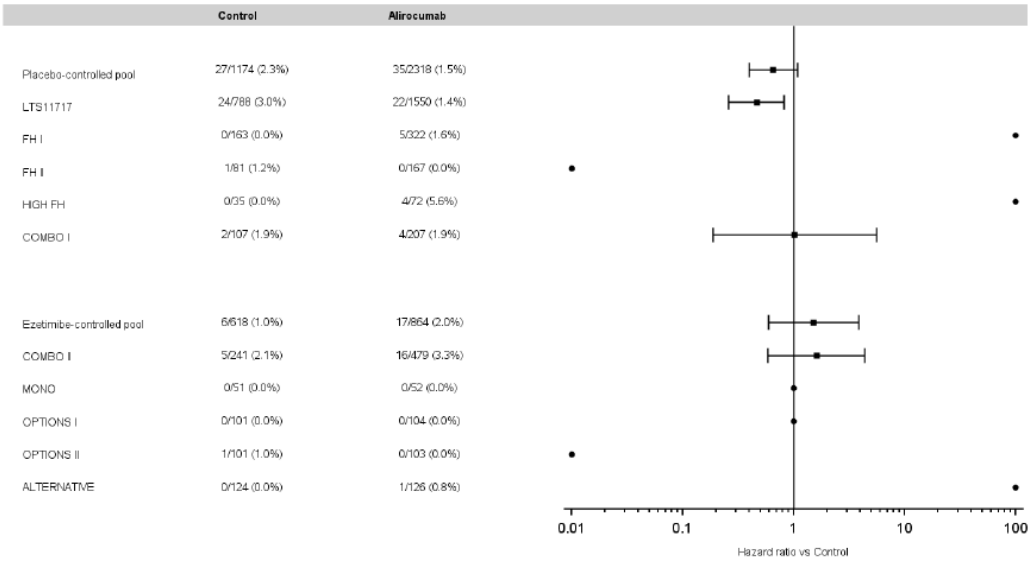
n(%) = number and percentage of patients with at least one event

[a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period

[b] calculated using a Cox model stratified on the study

Source: ISS, Table 29

Figure 40. Positively adjudicated MACE, by phase 3 study



Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)

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

Studies with no event in at least one treatment group are conventionally displayed as follows:

dot at HR=1 in case of no event in both groups, dot at right extremity in case of 0 event in control arm, dot at left extremity in case of 0 event in alirocumab arm

Source: ISS, Figure 19

When the definition of MACE was expanded to include endpoints of hospitalized congestive heart failure and coronary revascularization, the hazard ratio for alirocumab versus control increased to 1.08 (95% CI 0.78, 1.50), primarily driven by a greater incidence of revascularizations in the alirocumab group (2.3% vs. 1.7%). CV events by control group are shown in Table 129, and by study in Figure 41.

Table 129. MACE, CHF hospitalization, or revascularization, phase 3 studies by comparator

	Placebo-controlled pool		Ezetimibe-controlled pool	
Category of adjudication n(%)	Placebo (N=1174)	Alirocumab (N=2318)	Ezetimibe (N=618)	Alirocumab (N=864)
Any patients with treatment emergent MACE event, CHF hospitalization or revascularization				
n(%)	41 (3.5%)	83 (3.6%)	12 (1.9%)	27 (3.1%)
95% mid-p CI	2.6% to 4.7%	2.9% to 4.4%	1.1% to 3.3%	2.1% to 4.5%
Number of patients with an event per 100 patient year [a]	2.9	3.0	2.6	3.7
95% CI	2.1 to 4.0	2.4 to 3.7	1.4 to 4.6	2.5 to 5.4
Hazard ratio versus control (95% CI) [b]		1.03 (0.71 to 1.49)		1.28 (0.65 to 2.55)
CHD death (including undetermined cause)	7 (0.6%)	6 (0.3%)	2 (0.3%)	2 (0.2%)
Non-fatal MI	19 (1.6%)	17 (0.7%)	4 (0.6%)	13 (1.5%)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (0.2%)	11 (0.5%)	1 (0.2%)	1 (0.1%)
Unstable angina requiring hospitalization	1 (<0.1%)	1 (<0.1%)	0	1 (0.1%)
Congestive heart failure requiring hospitalization	5 (0.4%)	11 (0.5%)	1 (0.2%)	1 (0.1%)
Ischemia driven coronary revascularization procedure	24 (2.0%)	53 (2.3%)	7 (1.1%)	20 (2.3%)

Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)

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

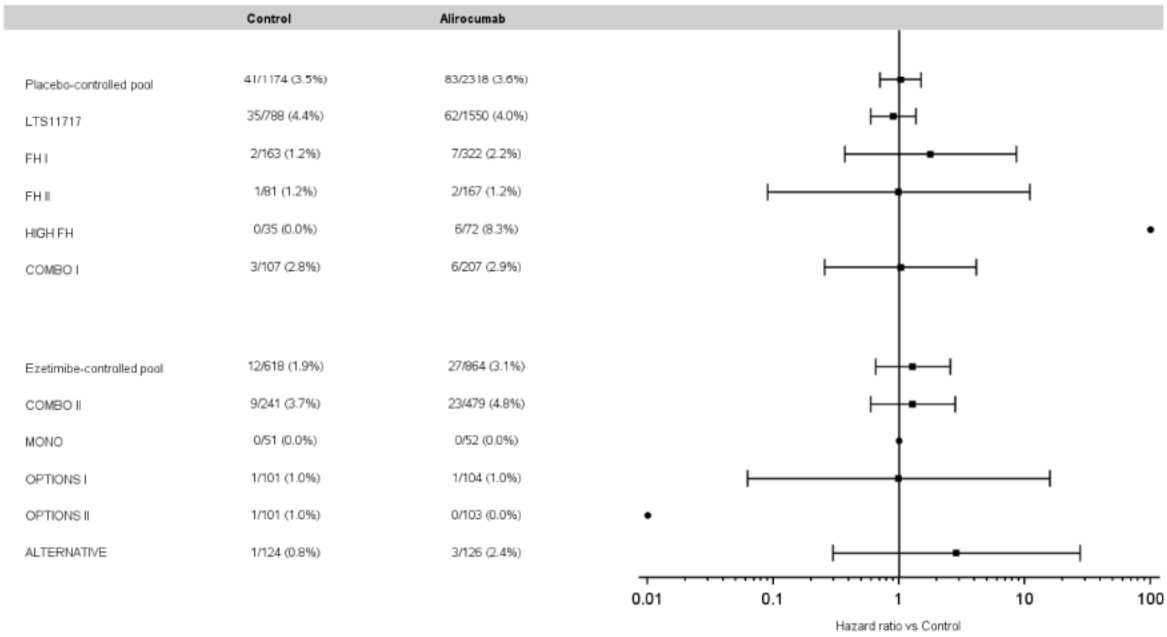
n(%) = number and percentage of patients with at least one event

[a] Calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period

[b] calculated using a Cox model stratified on the study

Source: ISS, Table 31

Figure 41. MACE, CHF hospitalization, or revascularization, by phase 3 studies



Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)

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

Studies with no event in at least one treatment group are conventionally displayed as follows:

dot at HR=1 in case of no event in both groups, dot at right extremity in case of 0 event in control arm, dot at left extremity in case of 0 event in alirocumab arm

Source: ISS, Figure 21

For this expanded analysis of cardiovascular events - MACE, hospitalization for CHF or ischemia driven coronary revascularization - a significant interaction was detected for type of hypercholesterolemia (HeFH, non-FH) p=0.04 and dose of statins (high dose, low dose, no background statin) p=0.05.

Table 130. Treatment interactions by instrinic and extrinsic factors – MACE, CHF hospitalization, or coronary revascularization (safety population) – global pool of phase 3 studies

	Control n/N (%)	Alirocumab n/N (%)	HR vs control[1] (95% CI)	Interaction p-value
Intrinsic Factors				
Gender				0.3677
Male	35/1098 (3.2)	82/1994 (4.1)	1.20 (0.81 to 1.78)	
Female	18/694 (2.6)	28/1188 (2.4)	0.91 (0.50 to 1.64)	
Age				0.6909
<65 years	31/1169 (2.7)	62/2069 (3.0)	1.08 (0.70 to 1.67)	
≥65 to <75 years	18/489 (3.7)	35/873 (4.0)	0.95 (0.54 to 1.68)	
≥75 years	4/134 (3.0)	13/240 (5.4)	1.74 (0.57 to 5.37)	
Race				0.5862
Caucasian	46/1617 (2.8)	100/2881 (3.5)	1.14 (0.80 to 1.61)	

	Control n/N (%)	Alirocumab n/N (%)	HR vs control[1] (95% CI)	Interaction p-value
Black or African American	4/84 (4.8)	4/139 (2.9)	0.38 (0.09 to 1.53)	
Asian	1/38 (2.6)	3/66 (4.5)	2.52 (0.26 to 24.52)	
Other	2/53 (3.8)	3/96 (3.1)	0.80 (0.13 to 4.96)	
Ethnicity				0.5565
Hispanic or Latino	1/96 (1.0)	5/179 (2.8)	1.93 (0.22 to 16.83)	
Not Hispanic or Latino	52/1692 (3.1)	105/2996 (3.5)	1.07 (0.77 to 1.49)	
BMI				0.4184
<25 kg/m^2	4/282 (1.40)	15/533 (2.8)	1.56 (0.52 to 4.69)	
≥25 to <30 kg/m^2	17/696 (2.4)	43/1261 (3.4)	1.30 (0.74 to 2.29)	
≥30 kg/m^2	32/811 (3.9)	52/1383 (3.8)	0.90 (0.58 to 1.41)	
Diabetes at baseline[2]				0.2548
Yes	25/545 (4.6)	42/975 (4.3)	0.85 (0.52 to 1.39)	
No	28/1247 (2.2)	68/2207 (3.1)	1.28 (0.82 to 1.99)	
eGFR				0.2871
<60 mL/min/1.73m^2	16/288 (5.6)	29/551 (5.3)	0.86 (0.47 to 1.58)	
≥60 to <90 mL/min 1.73m^2	27/1160 (2.3)	68/2030 (3.3)	1.33 (0.85 to 2.08)	
≥90 mL/min/1.73m^2	10/344 (2.9)	13/599 (2.2)	0.65 (0.28 to 1.48)	
Type of hypercholesterolemia[3]				**0.0366**
HeFH	5/461 (1.1)	26/877 (3.0)	2.66 (1.02 to 6.92)	
Non-FH	48/1331 (3.6)	84/2305 (3.6)	0.91 (0.64 to 1.30)	
Cardiovascular disease prevention				0.6205
Primary CVD prevention	2/550 (0.4)	6/913 (0.7)	1.67 (0.34 to 8.35)	
Secondary CVD prevention	51/1242 (4.1)	104/2269 (4.6)	1.07 (0.76 to 1.49)	
Hypertension				0.3945
Yes	47/1258 (3.7)	90/2211 (4.1)	1.03 (0.73 to 1.47)	
No	6/534 (1.1)	20/971 (2.1)	1.57 (0.63 to 3.92)	
Extrinsic factors				
Region				0.6815
North America	25/680 (3.7)	42/1106 (3.8)	0.86 (0.52 to 1.42)	
Western Europe	13/598 (2.2)	30/1085 (2.8)	1.13 (0.59 to 2.18)	
Eastern Europe	9/273 (3.3)	20/550 (3.6)	1.13 (0.51 to 2.48)	
Rest of World	6/241 (2.5)	18/441 (4.1)	1.66 (0.66 to 4.19)	
Statin treatment at randomization[4]				**0.0533**
High dose	37/945 (3.9)	57/1757 (3.2)	0.78 (0.51 to 1.18)	
Low dose	15/678 (2.2)	50/1245 (4.0)	1.75 (0.98 to 3.11)	
No background statin	1/165 (0.6)	3/176 (1.7)	2.66 (0.28 to 25.61)	

Source: NDA 125559 ISS appendix 1.4.2.1.28
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

1. Hazard ratio calculated using a Cox model stratified on the study in each subgroup. The interaction is tested in a separate Cox model including the study, the subgroup factor term, the treatment and the treatment-by-subgroup interaction
2. "Type 1 or type 2 diabetes" CMQ recorded in medical history.
3. Only for phase 3 studies. Patients included in MONO, COMBO I and COMBO II studies were counted as non-FH patients
4. High dose: atorvastatin above or equal 40 mg daily or rosuvastatin above or equal 20 mg daily or simvastatin 80 mg. Low dose: atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily or simvastatin below 80 mg daily

Reviewers' comment regarding the totality of adjudicated MACE results: Again it should be noted that while cardiovascular events within this development program are of interest, the results generated regarding overall hazard ratios and treatment interactions within subgroups are considered extremely preliminary

due to the small number of events overall and in subgroup populations, which prevent robust evaluation of the effect of alirocumab on cardiovascular events.

Hemolytic anemia

Due to concerns that low LDL-C levels and Vitamin E levels may contribute to red blood cell membrane fragility leading to increased hemolysis, reports of hemolytic anemia would be adverse events of special interest.

There were no reports of a hemolytic anemia TEAE reported in the phase 2/3 clinical development program as of the cut-off date of August 31, 2014.

Adverse events in patients with positive ADA response

A treatment-emergent positive ADA response was defined as 1) no ADA positive response at baseline but with any positive response in the post-baseline period (up to follow-up visit), or 2) positive ADA response at baseline and at least a 4-fold increase in titer in the post-baseline period (up to follow-up visit).

For treatment-emergent positive ADA, the duration of the ADA response was classified as 1) persistent when an ADA positive response was detected in at least 2 consecutive post-baseline samples separated by at least a 12-week period, 2) indeterminate when ADA was present only at the last sampling time point, and 3) transient for a response that is neither considered persistent nor indeterminate.

In the 10 phase 3 studies, a treatment-emergent ADA positive response was measured in 147 (4.8%) of patients treated with alirocumab compared with 10 (0.6%) in the control (ezetimibe or placebo) groups. In the alirocumab group, persistent treatment-emergent ADAs, defined as at least 2 consecutive post-baseline samples separated by at least a 12-week period, were measured in 39 (1.3%) patients. The median time to first occurrence of treatment-emergent ADA was approximately 12 weeks. Neutralizing antibodies, as determined using an ex vivo assay, were measured post-baseline in 1.2% of patients treated with alirocumab.

Of alirocumab-treated patients within the phase 3 trials, 75.9% of alirocumab-treated patients without a positive ADA response and 76.2% of alirocumab-treated patients with a positive ADA response reported a TEAE. Higher incidence rate (per 100 patient-years) of TEAEs (events reported at incidence rates ≥2.0 and with a ≥1.0 difference between groups) in patients with treatment-emergent ADA compared to patients with a negative treatment-emergent ADA response were injection site reactions (9.9 in patients with treatment-emergent ADA versus 5.4 in patients without treatment-emergent ADA), nasopharyngitis (12.0 versus 9.6), headache (6.3 versus 4.1), and back pain (6.9 versus 3.7), lower respiratory tract infection (3.1 versus 1.5), atrial fibrillation (3.1 versus 1.0).

Serious TEAEs were reported in 16.3% of patients with treatment-emergent ADA, compared to 14.1% of patients without treatment-emergent ADA. There were no events that were reported in greater than 2 patients with a treatment-emergent positive ADA response. The two patients with positive ADA response with a serious hypersensitivity event were discussed in the eariler section on allergic events.

Table 131. Number (%) and rate of SAEs in alirocumab-treated patients by ADA response – (anti-alirocumab antibody population – alirocumab treated) – global pool phase 3 studies

SOC Preferred term	Alirocumab-treated			
	No treatment-emergent positive ADA N=2866		Treatment-emergent positive ADA response N=147	
	n (%)	Per 100 pt/yr	n (%)	Per 100 pt/yr
Total Serious TEAE	**407 (14.1)**		**24 (16.3)**	
Infections and infestations	**60 (2.1)**	**1.9**	**5 (3.4)**	**3.1**
Diverticulitis	6 (0.2)	0.2	1 (0.7)	0.6
Hepatitis A	0	0	1 (0.7)	0.6
Lower respiratory tract infection	1 (<0.1)	<0.1	1 (0.7)	0.6
Pneumonia	11 (0.4)	0.3	1 (0.7)	0.6
Pyelonephritis acute	0	0	1 (0.7)	0.6
Immune system disorders	**1 (<0.1)**	**<0.1**	**2 (1.4)**	**1.2**
Hypersensitivity	0	0	2 (1.4)	1.2
Metabolism and nutrition disorders	**10 (0.3)**	**0.3**	**1 (0.7)**	**0.6**
Hypokalemia	1 (<0.1)	<0.1	1 (0.7)	0.6
Psychiatric disorders	**9 (0.3)**	**0.3**	**1 (0.7)**	**0.6**
Major depression	0	0	1 (0.7)	0.6
Nervous system disorders	**54 (1.9)**	**1.7**	**5 (3.4)**	**3.0**
Transient ischemic attack	5 (0.2)	0.2	2 (1.4)	1.2
Brain stem infarction	0	0	1 (0.7)	0.6
Carotid artery stenosis	1 (<0.1)	<0.1	1 (0.7)	0.6
Miller Fisher syndrome	0	0	1 (0.7)	0.6
Syncope	13 (0.5)	0.4	1 (0.7)	0.6
Cardiac disorders	**142 (4.9)**	**4.5**	**7 (4.8)**	**4.3**
Atrial fibrillation	12 (0.4)	0.4	2 (1.4)	1.2
Acute myocardial infarction	19 (0.7)	0.6	1 (0.7)	0.6
Angina pectoris	23 (0.8)	0.7	1 (0.7)	0.6
Angina unstable	33 (1.1)	1.0	1 (0.7)	0.6
Cardiac failure	7 (0.2)	0.2	1 (0.7)	0.6
Coronary artery disease	16 (0.6)	0.5	1 (0.7)	0.6
Gastrointestinal disorders	**33 (1.1)**	**1.0**	**1 (0.7)**	**0.6**
Abdominal pain	2 (<0.1)	0.1	1 (0.7)	0.6
Musculoskeletal and connective tissue disorders	**33 (1.1)**	**1.0**	**3 (2.0)**	**1.8**
Hemarthrosis	0	0	1 (0.7)	0.6
Intervertebral disc protrusion	4 (0.1)	0.1	1 (0.7)	0.6
Muscular weakness	0	0	1 (0.7)	0.6
Pain in extremity	0	0	1 (0.7)	0.6

SOC / Preferred term	Alirocumab-treated: No treatment-emergent positive ADA N=2866		Alirocumab-treated: Treatment-emergent positive ADA response N=147	
	n (%)	Per 100 pt/yr	n (%)	Per 100 pt/yr
General disorders and administration site conditions	**23 (0.8)**	**0.7**	**1 (0.7)**	**0.6**
Non-cardiac chest pain	15 (0.5)	0.5	1 (0.7)	0.6
Injury, poisoning, and procedural complications	**34 (1.2)**	**1.1**	**3 (2.0)**	**1.8**
Joint injury	0	0	1 (0.7)	0.6
Traumatic arthritis	0	0	1 (0.7)	0.6
Traumatic hematoma	1 (<0.1)	<0.1	1 (0.7)	0.6

Source: ISS Appendix 1.4.4.12
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Samples from phase 3 studies that were positive in the ADA assay were examined for neutralizing activity. Very few patients (36 patients;1.2%) exhibited neutralizing antibodies (NAb), all in the alirocumab group. Only 10 patients (0.3%) had 2 or more NAb positive samples. Review of the TEAEs occurring in patients with NAb did not demonstrate a specific safety concern. The table below only shows TEAEs that occurred in patients with NAb. Comparisions between groups should take into consideration the very small number of patients with NAb.

Table 132. Number (%) of TEAE in patients with NAb vs. patients with negative ADA response (safety population) – global pool of phase 3 studies

	Alirocumab-treated: Negative ADA N=2866 n (%)	Alirocumab-treated: NAb N=36 n (%)
Any TEAE	**2178 (76.0)**	**24 (66.7)**
Fungal infection	6 (0.2)	1 (2.8)
Tooth abscess	29 (1.0)	1 (2.8)
Tooth infection	14 (0.5)	1 (2.8)
Otitis media	16 (0.6)	1 (2.8)
Conjunctivitis	17 (0.6)	1 (2.8)
Bronchitis	120 (4.2)	1 (2.8)
Lower respiratory tract infection	48 (1.7)	1 (2.8)
Nasopharyngitis	290 (10.1)	4 (11.1)
Upper respiratory tract infection	188 (6.6)	3 (8.3)
Urinary tract infection	125 (4.4)	1 (2.8)
Hepatitis A	0	1 (2.8)
Hypothyroidism	6 (0.2)	1 (2.8)
Decreased appetite	12 (0.4)	1 (2.8)
Hypokalemia	14 (0.5)	1 (2.8)
Diabetes mellitus	37 (1.3)	1 (2.8)
Vitamin B12 deficiency	3 (0.1)	1 (2.8)
Eye pain	2 (<0.1)	1 (2.8)

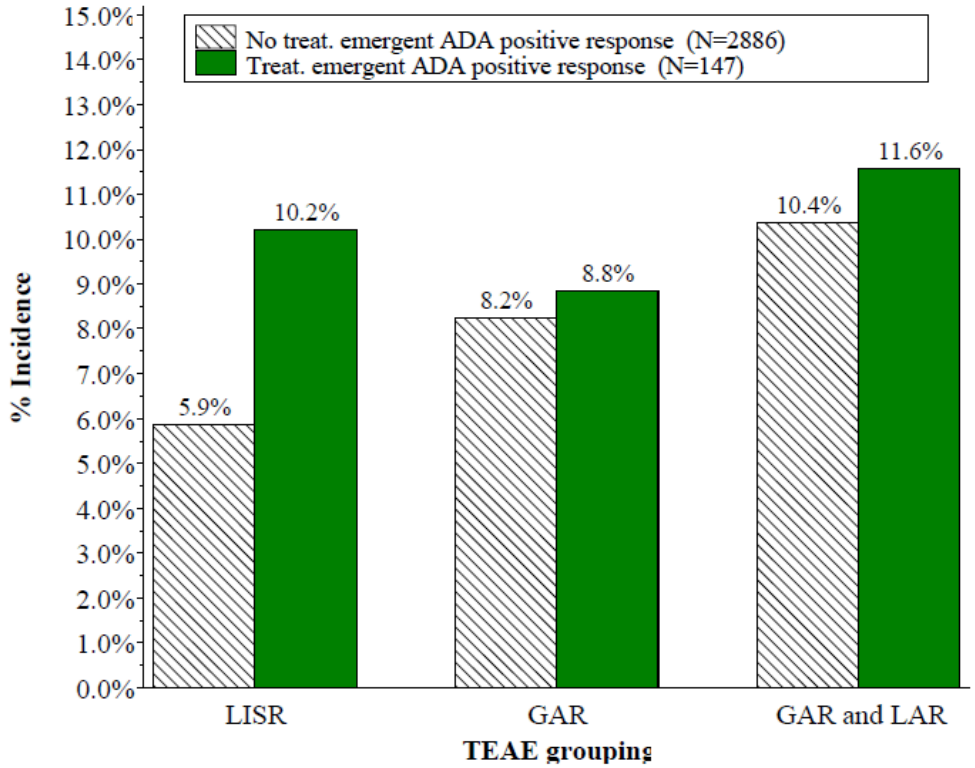
	Alirocumab-treated	
	Negative ADA N=2866 n (%)	NAb N=36 n (%)
Optic neuritis	0	1 (2.8)
Headache	129 (4.5)	2 (5.6)
Periorbital edema	0	1 (2.8)
Atrioventricular block	3 (0.1)	1 (2.8)
Atrioventicular block first degree	2 (<0.1)	1 (2.8)
Atrial fibrillation	33 (1.2)	1 (2.8)
Acute myocardial infarction	19 (0.7)	1 (2.8)
Angina pectoris	50 (1.7)	2 (5.6)
Angina unstable	38 (1.3)	1 (2.8)
Hypotension	17 (0.6)	1 (2.8)
Hypertension	94 (3.3)	2 (5.6)
Cough	72 (2.5)	1 (2.8)
Rhinitis allergic	9 (0.3)	1 (2.8)
Toothache	25 (0.9)	1 (2.8)
Diarrhea	129 (4.5)	3 (8.3)
Constipation	48 (1.7)	1 (2.8)
Abdominal discomfort	11 (0.4)	1 (2.8)
Vomiting	31 (1.1)	1 (2.8)
Joint swelling	11 (0.4)	1 (2.8)
Muscle spasms	84 (2.9)	2 (5.6)
Muscular weakness	8 (0.3)	1 (2.8)
Back pain	116 (4.0)	1 (2.8)
Musculoskeletal stiffness	13 (0.5)	1 (2.8)
Renal failure chronic	9 (0.3)	1 (2.8)
Micturition urgency	0	1 (2.8)
Hematuria	18 (0.6)	1 (2.8)
Nephrolithiasis	14 (0.5)	1 (2.8)
Injection site reaction	167 (5.8)	4 (11.1)
Influenza like illness	36 (1.3)	1 (2.8)
Blood cortisol decreased	10 (0.3)	1 (2.8)
International normalized ratio increased	3 (0.1)	1 (2.8)
Glycosylated hemoglobin increased	5 (0.2)	1 (2.8)
Fall	63 (2.2)	2 (5.6)
Traumatic hematoma	6 (0.2)	1 (2.8)
Tooth fracture	7 (0.2)	1 (2.8)
Accidental overdose	54 (1.9)	2 (5.6)

Source: Response to FDA IR dated 10 April 2015 Table 6
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

General allergic events and treatment-emergent positive ADA response

The applicant evaluated the incidence of general allergic events as defined by SMQ in patients with and without a positive ADA response. As shown in Figure 42, general allergic events and local injection site reactions (separately or combined) occurred at a higher incidence in alirocumab-treated patients with a positive treatment-emergent ADA response compared to alirocumab-treated patients without a positive treatment-

emergent ADA response; these results were mainly driven by local injection site reactions.



Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
LISR: local injection site reaction
GAR: general allergic event
GAR and LAR at IMP: general allergic event and local allergic reaction at IMP injection site
Source: NDA 125559 ISS Figure 24

Figure 42. Local injection site reaction and general allergic events by treatment-emergent positive ADA status in alirocumab-treated patients – pool of phase 3 studies

The following table lists the number and frequency of preferred terms that compose the general allergic SMQ in the alirocumab-treated group by presence or absence of a treatment-emergent ADA response. Overall, the proportion of patients with general allergic TEAE was similar with or without a treatment-emergent positive ADA response.

Table 133. Number (%) of patients with general allergic TEAE by PT by treatment-emergent ADA response (anti-alirocumab antibody population – alirocumab treated) – global pool of phase 3 studies

	Alirocumab-treated	
	No treatment-emergent ADA positive response N=2886 n (%)	Treatment-emergent ADA positive response N=147 n (%)
Any general allergic TEAE	**238 (8.2)**	**13 (8.8)**
Rash	36 (1.2)	3 (2.0)
Conjunctivitis	17 (0.6)	2 (1.4)
Hypersensitivity	4 (0.1)	2 (1.4)
Rhinitis allergic	9 (0.3)	1 (0.7)
Pruritus generalized	8 (0.3)	1 (0.7)
Urticaria	8 (0.3)	1 (0.7)
Dermatitis	3 (0.1)	1 (0.7)
Angioedema	2 (<0.1)	1 (0.7)
Pruritus allergic	2 (<0.1)	1 (0.7)
Periorbital edema	0	1 (0.7)
Rash pruritic	0	1 (0.7)
Pruritus	33 (1.1)	0
Seasonal allergy	22 (0.8)	0
Asthma	21 (0.7)	0
Eczema	20 (0.7)	0
Dermatitis contact	11 (0.4)	0
Drug hypersensitivity	8 (0.3)	0
Flushing	6 (0.2)	0
Conjunctivitis allegic	5 (0.2)	0
Dermatitis allergic	5 (0.2)	0
Erythema	5 (0.2)	0
Sneezing	4 (0.1)	0
Swelling face	4 (0.1)	0
Bronchospasm	3 (0.1)	0
Drug eruption	3 (0.1)	0
Rash erythematous	3 (0.1)	0
Wheezing	3 (0.1)	0
Bronchial hyperreactivity	2 (<0.1)	0
Eye swelling	2 (<0.1)	0
Photosensitivity reaction	2 (<0.1)	0
Rash generalized	2 (<0.1)	0
Rash maculo-papular	2 (<0.1)	0
Rash pustular	2 (<0.1)	0
Stomatitis	2 (<0.1)	0
Blister	1 (<0.1)	0
Dermatitis atopic	1 (<0.1)	0
Eczema nummular	1 (<0.1)	0
Eyelid edema	1 (<0.1)	0
Generalized edema	1 (<0.1)	0
Hand dermatitis	1 (<0.1)	0
Hypersensitivity vasculitis	1 (<0.1)	0
Interstital lung disease	1 (<0.1)	0

	Alirocumab-treated	
	No treatment-emergent ADA positive response N=2886 n (%)	Treatment-emergent ADA positive response N=147 n (%)
Mouth ulceration	1 (<0.1)	0
Rash macular	1 (<0.1)	0
Skin exfoliation	1 (<0.1)	0
Skin swelling	1 (<0.1)	0

Source: Response to FDA IR dated 10 April 2015 Table 2
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
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')

Device-related adverse events

The applicant used two different devices in the clinical development program: a pre-filled syringe (PFS) and pre-filled pen (PFP). The intention is to make both devices commercially available. The PFS in the 150 mg/mL strength was utilized in the LONG TERM study, 1550 patients received the alirocumab 150 mg dose and 788 patients received the placebo dose via the PFS. The remaining 9 phase 3 studies used the PFP device. Table 134 shows the number of patients using each device and the duration of use.

Table 134. Number of patients treated with alirocumab by device

	Pre-filled Syringe Number of patients	Pre-filled Pen Number of patients
Total number of patients treated with alirocumab	1550	1632[a]
Number of patients treated for 12 months with alirocumab	1343	1080
Number of patients treated for 18 months with alirocumab	405	79

Source: pre-BLA meeting background package Table 2
[a]Total number of patients treated with alirocumab 75 mg PFP plus number of patients treated with alirocumab 150 mg PFP in HIGH FH study

Injection site reactions by device

For local injection site reactions, the following symptoms were pre-listed in the "Local Injection Site Reaction complementary form": pain, tenderness, erythema/redness, swelling, itching. In addition, other signs or symptoms (for example, hematoma, discoloration), were reported by the Investigator in an open field and coded. In the global pool of phase 3 studies, in patients using the pre-filled syringe, 5.8% of patients receiving alirocumab and 4.3% of patients receiving the placebo injection reported an injection site reaction. In patients using the pre-filled pen, 6.1% of alirocumab-treated patients compared with 3.9% of placebo-treated patients reported a local injection site reaction. Signs and symptoms of injection site reactions were in general similar in alirocumab-treated patients.

Table 135. Local injection site reactions – description of symptoms (pre-listed) according to injection device (safety population) – global pool of phase 3 studies

	Pre-filled syringe		Pre-filled pen	
	Placebo N=788 n (%)	Alirocumab N=1550 n (%)	Placebo N=1004 n (%)	Alirocumab N=1632 n (%)
Any injection site reaction	34 (4.3)	90 (5.8)	39 (3.9)	99 (6.1)
Pain	12 (1.5)	31 (2.0)	11 (1.1)	29 (1.8)
Tenderness	4 (0.5)	23 (1.5)	10 (1.0)	28 (1.7)
Erythema/redness	12 (1.5)	42 (2.7)	8 (0.8)	50 (3.1)
Swelling	8 (1.0)	32 (2.1)	8 (0.8)	40 (2.5)
Itching	3 (0.4)	36 (2.3)	7 (0.7)	37 (2.3)

Source: Response to FDA IR dated 13 March 2015, Table 2
Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Selected specific symptoms pre-listed in the e-CRF

Device-related adverse events
The incidence of device-related events in patients using the PFS were similar regardless of treatment group assignment and were reported as "unknown", which according to the applicant were most likely needle sticks.

In contrast, alirocumab-treated patients treated with the PFP device had the highest incidence of device-related adverse events [142/1632 (8.7%)] compared to patients receiving a placebo injection using either the PFP [40/1004 (4.0%)] or the PFS [3 (0.4%)] device. The majority of the malfunctions were due to the device being jammed or failing to activate.

According to the applicant, as of August 31, 2014, across all completed and ongoing clinical studies, 4 nonserious AEs were associated with a prolonged injection time of the PFP, which in some cases led to a stalling of the device during the injection. One of these associated AEs was unusually long bleeding after the injection at the injection site, 2 events were bruising at the injection site and the fourth event was an overdose (with no clinical symptoms) because several stalling devices were injected and the sum of the injected volume may have exceeded the intended dose.

Of the device-related complaints concerning injection time, delivered volume and/or stalled PFPs in the clinical studies, 94% were for the 75 mg/mL dose, 4% were for the placebo, and only 2% were for the 150 mg/mL dose. (b) (4) [redacted] It should be noted that there were no significant differences in injection site reactions or associated symptoms in

alirocumab-treated patients regardless of whether the syringe or PFP (a combination of the 75 mg and 150 mg doses (b) (4)) were used. (b) (4) [redacted] Device-related adverse events will be monitored as part of routine post-marketing surveillance activities.

Table 136. Device-related events per patient (safety population) – pool of phase 3 placebo and ezetimbe-controlled studies

Safety pool	Placebo-controlled pool (phase 3)				Ezetimibe-controlled pool	
Device	Pre-filled syringe		Pre-filled pen			
Treatment group	Placebo N=788 n (%)	Alirocumab N=1550 n (%)	Placebo N=386 n (%)	Alirocumab N=768 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Any patient	**3 (0.4)**	**10 (0.6)**	**23 (6.0)**	**70 (9.1)**	**17 (2.8)**	**72 (8.3)**
Number of device related event per patient						
1	3 (0.1)	9 (0.4)	18 (1.6)	52 (4.5)	16 (2.6)	49 (5.7)
>1	0	1 (<0.1)	5 (0.4)	18 (1.6)	1 (0.2)	23 (2.7)
Type of device-related event						
Device is jammed	0	0	4 (1.0)	34 (4.4)	5 (0.8)	41 (4.7)
Activation difficulty/fault	0	0	18 (4.7)	27 (3.5)	9 (1.5)	27 (3.1)
Click/click sound missing	0	0	2 (0.5)	10 (1.3)	0	4 (0.5)
Unknown	3 (0.4)	10 (0.6)	1 (0.3)	3 (0.4)	1 (0.2)	2 (0.2)
No specific complaint	0	0	0	2 (0.3)	0	0
Other	0	0	1 (0.3)	2 (0.3)	1 (0.2)	1 (0.1)
Injection time	0	0	0	1 (0.1)	0	2 (0.2)
No investigation	0	0	0	1 (0.1)	1 (0.2)	0
Broken component	0	0	0	0	0	1 (0.1)
Leakage	0	0	0	0	0	1 (0.1)
Potential: dropped autoinjector	0	0	0	0	0	1 (0.1)
Packaging issue	0	0	0	0	1 (0.2)	0

Source: ISS Appendix 1.2.3.2, 1.2.3.4
Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

7.3.5 Submission Specific Primary Safety Concerns

Low LDL-C and adverse events

Approximately 20% and 40% of patients treated with alirocumab had at least one calculated LDL-C value less than 15 mg/dL and 25 mg/dL, respectively compared to less than 1% of control treated patients (Table 137). The majority of patients were

taking 150 mg Q2W of alirocumab at the time of these LDL-C values. The time to the first LDL-C value less than 25 mg/dL or 15 mg/dL was on average 12 to 16 weeks, respectively. A total of 796 (23.8%) of alirocumab-treated patients had a two consecutive LDL-C values less than 25 mg/dL.

Table 137. Number (%) of patients with LDL-C <25 mg/dL or <15 mg/dL (safety population) – global pool

	Control N=1894 n (%)	Alirocumab N=3340 n (%)
At least one LDL-C <25 mg/dL	12 (0.6)	1371 (41.0)
Two consecutive LDL-C <25 mg/dL	0	796 (23.8)
At least one LDL-C <15 mg/dL	1 (<0.1)	722 (21.6)
Two consecutive LDL-C <15 mg/dL	0	288 (8.6)

Source: ISS Appendix 1.5.4.1
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). Eze controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Baseline characteristics of patients who achieved and did not achieve 2 consecutive LDL-C <25 mg/dL are shown in the table below. The baseline characteristics of patients in these two subgroups (defined by post-randomization measurements) are different. The applicant provided a follow-up analysis that defined "significant" prognostic factors ($p<0.15$) for achieving 2 consecutive LDL-C <25 mg/dL in patients within the global pool of phase 3 trials. Patients with 2 consecutive LDL-C <25 mg/dL were more likely to be receiving 150 mg of alirocuamb and be men, older than 65 years of age, with prior history of CHD or CHD risk equivalents, diabetic, with lower baseline LDL-C, HDL-C and with higher TG levels. The applicant proposes that several of these differences are likely due to the design of the LONG TERM study, in which patients with diabetes plus 2 or more risk factors for CV disease or patients with prior history of CHD or CHD risk equivalents had treatment initiated with and maintained on 150 mg Q2W alirocumab despite only requiring a single screening LDL-C value >70 mg/dL. These differences in baseline characteristics of patients who reached LDL-C < 25 mg/dL could have an impact on the interpretation of the comparison of the safety profile between both LDL-C subgroups.

Table 138. Baseline demographics and characteristic in alirocumab-treated patients with or without two consecutive LDL-C <25 mg/dL (safety population) – global pool

		Alirocumab 2 LDL <25 N=796	Alirocumab LDL ≥ 25 N=2544
Age (years)	Mean (SD)	62.1 (9.7)	58.6 (11.4)
	≥65 years, n (%)	337 (42.3)	821 (32.2)
Sex, n (%)	Female	201 (25.3)	1076 (42.3)
Race, n (%)	Caucasian	723 (90.8)	2254 (88.6)

		Alirocumab 2 LDL <25 N=796	Alirocumab LDL ≥ 25 N=2544
	Black or African American	19 (2.4)	132 (5.2)
	Asian	27 (3.4)	89 (3.5)
	American Indian or Alaska Native	19 (2.4)	19 (0.7)
	Native Hawaiian or other Pacific Islander	0	1 (<0.1)
	Other	8 (1.0)	49 (1.9)
Ethnicity, n (%)	Hispanic	40 (5.1)	163 (6.5)
Region, n (%)	United States	241 (30.3)	881 (34.6)
BMI (kg/m^2)	Mean (SD)	29.6 (4.6)	30.1 (6.0)
HbA1c (%)	Mean (SD)	6.17 (0.98)	5.98 (0.84)
	≥5.7 to <6.5	330 (41.5)	1032 (40.7)
hsCRP (mg/L)	Median	1.55	1.63
Lipids/lipoproteins			
LDL-C (mg/dL)	Mean (SD)	100.2 (28.5)	133.7 (48.8)
HDL-C (mg/dL)	Mean (SD)	46.6 (10.9)	51.0 (14.3)
Fasting TG (mg/dL)	Median	147.0	122.0
Compliance	≥80% (%)	99.7	98.5
Dosing regimen	75 mg Q2W	182 (22.9)	989 (39.0)
	75 then 150 mg Q2W	23 (2.9)	384 (15.1)
	150 mg Q2W	591 (74.2)	1162 (45.8)
Exposure (weeks)	Mean (SD)	61.8 (18.6)	51.6 (24.1)

Source: Response to FDA IR request dated 28 January 2015, Table 1, 4
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTION I, OPTION II, ALTERNATIVE)
Patients with several races reported in the e-CRF are grouped in the "other" category
2 consecutive values are considered if spaced out by at least 21 days
Alirocumab LDL-C >= 25mg/dL group: Alirocumab patient without 2 consecutive LDL-C < 25mg/dL

Table 139. Medical history of specific interest: cardiovascular history and other factors of CV categorization for alirocumab-treated patients with or without two consecutive LDL-C <25 mg/dL (safety population) – global pool of phase 3 studies

	Alirocumab 2 LDL <25 N=768	Alirocumab LDL ≥ 25 N=2414
Any cardiovascular history risk factor	**741 (96.5)**	**1990 (82.4)**
Coronary heart disease[1]	590 (76.8)	1471 (60.9)
Acute Myocardial Infarction	343 (44.7)	766 (31.7)
Silent myocardial infarction	30 (3.9)	72 (3.0)
Unstable angina	101 (13.2)	314 (13.0)
Coronary revascularization procedures	420 (54.7)	1038 (43.0)
Other clinically significant CHD[2]	263 (34.2)	658 (27.3)
Coronary heart disease risk equivalents[1]	315 (41.0)	721 (29.9)
Ischemic stroke/transient ischemic attack	71 (9.2)	195 (8.1)
Peripheral arterial disease	37 (4.8)	93 (3.9)

	Alirocumab 2 LDL <25 N=768	Alirocumab LDL ≥ 25 N=2414
Abdominal aortic aneurysm	2 (0.3)	5 (0.2)
Carotid artery occlusion >50% without symptoms	0	10 (0.4)
Carotid endarterectomy or carotid artery stent procedure	0	6 (0.2)
Moderate chronic kidney disease[3]	112 (14.6)	254 (10.5)
Known history of diabetes (type 1 or 2) AND additional risk factors[4]	153 (19.9)	318 (13.2)

Source: Response to FDA IR request dated 28 January 2015, Table 2, 3
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTION I, OPTION II, ALTERNATIVE)
2 consecutive values are considered if spaced out by at least 21 days
Alirocumab LDL-C >= 25mg/dL group: Alirocumab patient without 2 consecutive LDL-C < 25mg/dL
A patient can be counted in several categories.

1. According to the items pre-listed in the e-crf.
2. Diagnosed by invasive or non-invasive testing
3. including patients from OPTIONS I, OPTIONS II and ALTERNATIVE studies even if this was not considered as a CHD risk equivalent in these protocols
4. At least 2 risks factors among ankle-brachial index ≤ 0.90, hypertension, nephropathy, retinopathy or family history of premature CHD in LONG TERM, FH I, FH II, HIGH FH, COMBO I, COMBO II studies only diabetes associated with target organ damage in OPTIONS I, OPTIONS II, ALTERNATIVE studies

Overall, the number of TEAE, SAEs, TEAEs leading to death, and discontinuations due to AEs in patients achieving very low LDL-C levels was similar to the incidences of these events in the total alirocumab and control (placebo or ezetimibe) treated populations. Please note the total alirocumab and control groups include the patients achieving low LDL-C levels. An analysis comparing adverse events between mutually exclusive groups defined by LDL-C thresholds is described in following paragraphs.

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

	Alirocumab			Total Alirocumab[1]	Total Control[1]
	1 LDL-C <25 N=1371 n (%)	2 LDL-C <25 N=796 n (%)	2 LDL-C <15 N=288 n (%)	N=3340 n (%)	N=1894 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). Ezetim be controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Only TEAEs that occurred, worsened or became serous 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

A numerically higher rate of TEAE occurred in the SOCs of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)", "Endocrine", "Congenital, familial, genetic disorders", "Metabolism and nutrition disorders" and "Eye disorders" of patients with LDL-C<25 mg/dL compared to patients with LDL-C ≥25 mg/dL. Looking at preferred terms within these SOCs, the number of patients reporting events was very

small. There were no preferred terms occurring at a rate greater than 1 per 100 patient-years in either LDL-C subgroup within the Endocrine, Neoplasm, or Congenital disorders SOC. In the Metabolism and nutrition disorders SOC, the rate was higher for 'diabetes mellitus' and 'type 2 diabetes mellitus' in the low LDL-C subgroups compared to the relatively higher LDL-C subgroups. In Eye disorders the preferred terms 'cataracts' and 'blurred vision' was higher in the low LDL-C groups. The table below lists the SOC and preferred terms within the 'Metabolism and nutrition' and 'Eye disorders' SOC that occurred at a higher rate in the both the <25 mg/dL and <15 mg/dL LDL-C subgroups compared to the complementary LDL-C subgroups and at ≥1 per 100 patient-years.

Table 141. TEAE occurring rate of ≥1 per 100 patient-year: SOC metabolism/nutrition and eye disorders (safety population) - global pool

	Alirocumab LDL-C ≥25 mg/dL N=2544		Alirocumab 2 LDL-C <25 mg/dL N=796		Alirocumab LDL-C ≥15 mg/dL N=3052		Alirocumab 2 LDL-C <15 mg/dL N=288	
	n	**Rate/100 py**	**n**	**Rate/100 py**	**n**	**Rate/100 py**	**n**	**Rate/100 py**
Metabolism and nutrition disorders	**164**	**6.5**	**56**	**7.4**	**206**	**6.6**	**21**	**7.8**
Type 2 DM	21	0.8	14	1.8	30	0.9	4	1.4
Diabetes mellitus	27	1.0	12	1.5	32	1.0	7	2.5
Eye disorders	**103**	**4.0**	**42**	**5.4**	**130**	**4.1**	**20**	**7.3**
Cataract	13	0.5	12	1.5	19	0.6	7	2.5
Vision blurred	10	0.4	6	0.8	13	0.4	3	1.1

Source: ISS Appendix 1.4.5.4, 1.4.6.4
Pbo controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361). Eze controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Diabetes and Ophthalmologic adverse events have been discussed in earlier sections. It should be noted in the global pool the number of patients reporting the TEAE 'cataract' was similar between treatment groups [control n=17 (0.9%), alirocumab n=26 (0.8%)].

Neurologic TEAEs defined by Standard MedDRA Queries (SMQs) for Demyelination, Peripheral neuropathy, and Guillain-Barre syndrome and Neurocognitive TEAEs defined by Company MedDRA Queries (CMQ) were assessed in the overall population and within patients achieving two consecutive LDL-C values less than 25 mg/dL. Of the 796 alirocumab-treated patients with two consecutive LDL-C <25 mg/dL within the phase 2/3 global pool, there were 15 (1.9%) patients with a SMQ-defined Neurologic TEAE and 4 (0.5%) with a CMQ-defined Neurocognitive TEAE. It does not appear there was a correlation with level of LDL-C achieved and neurocognitive events.

These analyses should be interpreted cautiously as these subgroups were defined using post-randomization assessments, and therefore unaccounted for characteristics of these subgroups may contribute to any observed differences. The table below lists

the adverse events of special interest by control group, alirocumab group, and alirocumab-treated patients by level of LDL-C achieved. Only TEAEs that occurred, worsened or became serious the day of or after the first of the 2 consecutive LDL-C<25 mg/dL are considered for alirocumab 2 LDL-C < 25 mg/dL group, therefore for adverse events occurring early (eg local injection site reactions) may be biased in favor of LDL-C<25 mg/dL group.

Table 142. Number (%) of patients with adverse events of special interest by LDL-C achieved (safety population) – global pool

	Control N=1894 n (%)	Alirocumab N=3340 n (%)	Alirocumab LDL-C ≥ 25 mg/dL N=2544 n (%)	Alirocumab 2 LDL-C <25 mg/dL N=796 n (%)
Neurologic TEAE (SMQ)	60 (3.2)	115 (3.4)	91 (3.6)	15 (1.9)
Neurocognitive TEAE (CMQ)	15 (0.8)	29 (0.9)	24 (0.9)	4 (0.5)
Local injection site reaction (SMQ)	78 (4.1)	205 (6.1)	160 (6.3)	26 (3.3)
General allergic TEAE (SMQ)	132 (7.0)	272 (8.1)	211 (8.3)	45 (5.7)
Ophthalmological TEAE (SMQ)	21 (1.1)	51 (1.5)	35 (1.4)	12 (1.5)
Diabetes mellitus or diabetic complications TEAE	71 (3.7)	128 (3.8)	83 (3.3)	41 (5.2)
Muscle-related TEAE (CMQ)	299 (15.8)	492 (14.7)	372 (14.6)	93 (11.7)
Hepatic disorders (SMQ)	37 (2.0)	77 (2.3)	64 (2.5)	9 (1.1)

Source: Response to FDA IR dated 13 March 2015, Appendix 2
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
MedDRA 17.0 . n(%) = number and percentage of patients with at least one TEAE. Only TEAEs that occurred, worsened or became serious the day or after the first of the 2 consecutive LDL-C<25 mg/dL (<0.65 mmol/L) are considered for alirocumab 2 LDL-C < 25 mg/dL group. 2 consecutive values are considered if spaced out by at least 21 days.
Alirocumab LDL-C ≥ 25mg/dL group: Alirocumab patients without 2 consecutive LDL-C < 25 mg/dL

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Two approaches were used to identify “common” adverse events. The first approach was a prespecified analysis of “Tier 2 TEAE” – defined as any TEAE (i.e. not prespecified, unlike Tier 1 adverse events of special interest) occurring in at least 9 patients (regardless of treatment assignment) in the placebo-control safety pool and 6 patients in the ezetimibe-control safety pool. These patient number thresholds would not permit the lower bound of the 95% confidence interval to be higher than 1 or the p value (exact Fisher test) to be less than 0.05 in the scenario where all events occurred in the alirocumab group and none in the control group.

This analysis revealed that the lower bound of the 95% CI for the HR versus placebo was greater than 1 for the following TEAEs (PT or HLT) in the placebo-controlled safety pool (Table 143) and ezetimibe-controlled safety pool (Table 144).

Table 143. Number (%) of patients with "Tier 2" TEAEs by HLT, PT with lower bound 95% CI ≥1.0 (safety population) – placebo-controlled studies

	Placebo N=1276			Alirocumab N=2476			
	n	Rate (%)	Per 100/pt yr[1]	n	Rate (%)	Per 100/pt yr[1]	HR vs pbo (95% CI)[2]
HLT: Injection site reactions	66	5.2	4.7	180	7.3	6.7	1.47 (1.11 to 1.95)
PT: Injection site reaction	61	4.8	4.3	166	6.7	6.1	1.40 (1.04 to 1.87)
HLT: Upper respiratory tract signs and symptoms	12	0.9	0.8	50	2.0	1.8	2.15 (1.14 to 4.03)
PT: Oropharyngeal pain	6	0.5	0.4	30	1.2	1.1	2.53 (1.05 to 6.09)
PT: Pruritus	5	0.4	0.3	28	1.1	1.0	2.84 (1.10 to 7.36)
HLT: Appetite disorders	1	0.1	0.1	22	0.9	0.8	11.17 (1.41 to 82.89)

Source: ISS Table 38
Placebo-controlled studies: phase 3 (LONG TERM FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
[1] Number of patients with an event per patient year, calculated as number of patients with an event divided by total patient years. For patients with event, number of patient years is calculated up to date of the first event, for patients without event, it corresponds to the length of TEAE period
[2] Calculated using a Cox model stratified on the study

Injection site reactions and pruritus were also prespecified as adverse events of special interest and are discussed in section 7.3.4.

Adverse events within the HLT "Upper respiratory tract signs and symptoms" occurred in 12 (0.9%) placebo treated patients and 50 (2.0%) alirocumab treated patients yielding a HR of 2.15 (1.14 to 4.03). Within this HLT, oropharyngeal pain was the only preferred term that occurred in ≥0.5% of patients. Oropharyngeal pain was reported in 6 (0.5%) of placebo-treated patients and 30 (1.2%) of alirocumab-treated patients.

Adverse events within the HLT "Appetite disorders" occurred in 1 (0.1%) placebo-treated patient and 22 (0.9%) alirocumab-treated patients. Of the 22 alirocumab-treated patients, 15 (0.6%) reported decreased appetite, 5 (0.2%) reported increased appetite, and 2 (<0.1%) reported food craving. The placebo-treated patient reported increased appetite.

Table 144. Number (%) of patients with "Tier 2" TEAEs by HLT, PT with lower bound 95% CI ≥1.0 (safety population) – ezetimibe-controlled studies

	Ezetimibe N=618			Alirocumab N=864			
	n	Rate (%)	Per 100/pt yr[1]	n	Rate (%)	Per 100/pt yr[1]	HR vs pbo (95% CI)[2]
HLT: Bronchospasm and obstruction	1	0.2	0.2	17	2.0	2.3	11.19 (1.48 to 84.54)

Source: ISS Table 40
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

The HLT "Bronchospasm and obstruction" was the only term within the ezetimibe-controlled safety pool with a lower bound of the 95% CI >1. Review of the terms within this HLT showed the majority of events were reported as chronic obstructive pulmonary disease (COPD) which occurred in 10 (1.2%) alirocumab-treated patients and no ezetimibe-treated patients. This imbalance was not observed in the placebo-controlled study pool, in which 23 (0.9%) alirocumab-treated patients versus 19 (1.5%) placebo-treated patients reported COPD.

The second approach evaluated events looking at different cutoffs of incidence (TEAE ≥5% or TEAE ≥2% and with a ≥0.5% higher incidence in alirocumab versus placebo or ezetimibe-treated patients).

The following table lists the adverse events by HLT and PT that occurred in a greater proportion of alirocumab-treated patients (≥2% and with a ≥0.5% higher incidence) compared to placebo (Table 145) and ezetimibe-treated patients (Table 146).

TEAEs (PT) reported in a higher proportion of patients in the alirocumab group compared to placebo (ie, incidence ≥2.0% in the alirocumab group and difference ≥0.5% versus placebo) were as follows: injection site reaction, influenza, myalgia, muscle spasms, contusion, and musculoskeletal pain. Within the HLT "Upper respiratory tract signs and symptoms", oropharyngeal pain was the most frequently reported PT (0.5% placebo, 1.2% alirocumab). In the HLT "Gastrointestinal and abdominal pains", the most frequently reported PT was abdominal pain (1.3% in placebo, 1.6% alirocumab).

Table 145. Number (%) of patients with TEAE by HLT or PT ≥2% and at least 0.5% higher in alirocumab than placebo (safety population) – pool of placebo-controlled studies

Primary System Organ Class HLT: High Level Term PT: Preferred Term	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)
Any TEAE	975 (76.4)	1876 (75.8)
Infections and infestations	516 (40.4)	1039 (42.0)
HLT: Influenza viral infections	59 (4.6)	141 (5.7)

Influenza	59 (4.6)	141 (5.7)
Respiratory, thoracic and mediastinal disorders	127 (10.0)	251 (10.1)
HLT: Upper respiratory tract signs and symptoms	12 (0.9)	50 (2.0)
Gastrointestinal disorders	231 (18.1)	434 (17.5)
HLT: Gastrointestinal and abdominal pains (excl oral and throat)	30 (2.4)	71 (2.9)
Musculoskeletal and connective tissue disorders	333 (26.1)	615 (24.8)
HLT: Musculoskeletal and connective tissue pain and discomfort	150 (11.8)	236 (9.5)
Musculoskeletal pain	20 (1.6)	53 (2.1)
HLT: Muscle pains	44 (3.4)	107 (4.3)
Myalgia	44 (3.4)	104 (4.2)
HLT: Muscle related signs and symptoms NEC	33 (2.6)	84 (3.4)
Muscle spasms	30 (2.4)	77 (3.1)
General disorders and administration site conditions	211 (16.5)	400 (16.2)
HLT: Injection site reactions	66 (5.2)	180 (7.3)
Injection site reaction	61 (4.8)	166 (6.7)
Injury, poisoning and procedural complications	171 (13.4)	327 (13.2)
HLT: Skin injuries NEC	31 (2.4)	81 (3.3)
Contusion	16 (1.3)	53 (2.1)

Source: ISS appendix 1.4.9.11
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)

The following TEAEs (PT) were reported in a higher proportion of patients in the alirocumab group compared to the ezetimibe group (incidence ≥2.0% in the alirocumab group and difference ≥0.5% versus ezetimibe): accidental overdose, headache, influenza, injection site reaction, fatigue, and constipation.

Within the HLT "Ischemic coronary artery disorders", no PTs occurred at an incidence of ≥2.0%. The most frequently reported PTs within this HLT in the alirocumab group were angina pectoris (1.8% ezetimibe, 1.5% alirocumab), angina unstable (0.3% ezetimibe, 1.4% alirocumab), and acute myocardial infarction (0.5% ezetimibe, 1.3% alirocumab).

Table 146. Number (%) of patients with TEAE by HLT or PT ≥2% and at least 0.5% higher in alirocumab than placebo (safety population) – pool of ezetimibe-controlled studies

Primary System Organ Class HLT: High Level Term PT: Preferred Term	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Any TEAE	421 (68.1)	607 (70.3)
Infections and infestations	171 (27.7)	247 (28.6)
HLT: Lower respiratory tract and lung infections	24 (3.9)	39 (4.5)
HLT: Influenza viral infections	14 (2.3)	32 (3.7)
Influenza	14 (2.3)	32 (3.7)
Nervous system disorders	75 (12.1)	120 (13.9)
HLT: Headaches NEC	25 (4.0)	36 (4.2)
Headache	21 (3.4)	34 (3.9)
Cardiac disorders	44 (7.1)	76 (8.8)
HLT: Ischemic coronary artery disorders	17 (2.8)	38 (4.4)

Gastrointestinal disorders	87 (14.1)	133 (15.4)
HLT: Gastrointestinal atonic and hypomotility disorders NEC	15 (2.4)	26 (3.0)
Constipation	8 (1.3)	17 (2.0)
General disorders and administration site conditions	71 (11.5)	104 (12.0)
HLT: Asthenic conditions	16 (2.6)	33 (3.8)
Fatigue	9 (1.5)	23 (2.7)
HLT: Injection site reactions	13 (2.1)	26 (3.0)
Injection site reaction	12 (1.9)	25 (2.9)
Injury, poisoning and procedural complications	71 (11.5)	101 (11.7)
HLT: Overdoses	21 (3.4)	38 (4.4)
Accidental overdose	21 (3.4)	37 (4.3)
HLT: Muscle, tendon and ligament injuries	11 (1.8)	22 (2.5)

Source: ISS appendix 1.4.9.12
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

7.4.2 Laboratory Findings

Laboratory values were assessed descriptively using measures of central tendency and categorically using pre-specified potentially clinical significant abnormalities (PCSA) cut-offs. The PCSA analyses evaluated the proportion of patients experiencing at least 1 post-baseline PCSA value regardless of baseline laboratory status and considering it (ie shift tables).

Red blood cells and platelets
In the phase 3 placebo-controlled pool and ezetimibe-controlled pool there were no pertinent mean changes from baseline in hemoglobin, hematocrit, or platelet counts.

Table 147. Mean change in hemoglobin and platelets (safety population) – pool of phase 3 placebo-controlled and pool of ezetimibe controlled studies

	Placebo-controlled pool				Ezetimibe-controlled pool			
	n	Placebo	n	Alirocumab	n	Ezetimibe	n	Alirocumab
Hemoglobin (g/L)								
Baseline (BL)	1174	143 (13.7)	2316	143 (13.7)	618	142.0 (14.7)	864	142.0 (13.9)
Mean change (SD) from BL to								
Last on-treatment[1]	1137	0.6 (8.6)	2244	0.7 (9.1)	589	0.2 (8.3)	822	1.3 (9.0)
Worst (lowest) on-treatment[2]	1137	-6.2 (7.4)	2244	-6.2 (8.5)	589	-3.9 (7.9)	822	-3.6 (8.5)
Week 52 (pbo)/ Week 24 (eze)	969	0.5 (7.8)	1945	0.5 (9.0)	492	-0.6 (8.2)	730	0.5 (8.6)
Platelets (10^9/L)								
Baseline (BL)	1171	250.5 (68.1)	2316	254.0 (69.2)	616	245.6 (63.5)	862	244.2 (63.4)
Mean change (SD) from BL to								
Last on-treatment[1]	1133	-1.7 (43.0)	2240	-3.6 (44.6)	586	2.4 (40.2)	820	1.9 (46.9)
Worst (lowest) on-treatment[2]	1133	-31.2 (38.5)	2240	-33 (39.9)	586	-14.6 (36.6)	820	-19.1 (39.0)
Week 52 (pbo)/ Week 24 (eze)	954	-3.6 (38.4)	1940	-3.7 (41.4)	487	2.9 (39.9)	726	0.6 (40.2)

Source: ISS appendix 1.5.1.1.1
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
[1]Defined as the last value collected up to 21 days after the last double-blind IMP injection.
[2]Defined as the nadir and/or the peak value according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
Patients who had parameter assessed at baseline and/or post-baseline are included. Only central laboratory values are taken into account.

Within the phase 3 placebo-controlled pool, a higher percentage of alirocumab-treated patients had at least 1 post-baseline low hemoglobin [≤11.5 g/dL (male); ≤9.5 g/dL (female)] and at least 1 post-baseline low hematocrit [≤37% (male) ≤32% (female) compared to placebo-treated patients] (Table 148). Among patients with normal baseline values, 1.9% of alirocumab-treated and 1.6% of placebo-treated patients experienced a low post-baseline hemoglobin value; 5.3% of alirocumab-treated and 4.3% of placebo-treated patients had a low post-baseline hematocrit.

Per the applicant, among patients with normal baseline hemoglobin value who experienced a low hemoglobin, 2 patients in the alirocumab group and no patients in the placebo group reported this abnormality as a SAE or TEAE leading to permanent treatment discontinuation. One of the patients while on clopidogrel was diagnosed with iron deficiency anemia which became serious on Day 190. Work-up suggested esophagitis was the cause of the anemia. The patient was treated and the patient had recovered from anemia while continuing alirocumab. The second patient, with a history of chronic anemia, reported a nonserious anemia of moderate intensity while hospitalized for osteomyelitis. Alirocumab was discontinued.

In the ezetimibe-controlled pool, among patients with normal baseline values, 1.1% of alirocumab-treated and 2.5% of ezetimibe-treated patients had a low hemoglobin value; 4.8% of alirocumab-treated and 4.0% of ezetimibe-treated patients had a low hematocrit.

The applicant reports among the 24 patients in the ezetimibe-controlled pool with normal/missing baseline hemoglobin values, who experienced a low hemoglobin, 2 patients (1 in each treatment group) reported this abnormality as a treatment-emergent SAE. The alirocumab-treated patient experienced a serious anemia, while taking concomitant clopidogrel and aspirin, in the context of recent catheterization and stent placement in the right superficial femoral artery. In the ezetimibe group, a patient treated with aspirin experienced a serious anemia requiring blood transfusion. Gastrointestinal bleeding was suspected, however colonoscopy was normal. The patient continued treatment, and as of the data cut-off the patient had not recovered from the event.

Table 148. Number of patients with PCSA (red blood cells, platelets) (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276 n/N1 (%)	Alirocumab N=2476 n/N1 (%)	Ezetimibe N=618 n/N1 (%)	Alirocumab N=864 n/N1 (%)
Hemoglobin (g/dL)				
≤11.5 g/dL (male); ≤9.5 g/dL (female)	23/1252 (1.8)	64/2426 (2.6)	22/604 (3.6)	17/839 (2.0)
Decrease from BL ≥1.5 g/dL	134/1252 (10.7)	261/2424 (10.8)	40/604 (6.6)	58/839 (6.9)

Decrease from BL ≥2.0 g/dL	50/1252 (4.0)	114/2424 (4.7)	15/604 (2.5)	24/839 (2.9)
Nml/Missing to ≤11.5 g/dL; ≤9.5 g/dL	20/1242 (1.6)	46/2402 (1.9)	15/593 (2.5)	9/825 (1.1)
Hematocrit (%)				
≤37% (male) ≤32% (female)	84/1251 (6.7)	182/2426 (7.5)	38/604 (6.3)	55/839 (6.6)
Nml/Missing to ≤37%; ≤32%	52/1202 (4.3)	123/2335 (5.3)	23/579 (4.0)	38/797 (4.8)
Platelet (10^3/uL)				
<100 10^3/uL	7/1249 (0.6)	7/2423 (0.3)	3/601 (0.5)	3/839 (0.4)
Nml/Missing to <100 10^3/uL	4/1246 (0.3)	6/2419 (0.2)	3/601 (0.5)	3/839 (0.4)

Source: ISS appendix 1.5.1.1.7
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period.
The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period, by baseline PCSA status.
PCSA classification is performed on the worst value
Only the worsening of the worst case for each patient is presented by baseline status.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period

Electrolytes

There were no relevant mean changes from baseline over time for sodium, potassium, chloride, calcium, phosphorus, or bicarbonate in the pool of placebo-controlled studies or ezetimibe-controlled studies.

The percentage of patients with PCSA changes in sodium, potassium, and chloride was low and similar among treatment groups.

Renal function

At baseline, moderate chronic kidney disease by medical history was present in approximately 12% of patients in the pool of placebo-controlled studies and approximately 9% of patients in the pool of ezetimbe-controlled studies. Baseline renal status assessed by estimated glomerular filtration rate (eGFR) showed the majority of patients in both the placebo and ezetimibe-controlled groups had mildly decreased eGFR.

The mean change in creatinine (and, therefore, eGFR) from baseline at different endpoints was small and similar between treatment groups (Table 149).

Table 149. Mean change in parameters of renal function (safety population) – pool of phase 3 placebo-controlled and pool of ezetimibe controlled studies

	n	Placebo	n	Alirocumab	n	Ezetimibe	n	Alirocumab
Creatinine (mg/dL)								
Baseline (BL)	1174	0.963 (0.272)	2316	0.969 (0.238)	618	0.977 (0.255)	864	0.990 (0.245)
Mean change (SD) from BL								
Last on-treatment[1]	1139	0.006 (0.183)	2241	0.008 (0.132)	591	0.010 (0.172)	825	0.005 (0.162)

Worst (highest) on-treatment[2]	1139	0.084 (0235)	2241	0.081 (0.153)	591	0.050 (0.167)	825	0.059 (0.166)
Week 52 (pbo)/ Week 24 (eze)	980	0.003 (0.189)	1948	-0.001 (0.121)	499	0.004 (0.152)	734	-0.003 (0.155)
eGFR (mL/min/1.73m2)								
Baseline (BL)	1174	77.1 (19.3)	2316	76.5 (18.6)	618	75.4 (18.3)	864	74.8 (17.7)
Mean change (SD) from BL								
Last on-treatment[1]	1134	-1.1 (11.2)	2228	-1.1 (11.2)	584	-0.5 (10.6)	820	-0.4 (10.5)
Worst (lowest) on-treatment[2]	1134	-7.0 (10.9)	2228	-6.8 (10.1)	584	-4.0 (9.6)	820	-4.7 (10.1)
Week 52 (pbo)/ Week 24 (eze)	979	-0.9 (11.5)	1943	-0.4 (10.8)	498	-0.3 (10.1)	734	0.2 (10.8)

Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
[1]Defined as the last value collected up to 21 days after the last double-blind IMP injection
[2]Defined as the nadir and/or the peak value according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
Note: For each parameter, patients who had that parameter assessed at baseline and/or post-baseline are included. Only central laboratory values are taken into account

The number and percentage of patients with at least 1 post-baseline PCSA increase in creatinine or decrease in eGFR was similar between treatment groups. However, a higher percentage of alirocumab-treated patients compared to the placebo or ezetimibe treated patients shifted from a normal/missing eGFR at baseline to a worse eGFR category. The majority of patients with a worsening shift displayed a mild eGFR decrease. A total of 7 alirocumab-treated patients with normal/missing eGFR values at baseline versus no placebo or ezetimibe-treated patients showed a moderate eGFR decrease. No alirocumab-treated patients with a normal eGFR at baseline advanced to severe or ESRD as determined by eGFR.

Table 150. Number of patients with PCSA (creatinine & eGFR) (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276 n/N1 (%)	Alirocumab N=2476 n/N1 (%)	Ezetimibe N=618 n/N1 (%)	Alirocumab N=864 n/N1 (%)
Creatinine				
≥1.7 mg/dL	46/1253 (3.7)	89/2424 (3.7)	12/604 (2.0)	23/842 (2.7)
≥30% increase from BL	70/1253 (5.6)	142/2422 (5.9)	18/604 (3.0)	27/842 (3.2)
≥100% increase from BL	7/1253 (0.6)	6/2422 (0.2)	2/604 (0.3)	1/842 (0.1)
Nml/Missing at BL to ≥1.7 mg/dL	33/1239 (2.7)	55/2386 (2.3)	5/593 (0.8)	14/828 (1.7)
eGFR (mL/min/1.73m2)				
Total regardless of BL status				
≥60 to <90 (mild CKD)	733/1145 (64.0)	1460/2257 (64.7)	395/601 (65.7)	548/837 (65.5)
≥30 to <60 (moderate CKD)	262/1145 (22.9)	556/2257 (24.6)	134/601 (22.3)	190/837 (22.7)
≥15 to <30 (severe CKD)	9/1145 (0.8)	17/2257 (0.8)	3/601 (0.5)	6/837 (0.7)
<15 (ESRD)	1/1145 (<0.1)	1/2257 (<0.1)	0	0
Normal/missing eGFR at BL				
Nml/missing to mild CKD	116/240 (48.3)	262/467 (56.1)	56/110 (50.9)	78/151 (51.7)
Nml/missing to moderate CKD	0	5/467 (1.1)	0	2/151 (1.3)
Nml/missing to severe CKD	0	0	0	0
Nml/missing to ESRD	1/240 (0.4)	0	0	0
Mild CKD at BL				
Mild CKD to moderate CKD	126/739 (17.1)	222/1418 (15.7)	45/394 (11.4)	77/548 (14.1)
Mild CKD to severe CKD	2/739 (0.3)	2/1418 (0.1)	1/394 (0.3)	0
Mild CKD to ESRD	0	0	0	0

	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276 n/N1 (%)	Alirocumab N=2476 n/N1 (%)	Ezetimibe N=618 n/N1 (%)	Alirocumab N=864 n/N1 (%)
Moderate CKD at BL				
Moderate CKD to severe CKD	7/165 (4.2)	14/369 (3.8)	1/97 (1.0)	6/137 (4.4)
Moderate CKD to ESRD	0	0	0	0

Source: ISS appendix 1.5.2.4.8
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period.
The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period, by baseline PCSA status.
PCSA classification is performed on the worst value
Only the worsening of the worst case for each patient is presented by baseline status.
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period

A review of TEAEs for renal failure or impairment in the placebo-controlled pool and ezetimibe-controlled pool showed the number of patients reporting an event within the HLT 'Renal failure and impairment' were similar between treatment groups. A total of 20 (1.6%) and 29 (1.2%) of patients in the placebo and alirocumab treated groups, respectively, reported an event. In the ezetimibe-controlled pool, 6 (1.0%) and 8 (0.9%) patients in the ezetimibe and alirocumab treated groups, respectively, reported an event.

Cortisol and adrenal function

Cortisol levels were obtained in the LONG TERM study at Week 0, 12, 24, 52, and 78/or early termination. Cortisol levels were not required to be obtained during the 6:00 AM to 8:00 AM window for which a normal range is established (>5 µg/dL or >138 nmol/L). Therefore, if a patient had a cortisol level less than the lower limit of normal, an ACTH was done. If the ACTH was greater than the upper limit of normal an ACTH stimulation test was conducted locally.

The proportion of patients with a cortisol value less than the lower limit of normal (LLN) range was similar between groups (154 [20.1%] in placebo group, and 295 [19.6%] in alirocumab group). Of the 154 patients in the placebo group with cortisol < LLN, only one had ACTH >ULN, and this patient had a normal ACTH stimulation test. Of the 295 patients in the alirocumab group with cortisol < LLN, two had ACTH >ULN, one of whom had an abnormal ACTH stimulation test. No action was taken with the alirocumab, and the patient completed the 78-week double-blind treatment. LDL-C values remained above 25 mg/dL (Patient ID. 011717-840-058- 002).

Another patient in the alirocumab group had a reported TEAE of decreased blood cortisol on study day 167, however the lowest cortisol value was >LLN. The LDL-C

value on the study day was 69.9 mg/dL. The patient decided to discontinue treatment (not due to any event). (Patient ID. 011717-616-007-055).

Four patients discontinued treatment due to TEAEs related to cortisol value <LLN: 1 patient in the alirocumab group due to Addison's disease (Patient ID. 11717-826-009-152) and 3 patients in the placebo group; in 2 of them, the event was reported as decreased cortisol (PT: blood cortisol decreased) (Patient IDs 011717-528-006-003 and 011717-840-022-001) and 1 patient due to adrenal insufficiency (Patient ID 011717-840-027-012).

Gonadal hormone assessment

Luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone, and sex hormone binding globulin (SHBG) for men was assessed in the LONG TERM study at Week 0, 12, 24, 52, and 78/or early termination. Mean changes were small and remained within the reference range.

Table 151. Mean change in testosterone (safety population) – LONG TERM study

	n	Placebo	n	Alirocumab
Total testosterone (ng/dL)				
Baseline	442	419.8 (154.4)	911	409.8 (159.4)
Change from BL				
Week 12	429	-2.8 (96.5)	851	-2.4 (111.0)
Week 24	388	-1.1 (108.7)	817	-0.2 (195.7)
Week 52	373	8.8 (111.1)	780	1.5 (1113.2)
Last on-treatment value	429	14.4 (128.3)	874	2.7 (127.2)

Source: Response to FDA IR dated 31 March 2015
Last on-treatment value: defined as the last value collected up to 21 days after the last double-blind IMP injection
Reference range testosterone: males 240-950 ng/dL

A higher proportion of men treated with alirocumab (19.7%) experienced at least 1 post-baseline testosterone level less than the lower limit of normal compared to men treated with placebo (15.3%). However, there were similar numbers of patients with low testosterone and high LH or FSH between treatment groups, which suggests feedback mechanisms were not triggered more frequently in alirocumab-treated patients. Review of TEAEs for signs or symptoms suggestive of androgen deficiency in men with a laboratory shift from normal/missing testosterone levels at baseline to less than the lower limit, identified 'erectile dysfunction' and 'blood testosterone decreased' each reported in a single patient in the alirocumab group. However it should be noted that erectile dysfunction and blood testosterone decreased were also reported in men that did not have shifts in testosterone. In the LONG TERM study, a total of 8 (0.5%) of alirocumab-treated men and 1 (0.1%) placebo-treated patient reported an adverse event of 'erectile dysfunction'; 'blood testosterone decreased' was reported in 3 patients (0.2%) in the alirocumab group and 1 patient (0.1%) in the placebo group.

Table 152. Number (%) of patients with PCSA (testosterone) (safety population) – LONG TERM study

	Placebo N=788 n/N1 (%)	Alirocumab 150 mg Q2W N=1550 n/N1 (%)
Total testosterone < LLN	67/439 (15.3)	179/909 (19.7)
Nml/Missing total testosterone to <LLN	41/397 (10.3)	96/800 (12.0)
Total testosterone < LLN and LH >ULN	16/439 (3.6)	27/909 (3.0)
Total testosterone < LLN and FSH >ULN	2/439 (0.5)	6/909 (0.7)

Source: LONG TERM post-text table 16.2.8.5.1.2
Reference range testosterone males 8.3-33 nmol/L

There was no apparent correlation observed with calculated LDL-C and total testosterone.

Fat soluble vitamins

Vitamins A, D, E, and K were measured in the LONG TERM study at Baseline and at Weeks 12 (Vitamin E only), 24, 52, and 78. For Vitamins A and D, the mean changes were small and similar between treatment groups. The mean change from baseline in Vitamin E and Vitamin K was greater in alirocumab-treated patients compared to placebo-treated patients at the Week 24, 52, and 78 timepoints. This pattern was also observed in the Vitamin E to calculated LDL-C ratio.

Table 153. Mean change in Vitamin E & K (safety population) – LONG TERM study

	n	Placebo	n	Alirocumab
Vitamin E (µmol/L)				
Baseline	761	35.84 (11.92)	1501	36.50 (12.68)
Change from BL				
Week 12		-2.47 (8.53)		-2.30 (13.41)
Week 24		-0.34 (9.8)		-11.06 (10.73)
Week 52		0.18 (11.41)		-11.38 (11.53)
Week 78		1.78 (11.95)		-10.40 (11.90
Vitamin E/calculated LDL-C ratio	739	11.926 (4.019)	1473	12.016 (4.054)
Change from BL				
Week 12		-0.712 (4.305)		10.010 (5.885)
Week 24		0.256 (4.174)		27.854 (113.939)
Week 52		-0.155 (4.201)		21.406 (41.728)
Week 78		-0.142 (4.124)		19.884 (67.351)
Vitamin K (nmol/L)	726	1.98 (1.97)	1410	2.05 (1.9)
Week 24		-0.02 (1.97)		-0.47 (1.98)
Week 52		-0.08 (2.03)		-0.40 (1.87)
Week 78		0.26 (2.06)		-0.30 (1.75)

Source: LONG TERM post-text table 16.2.8.6.1.1

Consistent with the mean changes in Vitamin E and K observed, there was a higher proportion of alirocumab-treated patients with Vitamin E and Vitamin K levels <LLN compared to placebo-treated patients. According to the applicant, among the 31

patients in the alirocumab group with PCSA for vitamin E (vitamin E < LLN), 7 patients had no reported TEAEs and 24 patients had at least 1 TEAE. No TEAEs of vitamin E deficiency were reported. Vitamin E deficiency may be associated with neurologic disorders and hemolysis. Ninety-two TEAEs were reported amongst the 24 patients. No patient had a confirmed hemolytic anemia. Two patients had TEAEs occurring in the nervous system disorders SOC (diabetic neuropathy and nerve compression).

Table 154. Number (%) of patients with PCSA (fat soluble vitamins) (safety population) – LONG TERM study

	Placebo N=788 n/N1 (%)	Alirocumab 150 mg Q2W N=1550 n/N1 (%)
Vitamin E <LLN	1/738 (0.1)	31/1461 (2.1)
Vitamin K <LLN	42/762 (5.5)	125/1496 (8.4)
Vitamin A <LLN	16/762 (2.1)	35/1494 (2.3)
Vitamin D <LLN	662/759 (87.2)	1279/1493 (85.7)

Source: LONG TERM post-text table 16.2.8.6.1.2

Hepatitis C Antibody

An HCV antibody test was performed at screening and at end of double-blind treatment period in phase 3 studies. Approximately one third of the overall safety population in the placebo-controlled pool and one half of the overall safety population in the ezetimibe-controlled pool contribute to this analysis. A patient with a positive HCV antibody test had reflexive testing with RNA quantification to confirm HCV status.

There were 2 placebo-treated patients with negative HCV antibody testing at screening with a positive Hepatitis C antibody but negative HCV RNA testing at end of treatment.

There were 5 patients (4 alirocumab and 1 ezetimibe-treated) with a negative Hepatitis C test at screening that developed a positive Hepatitis C antibody but at the time of the application submission, confirmatory HCV RNA testing was not available. The applicant provided an update of these 5 patients as part of an information request and the 4 month safety update, for 3 out of the 5 patients, an HCV RNA test was subsequently performed and was negative for all patients, further information was not available in the remaining two patients.

As of the cut-off date of this document, there were no cases of RNA confirmed Hepatitis C.

The four-month safety update, reported one alirocumab-treated patient enrolled in an ongoing study (CL-1308) that is not a part of the primary safety database, who developed acute hepatitis C. This case is summarized here.

- A 64-year-old male with hepatitis C virus (HCV) antibody test negative at baseline, history of new sexual partner in the previous 4 months, no history of blood transfusion, alcohol, addictive drug,

travel in country at risk of viral hepatitis, or recent tattoos, developed an increase in ALT and then was diagnosed with symptomatic acute hepatitis C infection about 8 months after starting the IMP. Routine tests showed ALT 605 U/L, AST 514 U/L and 6 days later ALT 1049 U/Land AST 750 U/L, hepatitis C RNA: 11.2 million IU/ml, and HCV antibody became positive. The IMP, simvastatin and codeine+paracetamol were discontinued Pt ID 1308-826-207-018.

Hs-CRP

High-sensitivity C-reactive protein (hs-CRP) is a biomarker of inflammation that is associated with the risk of cardiovascular disease.[58] In placebo-controlled trials the median change in hs-CRP was 0.04 mg/L in both alirocumab- and placebo-treated groups. In ezetimibe-controlled trials, the median changes were 0.0 mg/L and -0.13 mg/L, respectively, in the alirocumab- and ezetimibe-treated groups. The clinical implication is uncertain.

7.4.3 Vital Signs

Systolic blood pressure
In the placebo-controlled pool, the mean (SD) baseline value for SBP was 130.3 (15.8) mmHg in the alirocumab group and 130.7 (15.5) mmHg in the placebo group. No meaningful changes over time in SBP were observed up to Week 52 including last, or worst (lowest or highest) on treatment value.

In the ezetimibe-controlled pool, the mean (SD) baseline value for SBP was 129.3 (14.3) mmHg in the alirocumab group and 129.0 (13.5) mmHg in the ezetimibe group. No meaningful changes over time in SBP were observed up to Week 24 including last, or worst (lowest or highest) on treatment value.

Diastolic blood pressure (DBP)
In the placebo-controlled pool, the mean (SD) baseline value of DBP was 77.9 (9.7) mmHg in alirocumab group and 78.2 (9.6) mmHg in the placebo group. No meaningful changes over time in DBP were observed up to Week 52 including last, or worst (lowest or highest) on-treatment value.

In the ezetimibe-controlled pool, the mean (SD) baseline value of DBP was 77.3 (9.4) mmHg in the alirocumab group and 77.2 (8.8) mmHg in the ezetimibe group. No meaningful changes over time in DBP were observed up to Week 24 including last, or worst (lowest or highest) on-treatment value.

58 Ridker PM, et al. Relation of Baseline High-Sensitivity C-Reactive Protein Level to Cardiovascular Outcomes With Rosuvastatin in the Justification for Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER). Amer J Cardiol (2010); 106(2): 204–9.

Heart rate
In the placebo-controlled pool, the mean (SD) baseline value for heart rate was 67.9 (10.2) bpm in the alirocumab group and 67.5 (10.2) bpm in the placebo group. No meaningful changes over time in HR were observed up to Week 52 including last, or worst (lowest or highest) on-treatment value

In the ezetimibe-controlled pool, the mean (SD) baseline value of HR was 67.1 (9.7) bpm in the alirocumab group and 67.9 (9.8) bpm in the ezetimibe group. No meaningful changes over time in HR were observed up to Week 24 including last, or worst (lowest or highest) on-treatment value.

Table 155. Mean (SD) change in vital signs (safety population) – pool of placebo-controlled and pool of ezetimibe-controlled studies

	n	Placebo	n	Alirocumab	n	Ezetimibe	n	Alirocumab
Systolic blood pressure (mmHg)								
Baseline (BL)	1276	130.7 (15.5)	2473	130.3 (15.8)	618	129.0 (13.5)	864	129.3 (14.3)
Mean change (SD) from BL								
Last on-treatment[1]	1263	-1.1 (14.9)	2448	-1.0 (15.0)	607	0.67 (15.4)	846	0.8 (15.1)
Worst (highest) on-treatment[2]	1263	-13.4 (12.9)	2448	-13.6 (12.9)	607	-10.9 (12.6)	846	-11.8 (12.6)
Week 52 (pbo)/ Week 24 (eze)	990	-1.1 (15.0)	1966	-1.1 (14.9)	440	0.0 (15.7)	654	-0.4 (15.0)
Diastolic blood pressure (mmHg)								
Baseline (BL)	1276	78.2 (9.6)	2473	77.9 (9.7)	618	77.2 (8.8)	864	77.3 (9.4)
Mean change (SD) from BL								
Last on-treatment[1]	1263	-0.9 (9.3)	2448	-0.3 (9.7)	607	-0.3 (9.1)	846	0.2 (9.5)
Worst (highest) on-treatment[2]	1263	7.3 (8.1)	2448	7.7 (8.6)	607	6.3 (8.1)	846	7.2 (8.3)
Week 52 (pbo)/ Week 24 (eze)	990	-0.7 (9.3)	1966	-0.3 (9.8)	440	-0.9 (8.9)	654	-0.2 (9.6)
Heart rate (bpm)								
Baseline (BL)	1276	67.5 (10.2)	2473	67.9 (10.2)	618	67.9 (9.8)	864	67.1 (9.7)
Mean change (SD) from BL								
Last on-treatment[1]	1263	0.2 (9.1)	2448	0.5 (9.4)	607	0.2 (9.4)	846	0.4 (9.3)
Worst (highest) on-treatment[2]	1263	8.3 (9.4)	2448	8.5 (8.8)	607	6.6 (8.6)	846	7.6 (9.2)
Week 52 (pbo)/ Week 24 (eze)	990	0.1 (9.1)	1966	0.3 (9.4)	440	-0.2 (9.5)	654	-0.1 (9.8)

Source: ISS appendix 1.6.1
Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
[1]Defined as the last value collected up to 21 days after the last double-blind IMP injection
[2]Defined as the nadir and/or the peak value according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list

Table 156. Number (%) of patients with PCSA (vital signs) (safety population) – Pool of placebo-controlled and pool of ezetimibe-controlled studies

	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276 n/N1 (%)	Alirocumab N=2476 n/N1 (%)	Ezetimibe N=618 n/N1 (%)	Alirocumab N=864 n/N1 (%)
Systolic blood pressure				
≥160 mmHg and increase ≥20 mmHg from BL	97/1268 (7.6)	177/2456 (7.2)	34/614 (5.5)	58/852 (6.8)
Diastolic blood pressure				
≥110 mmHg and increase ≥10 mmHg from BL	11/1268 (0.9)	20/2456 (0.8)	5/614 (0.8)	7/852 (0.8)
Heart rate				
≥120 bpm and increase ≥20 bpm from BL	3/1268 (0.3)	1/2456 (<0.1)	0	2/852 (0.2)

Source: ISS appendix 1.6.11

7.4.4 Electrocardiograms (ECGs)

Centralized automatic and manual reading of all ECGs was used in the LONG TERM study. For the other phase 3 studies, ECGs were recorded by an automatic device at each investigator site and interpreted by the investigator as normal or abnormal. Any clinically significant abnormalities were to be documented as an AE/SAE as applicable.

The following analysis of categorical changes in ECG parameters is taken from the LONG TERM study. No consistent treatment group differences were observed in the incidence of patients with post-baseline ECG PCSAs.

Table 157. Number (%) of patients with PCSA (ECG) (safety population) – LONG TERM study

	Placebo N=788 n/N1 (%)	Alirocumab 150 mg Q2W N=1550 n/N1 (%)
QTcF – Fridericia's correction formula		
>450 ms (men); >470 ms (women); <500 ms	73/762 (9.6)	133/1505 (8.8)
≥500 ms	2/762 (0.3)	10/1505 (0.7)
Increase from BL >30 ms	89/752 (11.8)	158/1475 (10.7)
Increase from BL >60 ms	4/752 (0.5)	13/1475 (0.9)
QTcB – Bazett's correction formula		
>450 ms (men); >470 ms (women); <500 ms	98/762 (12.9)	197/1505 (13.1)
≥500 ms	9/762 (1.2)	21/1505 (1.4)
Increase from BL >30 ms	113/752 (15.0)	240/1475 (16.3)
Increase from BL >60 ms	10/752 (1.3)	23/1475 (1.6)
PR interval		
≥50% from BL if PR <200 ms	3/651 (0.5)	2/1232 (0.2)
≥25% from BL if PR ≥200 ms	2/88 (2.3)	2/192 (1.0)
QRS interval		
QRS ≥50% if QRS <100 ms	6/561 (1.1)	9/1076 (0.8)
QRS ≥25% if QRS ≥100 ms	5/196 (2.6)	7/402 (1.7)

Source: LONG TERM post-text table 16.2.7.2.9
Note: The number (n) represents the subset of the total number of patients who met the criterion at least once during the TEAE period

The denominator (/N1) for each parameter within a treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period
For PCSA including condition based only on change from baseline, the denominator is restricted on patients having (not missing) baseline and a post-baseline values during the TEAE period
Only the worst case for each patient is presented

An analysis was also done using a Company MedDRA query using preferred terms that could represent prolongation of cardiac repolarization or proarrhythmia which is shown in the table below. The incidence of these reported events were similar between treatment groups in both safety pools.

Table 158. Number (%) of patients with TEAE(s) within CMQ cardiac repolarization or proarrhythmia (safety population) – pool of placebo-controlled studies and pool and ezetimibe-controlled studies

Company MedDRA Query PT: Preferred Term	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276	Alirocumab N=2476	Ezetimibe N=618	Alirocumab N=864
Number of patients with CMQ	**81 (6.3)**	**143 (5.8)**	**45 (7.3)**	**62 (7.2)**
Arrhythmia related investigations, signs, and symptoms (SMQ)	**26 (2.0)**	**49 (2.0)**	**16 (2.6)**	**19 (2.2)**
Syncope	11 (0.9)	18 (0.7)	16 (2.6)	19 (2.2)
Palpitations	8 (0.6)	12 (0.5)	4 (0.6)	9 (1.0)
Bradycardia	2 (0.2)	9 (0.4)	2 (0.3)	0
Presyncope	0	3 (0.1)	0	0
Cardiac arrest	0	2 (<0.1)	1 (0.2)	2 (0.2)
Heart rate increased	0	2 (<0.1)	0	0
Loss of consciousness	0	2 (<0.1)	1 (0.2)	1 (0.1)
Tachycardia	1 (<0.1)	2 (<0.1)	0	2 (0.2)
ECG abnormal	1 (<0.1)	1 (<0.1)	0	1 (0.1)
Cardiorespiratory arrest	1 (<0.1)	0	0	0
Heart rate decreased	1 (<0.1)	0	0	0
Sudden cardiac death	1 (<0.1)	0	1 (0.2)	1 (0.1)
Sudden death	0	0	1 (0.2)	0
Torsade de pointes/QT prolongation (SMQ)	**18 (1.4)**	**36 (1.5)**	**12 (1.9)**	**12 (1.4)**
Syncope	11 (0.9)	18 (0.7)	7 (1.1)	3 (0.3)
ECG QT prolonged	2 (0.2)	6 (0.2)	0	2 (0.2)
Presyncope	0	3 (0.1)	0	0
Ventricular tachycardia	2 (0.2)	3 (0.1)	1 (0.2)	1 (0.1)
Cardiac arrest	0	2 (<0.1)	1 (0.2)	1 (0.1)
Loss of consciousness	0	2 (<0.1)	1 (0.2)	1 (0.1)
Ventricular arrhythmia	0	2 (<0.1)	0	1 (0.1)
Ventricular fibrillation	2 (0.2)	1 (<0.1)	0	1 (0.1)
Cardiorespiratory arrest	1 (<0.1)	0	0	0
Sudden cardiac death	1 (<0.1)	0	1 (0.2)	1 (0.1)
Sudden death	0	0	1 (0.2)	0
Conduction defects (SMQ)	**9 (0.7)**	**14 (0.6)**	**3 (0.5)**	**8 (0.9)**
ECG QT prolonged	2 (0.2)	6 (0.2)	0	2 (0.2)
Atrioventricular block second degree	1 (<0.1)	3 (0.1)	1 (0.2)	1 (0.1)

Atrioventricular block	0	2 (<0.1)	0	2 (0.2)
Atrioventricular block complete	1 (<0.1)	1 (<0.1)	0	2 (0.2)
Atrioventricular block first degree	3 (0.2)	1 (<0.1)	1 (0.2)	2 (0.2)
Atrioventricular dissociation	0	1 (<0.1)	0	1 (0.1)
Bundle branch block left	3 (0.2)	0	0	0
Defect conduction intraventricular	0	0	1 (0.2)	0
Ventricular tachyarrhythmias (SMQ)	**6 (0.5)**	**10 (0.4)**	**5 (0.8)**	**5 (0.6)**
Ventricular extrasystoles	2 (0.2)	4 (0.2)	5 (0.8)	2 (0.2)
Ventricular tachycardia	2 (0.2)	3 (0.1)	1 (0.2)	1 (0.1)
Ventricular arrhythmia	0	2 (<0.1)	0	1 (0.1)
Ventricular fibrillation	2 (0.2)	1 (<0.1)	0	1 (0.1)
Cardiac arrhythmia terms, nonspecific (SMQ)	**1 (<0.1)**	**5 (0.2)**	**0**	**3 (0.3)**
Arrhythmia	1 (<0.1)	3 (0.1)	0	2 (0.2)
Heart rate irregular	0	2 (<0.1)	0	1 (0.1)
Additional terms	45 (3.5)	79 (3.2)	26 (4.2)	31 (3.6)
Dizziness	44 (3.4)	71 (2.9)	25 (4.0)	29 (3.4)
Presyncope	1 (<0.1)	8 (0.3)	1 (0.2)	1 (0.1)
Convulsion	0	1 (<0.1)	0	2 (0.2)

Source: Response to FDA IR 23 Jan 2015, Table 3
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
Ezetim be-controlled studiess (excluding ALTERNATIVE): phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II)
MedDRA 17.0
n(%) = number and percentage of patients with at least one prolongation of cardiac repolarization or proarrhythmia
Note: Table sorted by decreasing frequency of PT within SMQ in alirocumab group
The selection of preferred terms is based on Standardized MedDRA Queries (SMQs): 'Arrhythmia related investigations, signs and symptoms' (broad + narrow), 'Cardiac arrhythmia terms, nonspecific' (narrow), 'Ventricular tachyarrhythmias' (narrow), 'Torsade de pointes/QT prolongation' (broad + narrow) and 'Conduction defects (narrow)' plus the following PTs ('dizziness',' presyncope', 'convulsion ')
Note: Selection of terms within SMQs is based on the LLT while selection of additional terms is based on the PT

7.4.5 Special Safety Studies/Clinical Trials

The ophthalmological sub-study of the LONG TERM trial is discussed in Section 7.3.4.

7.4.6 Immunogenicity

Please refer to Section 7.3.4 for assessment of adverse events according to presence or absence of treatment-emergent anti-drug antibodies (ADA), and section 6.1.10 for an assessment of the impact of alirocumab ADA on efficacy.

For additional information regarding immunogenicity, please refer to the Office of Biotechnology Products review by Dr. Amy Rosenberg for additional information. An exerpt is taken from Dr. Rosenberg's review of immunogenicity with respect to alirocumab safety.

"Overall, immunogenicity was not a prevalent problem with respect to clinical studies of alirocumab. Most antibody responses were transient. With regard to hypersensitivity

responses, although generalized hypersensitivity responses were infrequent, two patients had treatment discontinued due to such responses. Moreover, injection site reactions were notable and higher in the mAb treated group than in the control, presumably excipient only, treated group."

Hypersensitivity reactions and immunogenicity is addressed in labeling. PMRs to further assess alirocumab's effect on hypersensitivity and immunogenicity in long-term studies have been required as a condition of alirocumab's approval.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Within the ISS, the safety analyses combined the two dose regimens of alirocumab (75/150 mg Q2W and 150 mg Q2W) and compared this alirocumab-treated group against the comparator. There is no phase 3 trial which randomized patients to either alirocumab 75 mg or 150 mg Q2W for the duration of treatment. However, this pooling of alirocumab doses is acceptable based on the following analyses which did not demonstrate a meaningful difference in adverse events by dose or treatment regimen.

Adverse events: 75 mg Q2W dose
Eight of ten of the Phase 3 trials initiated treatment with the 75 mg Q2W dose until Week 12.[59] Based upon the results of LDL-C levels at Week 8, the dose of alirocumab could be up-titrated at Week 12 to 150 mg Q2W in a blinded manner.

The first analysis compares TEAEs within the first 12 weeks between alirocumab 75 mg and the comparator group (placebo or ezetimibe). Overall, the incidence of TEAEs, SAEs, TEAEs leading to death, and discontinuations due to TEAEs were similar between alirocumab and their respective treatment groups (Table 159).

Within both the placebo- and ezetimibe-controlled pools, injection site reaction was the only TEAE that was reported at a higher incidence (≥2%) with alirocumab 75 mg Q2W compared to controls. Other TEAEs, specific to the placebo-control pool that occurred with a higher incidence(≥2% and a difference ≥0.5% between treatment groups) in the alirocumab 75 mg group compared to the placebo group were nasopharyngitis (4.9% versus 3.4%), influenza (2.9% versus 2.3%) and diarrhea (2.3% versus 1.1%). Specific to the ezetimibe-controlled pool, the TEAEs of upper respiratory tract infection (3.0% versus 1.9%), and headache (2.4% versus 1.8%) were reported with higher incidence (≥2% and a difference ≥0.5% between treatment groups).

59 Phase 3 trials with 75/150 up-titration regimen: Placebo-control FH I, FH II, COMBO I; Ezetimibe-control: COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, MONO

Table 159. TEAE at 75 mg Q2W versus comparator up to week 12 (safety population) – Phase 3 placebo and ezetimibe controlled pools

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=351 n (%)	Alirocumab 75 mg N=696 n (%)	Ezetimibe N=618 n (%)	Alirocumab 75 mg N=864 n (%)
TEAE	165 (47.0)	338 (48.6)	288 (46.6)	402 (46.5)
SAE	9 (2.6)	21 (3.0)	24 (3.9)	42 (4.9)
TEAE leading to death	2 (0.6)	3 (0.4)	2 (0.3)	0
TEAE leading to treatment discontinuation	8 (2.3)	15 (2.2)	47 (7.6)	56 (6.5)

Source: ISS appendix Table 1.4.14.2.1
Phase 3: Placebo-controlled (FH I, FH II, COMBO I); Ezetimibe-controlled (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

Adverse events: 75 mg Q2W versus up-titration to 150 mg Q2W
An exploratory analysis was conducted to evaluate the incidence of TEAEs in patients remaining on 75 mg Q2W versus patients who had their dose increased to 150 mg Q2W at week 12. Overall, there were no substantial differences in the incidence of TEAEs, SAEs, TEAEs leading to death, and discontinuations due to TEAEs by up-titration status after week 12.

Table 160. Adverse events at 75 mg Q2W versus up-titration to 150 mg Q2W[1]

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Alirocumab 75 mg[2] N=432 n (%)	Alirocumab 75/150 mg[3] N=228 n (%)	Alirocumab 75 mg N=606 n (%)	Alirocumab 75/150 mg N=180 n (%)
TEAE	286 (66.2)	150 (65.8)	343 (56.6)	96 (53.3)
SAE	41 (9.5)	19 (8.3)	64 (10.6)	15 (8.3)
TEAE leading to death	3 (0.7)	1 (0.4)	1 (0.2)	1 (0.6)
TEAE leading to treatment discontinuation	9 (2.1)	7 (3.1)	15 (2.5)	6 (3.3)

Source: ISS appendix Table 1.4.14.1.1
Phase 3: Placebo-controlled (FH I, FH II, COMBO I); Ezetimibe-controlled (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
1. Covers period from first injection post week 12
2. 75 mg (NOT uptitrated)
3. 75/150 mg (uptitrated)

There was not an increase in injection site reactions reported in the group up-titrated to 150 mg Q2W of alirocumab compared to those remaining on 75 mg Q2W. Events reported with an incidence of ≥2% and ≥0.5% larger difference in the group up-titrated to 150 mg Q2W of alirocumab compared to patients not up-titrated are listed in the table below. Conversely, in the placebo-controlled pool TEAEs that occurred in a higher incidence in the 75 mg (not up-titrated group) (≥2 and 0.5% difference) compared to the up-titrated group were influenza (5.1% not uptitrated versus 3.9% uptitrated), nasopharyngitis (6.7% versus 5.7%), upper respiratory infection (4.4% versus 3.1%),

urinary tract infection (3.7% versus 3.1%), bronchitis (3.5% versus 1.8%), dizziness (2.3% versus 1.8%), hypertension (2.5% versus 0.9%), nausea (2.3% versus 0.9%), arthralgia (2.8% versus 1.8%), osteoarthritis (2.3% versus 0.9%).

Table 161. TEAEs ≥2% and ≥0.5% difference in up-titrated group (75/150 mg) versus not up-titrated (75 mg)

	Placebo-controlled pool	
Preferred term	Alirocumab 75 mg N=432	Alirocumab 75/150 mg N=228
Sinusitis	2.8%	3.5%
Gastroenteritis	1.9%	3.1%
Diarrhea	1.2%	3.1%
Abdominal pain	0.5%	3.1%
Back pain	1.9%	3.9%
Muscle spasms	1.6%	2.2%
Peripheral edema	0.7%	2.6%
Influenza-like illness	1.4%	2.2%
Blood creatine phosphokinase increased	0.9%	2.2%
	Ezetimibe-controlled pool	
Preferred term	Alirocumab 75 mg N=606	Alirocumab 75/150 mg N=180
Sinusitis	1.3%	2.2%
Bronchitis	0.8%	2.2%
Headache	1.3%	3.9%
Hypertension	2.0%	5.0%
Myalgia	3.0%	3.9%
Accidental overdose	3.3%	3.9%

Source: ISS appendix Table 1.4.14.1.3
Phase 3: Placebo-controlled (FH I, FH II, COMBO I); Ezetimibe-controlled (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
Covers period from first injection post week 12

Adverse events: 150 mg as starting dose versus dose titration regimen

Of the five Phase 3 placebo-controlled studies, there were 2 studies (LONG TERM and HIGH FH) which initiated treatment at 150 mg Q2W and 3 studies (FH I, FHII, COMBO I) that employed the up-titration dose regimen. In this exploratory analysis, the incidences of TEAEs, SAEs, TEAEs leading to death, and discontinuations due to TEAEs were similar between the alirocumab group and their respective placebo control groups. The HIGH FH study enrolled patients with LDL-C >160 mg/dL and may represent a population with higher risk which may have contributed to the higher incidences of TEAEs observed in the studies with the 150 mg starting dose compared to the studies with the up-titration regimens (Table 162).

Table 162. Adverse events in studies with 150 mg starting dose or up-titration dose regimen (safety population) Phase 3 placebo trials

	Studies with 150 mg starting dose		Studies with up-titration regimen	
	Placebo N=823 n (%)	Alirocumab 150 mg N=1622 n (%)	Placebo N=351 n (%)	Alirocumab 75/150 mg N=696 n (%)
TEAE	660 (80.2)	1262 (77.8)	265 (75.5)	523 (75.1)
SAE	143 (17.4)	263 (16.2)	36 (10.3)	75 (10.8)
TEAE leading to death	8 (1.0)	7 (0.4)	3 (0.9)	6 (0.9)
TEAE leading to treatment discontinuation	44 (5.3)	99 (6.1)	17 (4.8)	28 (4.0)

Source: ISS appendix Table 1.4.14.3.1
150 mg starting dose: LONG TERM, HIGH FH
Up-titration: FH I, FH II, COMBO I

As mentioned previously, injection site reactions were reported with higher incidence in alirocumab-treated versus control patients receiving placebo subcutaneous injections. This imbalance is observed regardless of starting dose. However, it did not appear that patients up-titrated to 150 mg versus those remaining on 75 mg reported a higher incidence of injection site reactions.

7.5.2 Time Dependency for Adverse Events

Prompted by concern that exposure to alirocumab over a longer duration of time would precipitate events that would not be observed in the immediate treatment period, an assessment of risk over time using study-adjusted Kaplan-Meier curves for time to first occurrence of adverse events of special interest and actuarial methods was performed.

The applicant provided an analysis of all TEAEs presented by number (% per patient-month) of patients experiencing an adverse event during the [0> to ≤24 weeks], [24 to ≤52 weeks] and [>52 to ≤78 weeks] treatment periods in the alirocumab and the placebo group. The table below presents adverse events of special interest (defined by SMQ/CMQ) and system organ class.

In general, the number of patients with a new TEAE decreased over time. Looking at the >52 to ≤78 week time period between the placebo and alirocumab treated groups the greatest difference was observed with the AESI of hepatic disorders and diabetes mellitus. There was also a higher rate of patients within the alirocumab-treated group that reported a diabetes mellitus event in the >52 to ≤78 week time period compared to the previous time periods.

Most of the other AESI and SOC showed similar rates of occurrence by treatment period. In some instances where small differences occurred, the number of patients experiencing an event was small and therefore conclusions regarding development of a risk with longer exposure are limited.

Table 163. Number (% per patient-month) of patients experiencing event during treatment period by time to first onset, presented by SMQ or CMQ group or SOC

	Placebo			Alirocumab		
	>0 to ≤24 wks N=1174 n (% per pt-mo)	>24 to ≤52 wks N=1086 n (% per pt-mo)	>52 to ≤78 wks N=1012 n (% per pt-mo)	>0 to ≤24 wks N=2318 n (% per pt-mo)	>24 to ≤52 wks N=2140 n (% per pt-mo)	>52 to ≤78 wks N=2011 n (% per pt-mo)
Adverse events special interest (SMQ or CMQ)						
Local injection site reaction	45 (0.735)	11 (0.170)	4 (0.117)	129 (1.076)	28 (0.223)	6 (0.090)
General allergic reactions	53 (0.868)	34 (0.535)	9 (0.270)	114 (0.948)	60 (0.478)	24 (0.364)
Hepatic disorders	9 (0.145)	11 (0.165)	1 (0.028)	30 (0.245)	14 (0.106)	13 (0.184)
Neurologic disorders	20 (0.323)	15 (0.227)	8 (0.229)	47 (0.386)	28 (0.215)	8 (0.115)
Neurocognitive	7 (0.113)	2 (0.030)	0	8 (0.065)	7 (0.053)	2 (0.028)
Diabetes mellitus	15 (0.242)	18 (0.272)	3 (0.085)	25 (0.204)	28 (0.213)	27 (0.384)
Ophthalmologic disorders	11 (0.177)	4 (0.060)	2 (0.056)	22 (0.180)	13 (0.098)	7 (0.099)
SOC						
Infections and infestations	325 (6.024)	128 (2.881)	41 (1.982)	630 (5.914)	290 (3.320)	80 (1.991)
Neoplasms	16 (0.258)	14 (0.210)	4 (0.112)	20 (0.163)	21 (0.159)	11 (0.155)
Blood and lymphatic system	10 (0.161)	17 (0.256)	3 (0.085)	22 (0.180)	14 (0.106)	13 (0.183)
Immune system disorders	6 (0.096)	3 (0.045)	2 (0.055)	20 (0.163)	11 (0.083)	6 (0.084)
Endocrine disorders	3 (0.048)	3 (0.045)	2 (0.055)	6 (0.049)	6 (0.045)	8 (0.112)
Metabolism and nutrition	32 (0.520)	35 (0.541)	10 (0.294)	92 (0.762)	58 (0.457)	33 (0.489)
Psychiatric disorders	42 (0.684)	28 (0.434)	7 (0.205)	72 (0.594)	36 (0.280)	15 (0.219)
Nervous system disorders	120 (2.021)	55 (0.930)	22 (0.724)	283 (2.033)	92 (0.781)	28 (0.456)
Eye disorders	34 (0.552)	15 (0.230)	7 (0.202)	67 (0.552)	35 (0.271)	20 (0.291)
Ear and labyrinth disorders	26 (0.422)	8 (0.122)	2 (0.057)	17 (0.139)	14 (0.106)	9 (0.127)
Cardiac disorders	41 (0.668)	42 (0.655)	22 (0.657)	77 (0.636)	78 (0.613)	37 (0.552)
Vascular disorders	48 (0.785)	34 (0.533)	8 (0.239)	80 (0.661)	48 (0.375)	23 (0.338)
Respiratory, thoracic, and mediastinal disorders	63 (1.036)	41 (0.653)	13 (0.395)	136 (1.139)	59 (0.476)	38 (0.584)
Gastrointestinal disorders	135 (2.289)	57 (0.979)	19 (0.626)	270 (2.323)	102 (0.884)	38 (0.639)
Hepatobiliary disorders	9 (0.145)	5 (0.075)	2 (0.056)	13 (0.106)	12 (0.090)	3 (0.042)
Skin and subcutaneous disorders	51 (0.835)	32 (0.502)	8 (0.239)	121 (1.008)	54 (0.430)	20 (0.302)
Musculoskeletal and connective tissue disorders	201 (3.502)	83 (1.538)	32 (1.183)	377 (3.329)	155 (1.451)	58 (1.083)
Renal and urinary disorders	22 (0.356)	23 (0.350)	12 (0.345)	43 (0.353)	28 (0.215)	21 (0.302)
Reproductive system/breast disorders	12 (0.193)	9 (0.135)	10 (0.282)	30 (0.245)	17 (0.129)	9 (0.128)
Congential, familial, genetic disorders	2 (0.032)	1 (0.015)	0	0	2 (0.015)	3 (0.042)
General disorders and administration site conditions	134 (2.264)	42 (0.709)	19 (0.615)	269 (2.311)	85 (0.733)	23 (0.382)
Investigations	40 (0.651)	24 (0.370)	10 (0.288)	70 (0.576)	61 (0.475)	30 (0.440)
Injury, poisoning, and procedural complications	87 (1.445)	55 (0.901)	23 (0.733)	174 (1.470)	102 (0.851)	32 (0.513)
Social circumstances	0	0	0	2 (0.016)	3 (0.022)	0

Source: ISS appendix 1.4.7.7
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I)
N = Number of patients who entered the time interval. n = number of patients with first onset of AE in the time interval. % per patient-month = hazard rate over 1 month estimated using a time-to-event method with life table (actuarial) estimates. Patients are censored at the end of the treatment period (last injection of study treatment + 21 days)

7.5.3 Drug-Demographic Interactions

The following factors were evaluated for adverse events of special interest: gender, age in years (<65, ≥65 to <75, and ≥75 years), race, ethnicity, baseline BMI category (<25,

25 to <30, ≥30, baseline eGFR categories, and region (North America, Western Europe, Eastern Europe, Rest of World). An interaction was considered significant at a 10% level. However, any observed interaction should be interpreted cautiously as these analyses were not corrected for multiple comparisons and were not adequately powered to detect a significant treatment difference.

Age: Significant ($p<0.10$) interactions were observed between the treatment groups and Age for General allergic events and local allergic reactions at the injection site in the placebo-controlled and ezetimibe-controlled pools. The trend suggests patients less than 65 years of age taking alirocumab have a higher incidence of these reactions compared to control and patients ≥75 years of age would have a lower incidence compared to control. It is unlikely that this interaction is of clinical relevance.

In the placebo-controlled pool, an interaction ($p=0.0907$) was observed between treatment groups and Age for Neurologic events. Patients less than 65 years old in the alirocumab-treatment group had a higher incidence of neurologic events compared to their similarly aged counterparts in the control group. This interaction was not observed in the ezetimibe-controlled pool.

eGFR: An interaction was observed between the treatment groups and baseline eGFR for local injection site reactions in the global pool which combined the placebo and ezetimbe pools (interaction $p=0.0454$). When separated by either placebo or ezetimibe pool, no interaction was observed. An interaction was observed for neurologic events in the placebo-controlled pool but not in the ezetimibe controlled pool. These findings are not considered clinically meaningful.

Region: A treatment interaction was noted for General allergic reactions by region. Patients treated with alirocumab in North America tended to have a higher incidence of these reactions compared to placebo-treated patients in North America and alirocumab-treated patients in other regions of the world.

Gender, Race, Ethnicity, BMI: No significant interaction was reported for these factors.

Table 164. Hazard ratio versus control by demographics and baseline characteristics with treatment interactions at p=0.10 (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

		Placebo-controlled pool				Ezetimibe-controlled pool			
Adverse event	Factor	Placebo n/N (%)	Alirocumab n/N (%)	HR versus control[1] (95% CI) 1	Interaction p-value[2]	Ezetimibe n/N (%)	Alirocumab n/N (%)	HR versus control[1] (95% CI)	Interaction p-value[2]
General allergic reactions and local allergic reactions	**Age (y)**								
	<65	63/878 (7.2)	188/1671 (11.3)	1.57 (1.18 to 2.09)	**0.0149**	17/375 (4.5)	47/511 (9.2)	2.22 (1.27 to 3.89)	**0.0322**
	≥65 to <75	38/322 (11.8)	71/642 (11.1)	0.95 (0.64 to 1.40)		14/185 (7.6)	15/275 (5.5)	0.64 (0.31 to 1.35)	
	≥75	10/76 (13.2)	11/163 (6.7)	0.55 (0.23 to 1.29)		5/58 (8.6)	5/78 (6.4)	0.72 (0.20 to 2.55)	
Neurologic events	<65	20/878 (2.3)	54/1671 (3.2)	1.43 (0.86 to 2.40)	**0.0907**	10/375 (2.7)	14/511 (2.7)	1.02 (0.45 to 2.33)	0.5870
	≥65 to <75	18/322 (5.6)	22/642 (3.4)	0.61 (0.33 to 1.13)		3/185 (1.6)	9/275 (3.3)	1.73 (0.47 to 6.43)	
	≥75	7/76 (9.2)	10/163 (6.1)	0.73 (0.28 to 1.91		2/58 (3.4)	6/78 (7.7)	2.38 (0.46 to 12.26)	
General allergic events	**Allergic hx**								
	Yes	51/544 (9.4)	117/12.8)	1.39 (1.00 to 1.93)	**0.0211**	22/294 (7.5)	38/396 (9.6)	1.28 (0.75 to 2.17)	0.9492
	No	48/630 (7.6)	85/1404 (6.1)	0.79 (0.55 to 1.12)		11/324 (3.4)	21/468 (4.5)	1.31 (0.62 to 2.75)	
Neurologic events	**eGFR (mL/min/1.73m2)**								
	<60	7/189 (3.7)	19/405 (4.7)	1.27 (0.53 to 3.01)	**0.0105**	3/104 (2.9)	8/152 (5.3)	2.20 (0.56 to 8.73)	0.7495
	≥60 to <90	36/794 (4.5)	46/1557 (3.0)	0.66 (0.42 to 1.01)		11/413 (2.7)	20/570 (3.5)	1.32 (0.63 to 2.78)	
	≥90	2/293 (0.7)	21/512 (4.1)	5.47 (1.28		1/101 (1.0)	1/142 (0.7)	0.43 (0.03	

		Placebo-controlled pool				Ezetimibe-controlled pool			
Adverse event	Factor	Placebo n/N (%)	Alirocumab n/N (%)	HR versus control[1] (95% CI) 1	Interaction p-value[2]	Ezetimibe n/N (%)	Alirocumab n/N (%)	HR versus control[1] (95% CI)	Interaction p-value[2]
				to 23.39)				to 6.88)	
General allergic events	**Region**								
	North America	21/426 (4.9)	81/795 (10.2)	1.99 (1.23 to 3.23)	**0.0134**	21/331 (6.3)	35/419 (8.4)	1.24 (0.72 to 2.14)	0.4894
	Western Europe	51/467 (10.9)	86/929 (9.3)	0.86 (0.61 to 1.22)		7/131 (5.3)	13/156 (8.3)	1.51 (0.59 to 3.86)	
	Eastern Europe	13/200 (6.5)	15/403 (3.7)	0.59 (0.28 to 1.25)		2/73 (2.7)	1/147 (0.7)	0.25 (0.02 to 2.76)	
	Rest of World	14/183 (7.7)	31/349 (8.9)	1.14 (0.61 to 2.15)		3/83 (3.6)	10/142 (7.0)	2.28 (0.61 to 8.46)	
	Type of hypercholesterolemia								
	HeFH	5/418 (1.2)	3/837 (0.4)	0.30 (0.07 to 1.25)	**0.0308**	0	2/40 (5.0)	NA	0.9899
	Non-FH	4/756 (0.5)	17/1481 (1.1)	2.17 (0.73 to 6.44)		6/575 (1.0)	6/824 (0.7)	0.64 (0.20 to 2.01)	

Source: ISS appendix
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
n(%) = number and percentage of patients with at least one Local injection site reaction TEAE

1. Hazard ratio calculated using a Cox model stratified on the study in each subgroup.
2. The interaction is tested in a separate Cox model including the study, the subgroup factor term, the treatment and the treatment-by-subgroup interaction

Table 165. Hazard ratio versus control by demographics and baseline characteristics with treatment interactions at p=0.10 (safety population) – global pool

Adverse event	Factor	Control n/N (%)	Alirocumab n/N (%)	HR versus control (95% CI)[1]	Interaction p-value[2]
	eGFR (ml/min/1.73m2)				
Local injection site reactions	<60	5/293 (1.7)	27/557 (4.8)	2.83 (1.07 to 7.46)	**0.0454**
	≥60 to <90	61/1207 (5.1)	132/2127 (6.2)	1.19 (0.87 to 1.61)	
	≥90	12/394 (3.0)	45/654 (6.9)	2.68 (1.36 to 5.25)	

Source: ISS appendix 1.4.1.1.37
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)

Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
n(%) = number and percentage of patients with at least one Local injection site reaction TEAE

3. Hazard ratio calculated using a Cox model stratified on the study in each subgroup.
4. The interaction is tested in a separate Cox model including the study, the subgroup factor term, the treatment and the treatment-by-subgroup interaction

7.5.4 Drug-Disease Interactions

The following factors were evaluated for adverse events of special interest: type of hypercholesterolemia (heFH, non-FH) and diabetes at baseline (per medical history). For the analysis of general allergic reaction events, the medical history of allergy was considered.

Type of hypercholesterolemia: An interaction was measured between the treatment groups and the type of hypercholesterolemia in the global pool for 'MACE events, CHF hospitalization and revascularization 'endpoints.

An interaction was observed between treatment groups and the type of hypercholesterolemia in the placebo pool for neurologic events (p=0.0308), with a higher incidence of these events in the non-FH alirocumab-treated group compared to control.

Medical history of allergy: An interaction was measured between the treatment groups and the medical history of allergy for General allergic events in the placebo-controlled pool with a higher HR of the comparison of alirocumab over placebo in patients with a medical history of allergy. This interaction was not observed in the ezetimibe-controlled pool.

Diabetes at baseline per medical history: There were no significant interactions reported.

7.5.5 Drug-Drug Interactions

Please see the clinical pharmacology team's review for further details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

In the placebo-controlled safety pool, 57 (2.3%) patients in the alirocumab group and 35 (2.7%) patients in the placebo group reported a TEAE in the neoplasm SOC. Basal cell carcinoma was the TEAE most commonly reported in both treatment groups (0.5% placebo; 0.4% alirocumab). The most frequent neoplasms by high level term in both treatment groups were skin neoplasms malignant and unspecified (excluding

melanoma) reported in 15 (0.6%) patients in the alirocumab group and6 (0.5%) in the placebo group, and prostatic neoplasms malignant reported in 5 (0.2%) patients in the alirocumab group and 4 (0.3%) in the placebo group.

In the ezetimibe-controlled safety pool, 28 (3.2%) of patients in the alirocumab group and 13 (2.1%) in the ezetimibe group reported a TEAE in the neoplasm SOC. Seborrheic keratosis was the most commonly reported preferred term in alirocumab-treated patients (0 ezetimbe; 0.7% alirocumab).

The following table lists the neoplastic preferred terms that occurred in at least 2 or more patients per treatment group.

Table 166. Number (%) of patients with TEAE in Neoplasm SOC (safety population) – pool of placebo-controlled studies and pool of ezetimibe-controlled studies

SOC Preferred term	Placebo-controlled		Ezetimibe-controlled	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Ezetimibe N=618 n (%)	Alirocumab N=864 n (%)
Neoplasm SOC	**35 (2.7)**	**57 (2.3)**	**13 (2.1)**	**28 (3.2)**
Basal cell carcinoma	6 (0.5)	11 (0.4)	1 (0.2)	3 (0.3)
Colon adenoma	1 (<0.1)	3 (0.1)	2 (0.3)	1 (0.1)
Prostate cancer	3 (0.2)	3 (0.1)	0	3 (0.3)
Squamous cell carcinoma of skin	0	3 (0.1)	0	2 (0.2)
Breast cancer	1 (<0.1)	2 (<0.1)	0	0
Lipoma	4 (0.3)	2 (<0.1)	1 (0.2)	1 (0.1)
Seborrheic keratosis	3 (0.2)	2 (<0.1)	0	6 (0.7)
Squamous cell carcinoma	1 (<0.1)	2 (<0.1)	0	1 (0.1)
Thyroid neoplasm	1 (<0.1)	2 (<0.1)	0	1 (0.1)
Benign neoplasm of thyroid gland	2 (0.2)	1 (<0.1)	0	0
Malignant melanoma	1 (<0.1)	0	0	2 (0.2)

Source: ISS appendix 1.4.9.7
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported in patients treated with alirocumab group during the TEAE time period.

There were 2 spontaneous abortions reported in 1 patient during the post-treatment period on Days 541 and 647. A 30-year-old female with HeFH, who discontinued treatment due to poor compliance and planned pregnancy, reported approximately 10 months after the last administration of alirocumab a spontaneous miscarriage at approximately 7 weeks. Two months later a second pregnancy was diagnosed followed

by a spontaneous abortion a month later. The patient's obstetric history included an abortion in 2004, live birth in 2008, and miscarriage in 2013 and 2014.
Four pregnancies of a partner of an alirocumab-treated patient have been reported; one had a normal delivery, one a spontaneous abortion, and no information was provided for the remaining 2 pregnancies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdoses with study drug were defined as a shorter interval than 7 calendar days between 2 injections. Overall, 39 (1.2%) patients treated with alirocumab and 25 patients (1.3%) treated with the placebo injection reported an overdose. All cases were asymptomatic and no patients discontinued treatment due to this event.

Table 167. Number (%) of patients with overdose with IMP injections (safety population) – Pool of placebo-controlled studies and pool of ezetimibe-controlled studies

	Placebo-controlled pool		Ezetimibe-controlled pool	
	Placebo N=1276 n (%)	Alirocumab N=2476 n (%)	Placebo N=618 n (%)	Alirocumab N=864 n (%)
Any overdose with IMP	15 (1.2)	27 (1.1)	10 (1.6)	12 (1.4)
Accidental overdose	15 (1.2)	26 (1.1)	10 (1.6)	12 (1.4)
Intentional overdose	0	1 (<0.1)	0	0

Source: ISS Table 36
Placebo-controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361)
Ezetim be-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE)
MedDRA 17.0 . The selection of PTs is based on the HLT 'Overdose' and the tick box 'Overdose with IMP/IMP auto-injectors' in the AE complementary e-CRF form

7.7 Additional Submissions / Safety Issues

The four month safety update was reviewed. Events of interest noted in the four month safety update were highlighted in the respective sections of this document.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

Medical and scientific literature is referenced throughout the document.

9.2 Labeling Recommendations

A complete labeling review was conducted separately. Major recommendations included:

- Modifying the indication: *PRALUENT is 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*
- Relying on the placebo-controlled pool for the discussion of adverse reactions
- Including all TEAEs in alirocumab-treated patients ≥ 2% and greater than placebo in the table of adverse reactions
- Including in the Adverse Reactions section additional descriptions of local injection site reactions, allergic reactions, neurocognitive reactions, and liver-related AEs and liver enzyme abnormalities
- Describing potential loss-of-efficacy with neutralizing antibodies in the Immunogenicity section
- Updating the Pregnancy and Lactation section as per PLLR
- Streamlining information included in the Mechanism-of-Action and Pharmacodynamics sections
- In the Clinical Studies section:
    - Including only the description and results of five phase 3 placebo-controlled trials
    - Limiting efficacy results to LDL-C, apo B, non-HDL-C, and total cholesterol
    - Presenting efficacy results using the pattern mixture model to more appropriately account for missing data

9.3 Advisory Committee Meeting

The Endocrinologic and Metabolic Drugs Advisory Committee convened on 9 June 2015 to discuss this application. Questions to the committee, discussion, and voting results as captured in the summary minutes are below (when published, can be found at 60):

60 http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolic

1. Discuss the safety of alirocumab as observed in the clinical development program, and in your discussion comment on the following:

   a. Discuss your interpretation of the safety data with respect to any adverse effects related to diabetes, liver-related safety, muscle, neurological/neurocognitive events, hypersensitivity, immunogenicity, as well as any other concerns you may identify.

      Committee Discussion: *The committee agreed that there are no alarming safety signals from the data of the alirocumab clinical development program at this time. However, the committee emphasized that the current safety data are limited and that adverse events related to diabetes, liver-related safety, neurological/neurocognitive events, and fat soluble vitamin (A, D, E, and K) deficiencies may take a longer time to develop in patients and might not have been detected during the relatively short (6 to 18 months) study durations. The committee agreed that the potential for new or more clearly defined adverse events could not be ruled out given that alirocumab would be used by a larger number of patients over a longer period of time if approved.*

   b. Discuss the adequacy of the current clinical database to characterize the safety of alirocumab. Consider the extent of drug exposure (i.e., number of patients and duration of exposure), the strengths/limitations of the study designs themselves, and the generalizability of the trial populations to the target population(s), if approved.

      Committee Discussion: *The committee agreed that the current clinical database is inadequate to characterize the safety of alirocumab for the intended (broad) patient population. The committee stated that alirocumab may have unanticipated side effects that might only become evident with more patient experience and longer-term studies. The committee emphasized the importance of the applicant's on-going cardiovascular outcomes trials to characterize the drug's safety profile and to further inform alirocumab's benefit/risk assessment. The committee also stated that many patient groups, including minorities and patients unable to take statins, were underrepresented and the effect of alirocumab on patients in certain circumstances (pregnancy, hospitalization in ICU) were unknown and that more data on the use of this alirocumab in these groups are necessary to better determine its safety in the broader population.*

   c. Discuss your level of concern regarding the safety of achieving very low levels of

LDL-C induced by alirocumab.

Committee Discussion: *The committee acknowledged that there is little evidence to suggest that very low levels of LDL-C levels are harmful. However, the committee had varying degrees of concern with regards to achieving long-term low levels of LDL-C induced by alirocumab. Some members listed potential unanticipated effects on fat-soluble vitamin (A, D, E, and K) levels and neurocognitive/neurological events. A concern was raised that there is potential for physicians to respond to low levels of LDL-C by lowering or discontinuing of statins, which have more safety data and demonstrated cardiovascular benefit. The committee stated that the FDA and applicant should consider providing guidance in the labeling to avoid this type of situation if alirocumab is approved.*

2. **DISCUSSION**: The goal of LDL-C-lowering therapy is to reduce the risk of cardiovascular (CV) disease. Historically, a change in LDL-C has been considered sufficient to establish the effectiveness of a lipid-altering drug intended for use to reduce cardiovascular risk, without any regulatory requirement to demonstrate evidence for benefit in a CV outcomes trial, provided the reduction is sufficiently robust and the product (or its class) does not have safety issues that raise concern that risk exceeds benefit.

   Discuss whether alirocumab-induced LDL-C lowering is sufficient to substitute for demonstrating its effect on clinical outcomes (i.e., to substitute for investigation in a CV outcomes trial) in one or more populations (e.g., different degrees of CV risk, familial vs. non-familial etiologies of hyperlipidemia, use with or without concomitant statins, etc.).

   Committee Discussion: *In general, the committee expressed uncertainty regarding whether changes in LDL-C are sufficient to substitute for an effect on clinical outcomes, especially given that alirocumab is a new class of drug. Many agreed, however, that alirocumab-induced LDL-C lowering may be sufficient to substitute for demonstrating its effect on clinical outcomes in specific patient populations, such as familial hypercholesterolemia. There was concern, however, about extending this to patients unable to tolerate statins, mixed dyslipidemia, or diabetic dyslipidemia. Some members of the committee added that LDL-C lowering may be an endpoint in itself, rather than a surrogate, for patients with familial hypercholesterolemia. Some cited the mechanism of action of PCSK9 inhibitors and the Mendelian randomization studies that support a cardioprotective effect of PCSK9 loss-of-function as reasons to support LDL-C reduction as evidence of clinical benefit, especially for those with familial hypercholesterolemia. One member of the committee stated that regulatory standards with regards to LDL-C as a surrogate endpoint need to be re-evaluated.*

3. **VOTE**: Has the applicant sufficiently established that the LDL-C-lowering benefit of alirocumab exceeds its risks to support approval in one or more patient populations?

We remind you that under the current regulatory pathway, it would not be required to successfully demonstrate an effect of alirocumab on CV outcomes after an approval based on changes in LDL-C.

Vote Results: YES = 13 NO = 3 ABSTAIN = 0

a. If yes, please explain your rationale and describe the patient population(s) for whom you believe that the benefit/risk is favorable.

Committee Discussion: *The majority of the committee (13 members) voted that the applicant sufficiently established that the LDL-C lowering benefit of alirocumab exceeds its risk to support approval for at least one patient population. Members who voted "yes" varied with respect to the specific patient populations for which the drug should be indicated with the exception of unanimous support for heterozygous familial hypercholesterolemia (HeFH). Some, but not all, believed that benefit/risk would also be favorable for patients at high cardiovascular risk whose LDL-C is not adequately controlled with maximally tolerated (or high-dose) statin, or in the setting of secondary prevention with insufficient response to maximally tolerated statin. These members agreed that this drug should not be approved for the general population, including patients with mixed dyslipidemia, until cardiovascular outcomes trials have demonstrated a benefit.*

b. If no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit/risk to support approval.

Committee Discussion: *Three members of the committee did not agree that the applicant sufficiently established that the LDL-C lowering benefit of alirocumab exceeds its risk to support approval for any patient population. These members stated that this drug should not be approved until a cardiovascular outcomes trials (CVOTs) establishes benefit. One of these members added that approval of alirocumab prior to the completion of the on-going CVOT could lead to patients prematurely discontinuing study medication in the trial..*

9.4 Neutralizing Antibodies

The first patient discussed below appeared to have loss of efficacy with worsening of LDL-C coincident with NAbs; however, upon review of the case, the increase in LDL-C was due to interruption of alirocumab, statin, and ezetimibe therapy.

- Patient 01112-528-202-003: This is a patient with HeFH, with a baseline LDL-C of 149 mg/dL. As seen in Table 168 below, it was noted that LDL-C increased to over twice baseline coincident with NAbs, and then decreased coincident with loss of

neutralizing activity while the patient was still off of drug. However, the patient had an adverse event of hepatitis A early in the trial associated with increases in ALT, and alirocumab as well as background atorvastatin and ezetimibe were discontinued prior to the assessment that revealed the increase in LDL-C. At the time of detecting positive ADA with 960 titer and positive neutralizing ADA, the patient had not received alirocumab (or atorvastatin + ezetimibe) for about 8 weeks.

Table 168. ADA and LDL-C, Patient 01112-528-202-003

Study Week	ALT (IU/L)	Alirocumab	Atorvastatin+Ezetimibe	ADA titer (titer/negative Neutralizing ADA)	LDL-C (mg/dL)
Baseline	37		X	Negative	149
Week 1	125	X	X	Negative	148
Week 4	1141	X	X	No Sample	94
Weeks 5-11	Ranged between 1052-2094	Off drug	Off drug	No Sample	Not tested
Week 12	966	Off drug	Off drug	960 (positive)	316
Week 16	543	Off drug	Off drug	No Sample	296
Week 17	79	Off drug	X	No Sample	Not tested
Week 24	70	Off drug	X	120 (negative)	156
Week 36	18	X	X	No Sample	135
Week 52	22	X	X	Negative	44

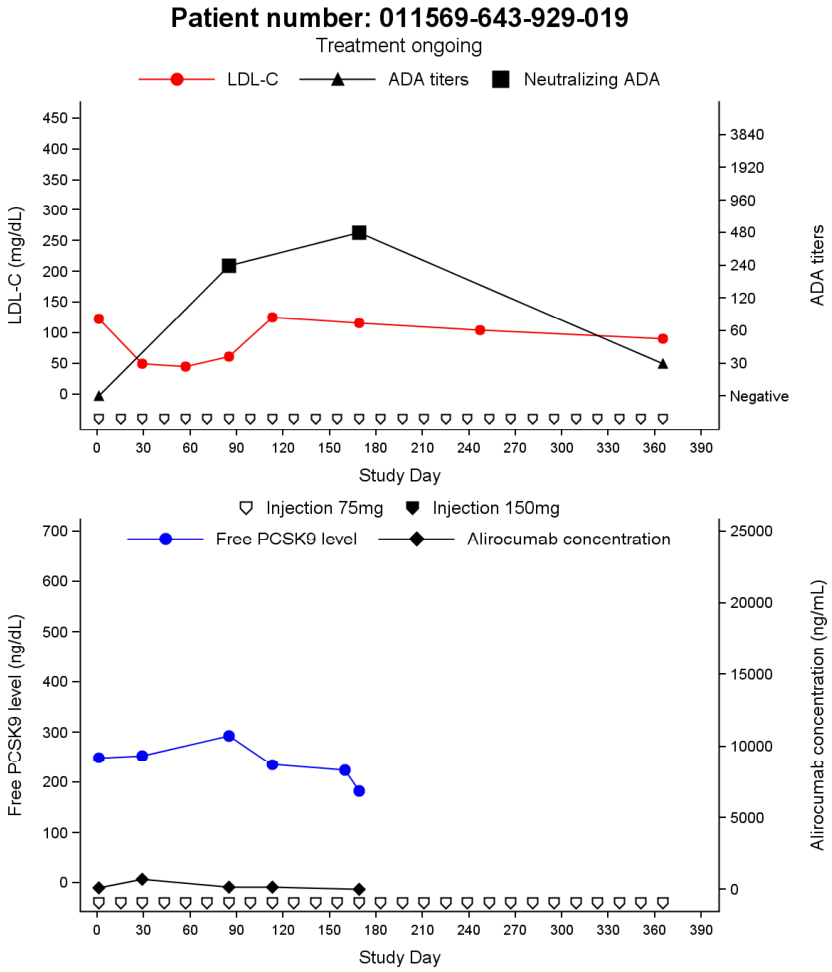
Source: Response to Agency Request Item no. 5 dated 10 Mar 2015, Table 6

In nine patients (Pattern 1), high titer (> 240) ADA or NAbs appeared to correlate with loss of efficacy.

Pattern 1

- Patient 011569-643-929-019: This patient appears to have experienced loss of efficacy coincident with the development of NAbs (titer 240 then 480); LDL-C returned to baseline. ADA had returned to low titers by the end of the trial; however, LDL-C never returned to its lowest value. Alirocumab concentrations were low throughout.

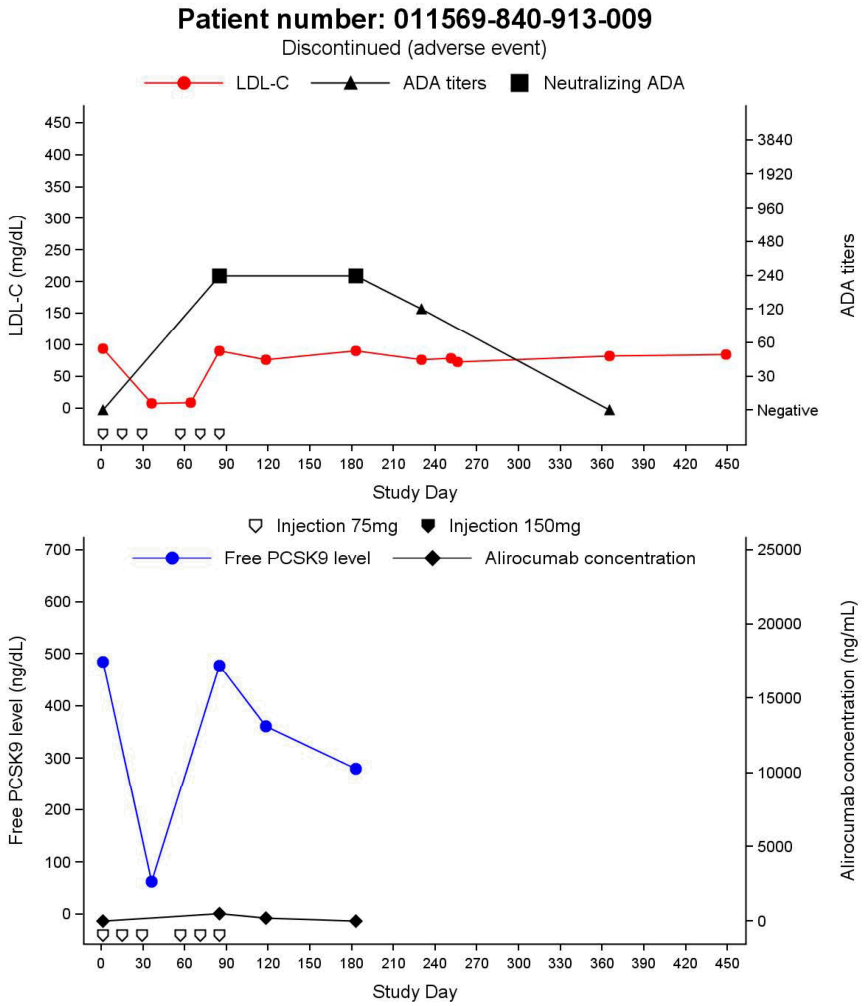
Figure 43. Time Course of ADA, LDL-C, PK, and PD, Patient 011569-643-929-019



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 3

- Patient 011569-840-913-009: This patient appeared to experience loss of efficacy coincident with NAbs (as well as an abrupt increase in free PCSK9); however, the patient stopped treatment due to an adverse event shortly thereafter, which makes the long-term impact of the NAbs unknown.

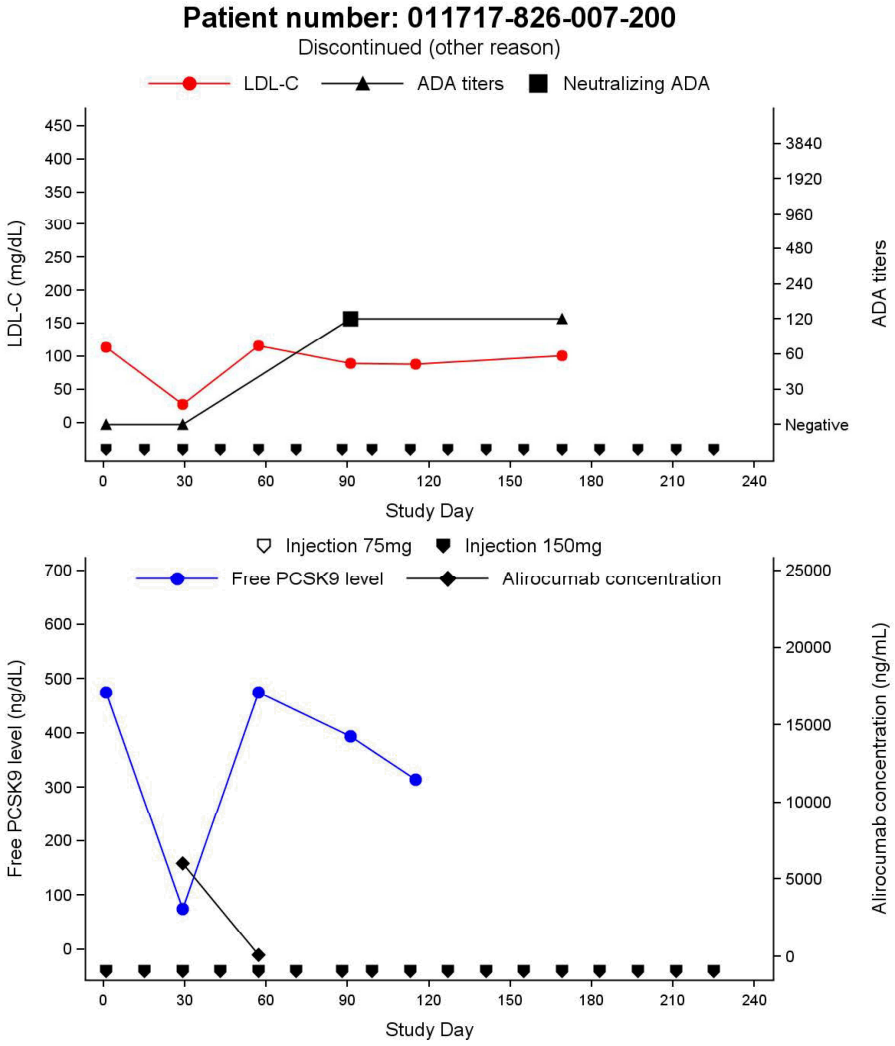
Figure 44. Time Course of ADA, LDL-C, PK, and PD, Patient 011569-840-913-009



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 4

- Patient 011717-826-007-200: This patient experienced loss of efficacy, an increase in free PCSK9, and a decrease in alirocumab concentrations coincident with development of NAbs.

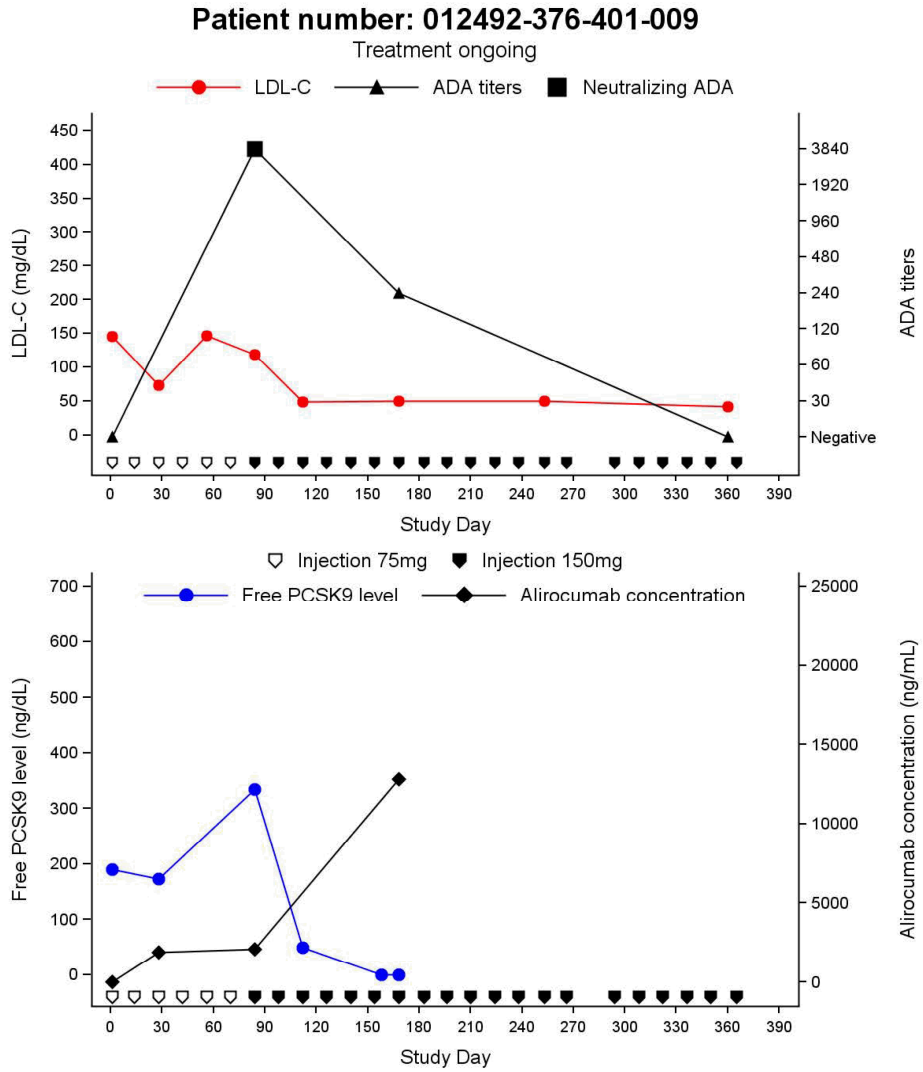
Figure 45. Time Course of LDL-C, ADA, PK, and PD, Patient 11717-826-007-200



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 7

- Patient 012492-376-401-009: In this case, high titer NAbs were observed coincident with lack of efficacy, but they were transient, with a reduction in titer to negative over time. Increasing the alirocumab dose appeared to improve efficacy along with decreasing free PCSK9 and increasing alirocumab concentrations.

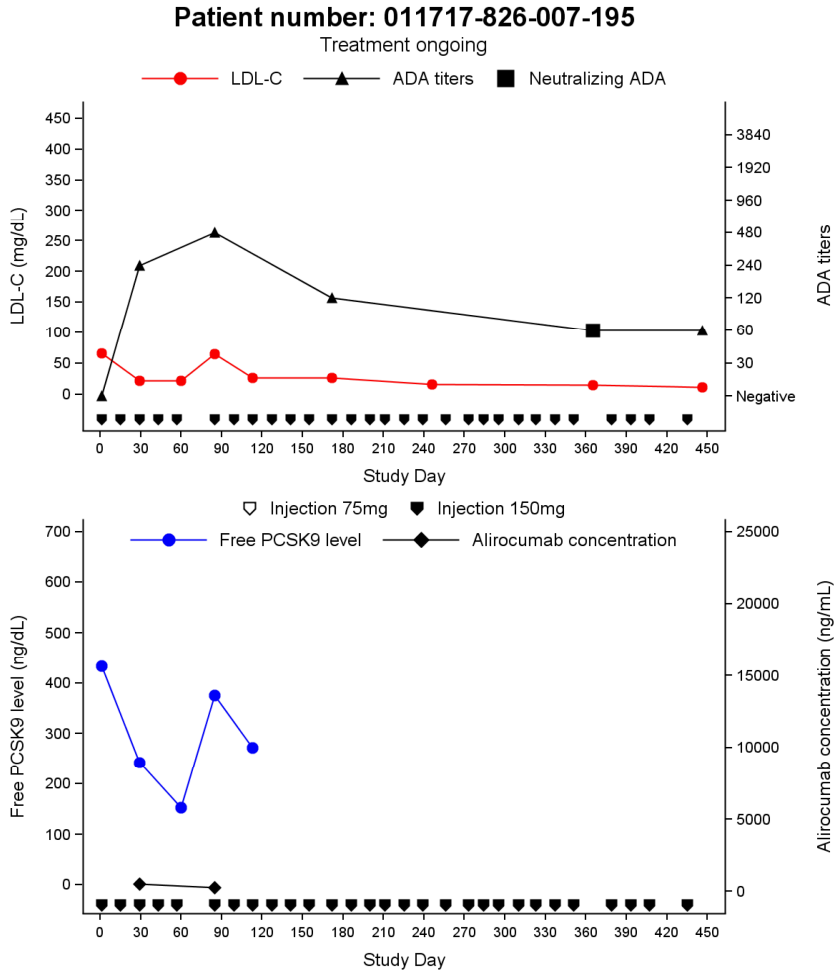
Figure 46. Time Course of ADA, LDL-C, PK, and PD, Patient 012492-376-401-009



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 8

- Patient 011717-826-007-195: A brief period of loss of efficacy and an increase in free PCSK9 were associated with a transient ADA titer of 480. Despite ADA titers of 120 and development of NAbs later in the trial, LDL-C decreased while the patient remained in the trial.

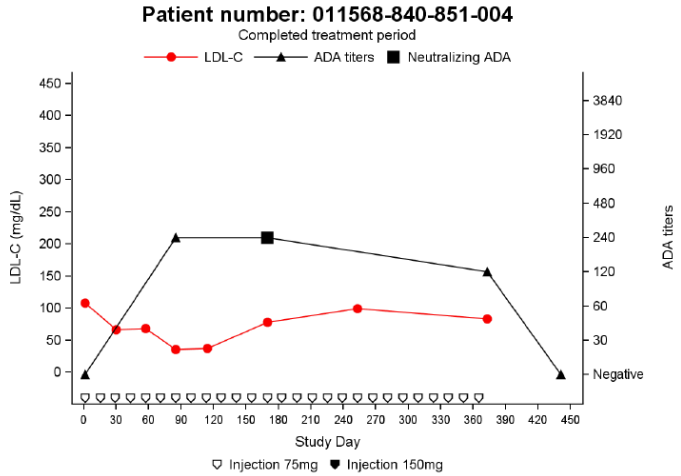
Figure 47. Time Course of ADA, LDL-C, PK, and PD, Patient 011717-826-007-195



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 15

- Patient 011568-840-004: This patient experienced loss of efficacy coincident with the development of NAbs (titer 240). PK and PD were not reported.

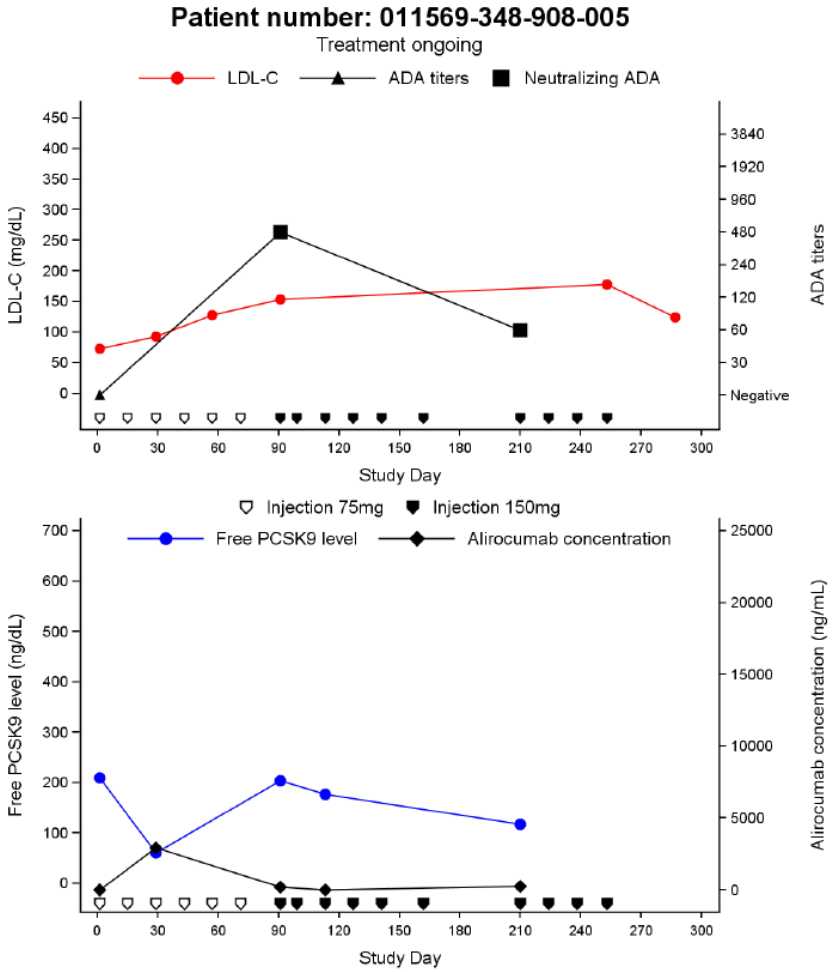
Figure 48. Time Course of ADA and LDL-C, Patient 011568-840-851-004



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 73

- Patient 011659-348-908-005: This was a 63-year-old white male on atorvastatin 80 mg with an LDL-C of 73 mg/dL at baseline. The patient had no history of down titration of any statin dose or change to a different statin due to tolerability issue, and there was no report of change in statin dose during the trial. An increase of LDL-C was noted throughout the trial. The patient had a negative ADA status at study entry. On Day 91, the patient's ADA status was found to be positive (neutralizing), and ADA concentration was 480. The ADA concentration decreased to 60 on Day 210 (still neutralizing). No further ADA tests have been reported. The patient did not report any adverse events during the trial.

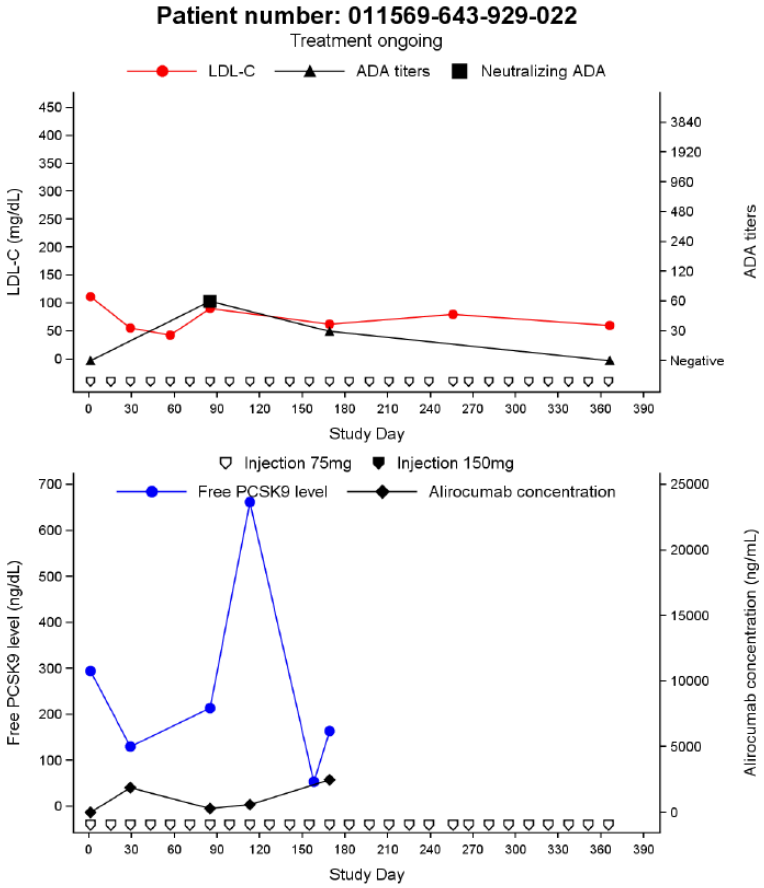
Figure 49. Time Course of ADA, LDL-C, PK, and PD Patient 011569-348-908-005



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 89

- Patient 0115643-929-022: This patient experienced loss of efficacy coincident with the development of NAbs. A large spike in free PCSK9 was noted shortly thereafter.

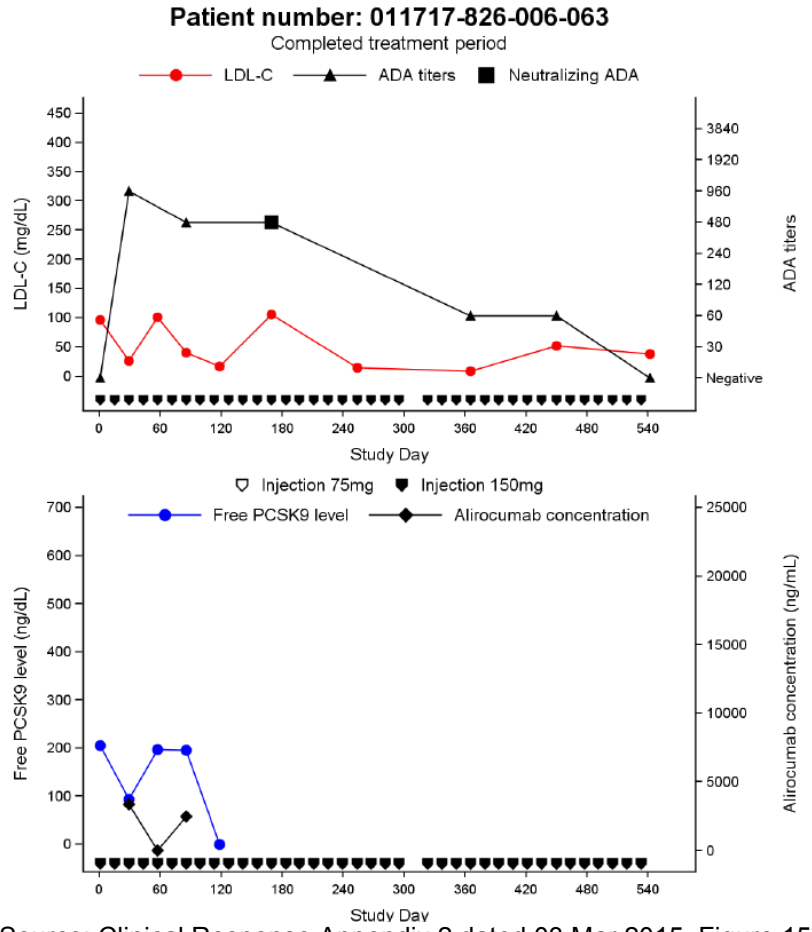
Figure 50. Time Course of ADA, LDL-C, PK, and PD, Patient 011569-643-929-022



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 94

- Patient 011717-826-063: This patient's LDL-C concentrations fluctuated in the setting of high titer and/or neutralizing antibodies. PK and PD cncentrations fluctuated as well, but the data were very limited.

Figure 51. Time Course of ADA, LDL-C, PK, and PD, Patient 011717-826-006-063



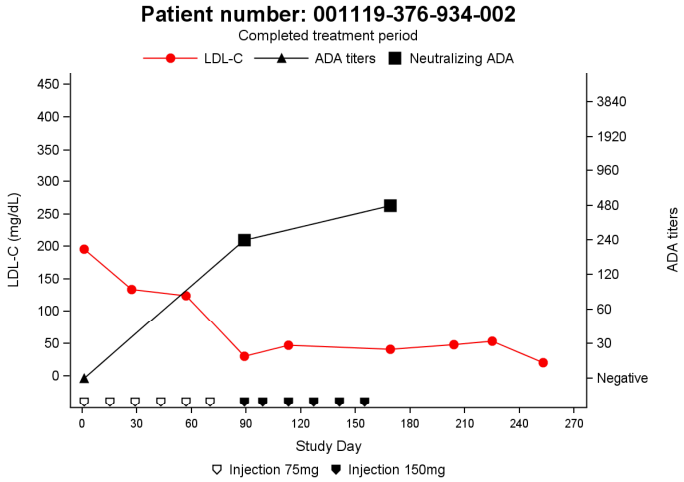
Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 157

Two patients were observed to develop ADA that might have enhanced the efficacy of alirocumab (which could occur if the NAb prolongs PK and PD).

Pattern 2

- Patient 001119-376-934-002: This patient (from the ALTERNATIVE trial, therefore not on concomitant statin) had persistently low LDL-C out to day ~250 in the setting of NAbs, despite discontinuing alirocumab at day 160. ADA data are not available past day 180, nor are PK/PD analyses available.

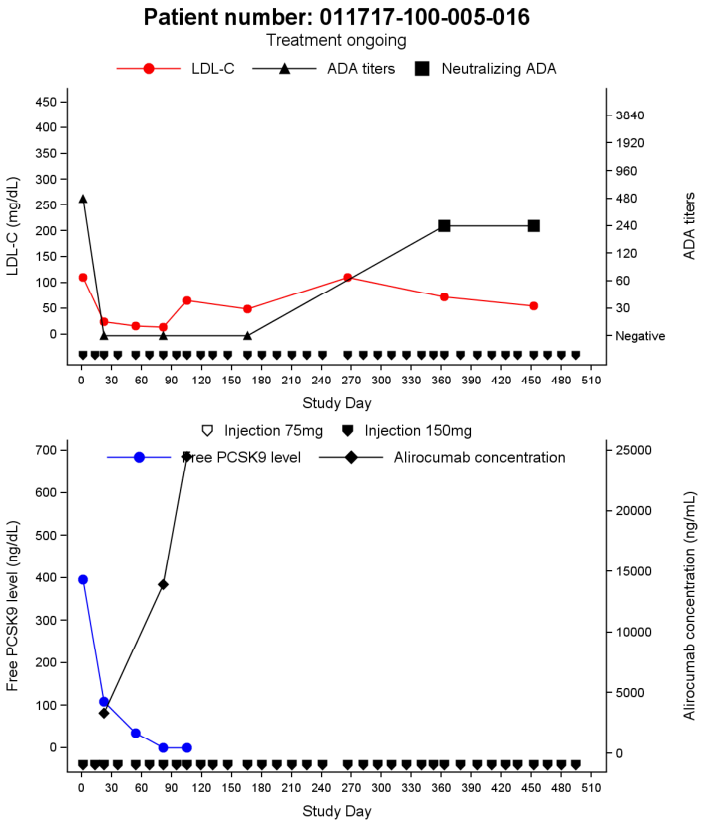
Figure 52. Time Course of ADA and LDL-C, Patient 01119-376-934-002



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 11

- Patient 011717-100-005-016: After an initial reduction in LDL-C during the first 12 weeks, this patient had a subsequent increase in LDL-C over time in association with negative or unmeasured ADA. However, on ~day 360, NAbs were identified and were associated with a reduction in LDL-C.

Figure 53. Time Course of ADA, LDL-C, PK, and PD, Patient 011717-100-005-016



Source: Clinical Response Appendix 2 dated 03 Mar 2015, Figure 12

9.5 Cardiovascular Endpoint Definitions

Death:
All deaths will be categorized as Cardiovascular, non-Cardiovascular or Undetermined based on the definitions below. In addition, all deaths will also be categorized as Coronary Heart Disease Death and further subtyped based on the specific Cardiovascular and non-Cardiovascular categories defined below.

Cardiovascular Death:
Cardiovascular Death is defined as death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV proceducres, death due to CV hemorrhage, and death due to other cardiovascular causes. Coronary Heart Disease (CHD) Death is defined as the subset of Cardiovascular deaths for which there is a clear relationship to underlying coronary heart disease, including death secondary to acute MI, sudden death, heart failure, complication of a coronary revascularization procedure performed for symptoms, coronary disease progression, or new myocardial ischemia where the cause of death is clearly related to the procedure, unobserved and unexpected death, and other death that cannot definitely be attributed to a nonvascular cause.

1. Death due to Acute Myocardial Infarction:
   Death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus.
   Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
   Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Sudden Cardiac Death:
   Death that occurs unexpectedly, not following an acute MI, and includes the following deaths:
   - Death witnessed and occurring without new or worsening symptoms.
   - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.
   - Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review).
   - Death after unsuccessful resuscitation from cardiac arrest.
   - Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology.
   - Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

   General Considerations
   A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."

Typical scenarios include:
- Subject well the previous day but found dead in bed the next day
- Subject found dead at home on the couch with the television on Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

3. Death due to Heart Failure or Cardiogenic Shock:
   Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
   Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:
   - Cool, clammy skin *or*

- Oliguria (urine output < 30 mL/hour) *or*
- Altered sensorium *or*
- Cardiac index < 2.2 L/min/m²

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

4. Death due to Stroke:
   Refers to a death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death due to Cardiovascular procedures:
   Refers to a death caused by the immediate complciations of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI

6. Death due to Cardiovascular Hemorrhage:
   Refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g. aortic aneurysm), or hemorrhage causing cardiac tamponade

7. Death due to Other Cardiovascular Causes:
   Refers to a cardiovascular death not included in the above categories (e.g.,pulmonary embolism or peripheral arterial disease).

Non-cardiovascular Death: Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following categories may be collected

<u>Non-Malignant Causes</u>

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Hemorrhage*, excluding hemorrhagic strokes and bleeding in the setting of coronary revascularization
- Non-cardiovascular procedure or surgery
- Accidental (e.g., physical accidents or drug overdose) or trauma
- Suicide

- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction)
- Neurological process that is not a stroke or hemorrhage
- Other non-cardiovascular, specify: _____

*Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal hematoma following PCI is considered CV death. Death due to intracerebral hemorrhage is considered CV death.

Malignant Causes

- Death results directly from the cancer;

OR

- Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy);

OR

- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently should be further classified (worsening prior malignancy; new malignancy).

Undetermined Cause of Death:
Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is “patient died”). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper). In all circumstances the reviewer will use all available information to attribute to one of the categories based on best clinical judgment.

9.6 Financial Disclosure Template

Covered Clinical Study (Name and/or Number): DFI11565

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 165		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): R727-CL-1003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 75		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced		

by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): EFC11568

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 354		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): EFC11569

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 514		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): EFC12492

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 294		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4		

Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): EFC12732

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 113		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): EFC11716

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 36		

Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): LTS11717

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1553		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to	Yes ☐	No ☐ (Request information from

minimize potential bias provided:		applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): R727-CL-1112

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 95		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): R727-CL-1119

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 273		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and		

(f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): R727-CL-1110

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 410		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Covered Clinical Study (Name and/or Number): R727-CL-1118

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 394		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reviewer comment: The applicant has adequately disclosed financial interests/arrangements with clinical investigators. Disclosed interests/arrangements or lack of disclosure despite due diligence do not raise questions about the integrity of the data. These were large, randomized controlled trials with objective endpoints and many investigators. It is unlikely the small number of investigators with disclosed interests would impact the overall results. There were no investigators who are sponsor employees.

9.7 Supplemental Tables

Table 169. Death narratives of alirocumab-treated patients

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
	Alirocumab-treated						
1	011717-056-002-011 LONG TERM Alirocumab 150Q2W Belgium	69/W/M	Cardiovascular CHD Acute MI (I/C)		166/155/on-study during TEAE	Cardiovascular Sudden cardiac death (acute MI)	History of non-FH, treated with statins, former smoker, T2DM, afib, HTN Baseline LDL 98 mg/dL On simvastatin 20 mg at screening On Day 164 of the study, the patient had a SAE of severe intensity reported as "asystolia". The patient was found in asystole state, and an ECG showed fading heart waves. He was administered with 0.5 mg atropine. After 20 minutes of resuscitation and administering 5 mg adrenaline, his BP and heart rhythm returned to normal. The patient was hospitalized. ECG revealed acute inferior posterior myocardial infarction, Troponin T at 6217 ng/L (upper reference limit: 14 ng/L), fibrin D-dimer at 28900 ng/mL (normal range not available), and creatine kinase (CK) at 1527 IU/L (normal range: 18-198 IU/L; baseline value within normal range). The patient was treated for non-ST elevation myocardial infarction (NSTEMI). On Day 166 of the study it was decided with the family to discontinue therapy. The patient died in the hospital due to multiple organ failure and acute myocardial infarction.

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
2	011717-710-004-014 LONG TERM Alirocumab 150Q2W South Africa	53/B/M	Cardiovascular CHD Heart failure or cardiogenic shock (I/C)		286/254/on-study during TEAE	Cardiovascular Heart failure or cardiogenic shock (Cardiac Failure)	History of non-FH, treated with statins (atorva 10 mg at screening). Baseline LDL 92 mg/dL, T2DM, HTN, CABG, ischemic cardiomyopathy. On Day 254 worsening of heart failure, which progressed requiring hospitalization 8 days later. The patient was diagnosed with worsening of heart failure (New York Heart Association [NYHA] functional, Class II). He received furosemide and dobutamine hydrochloride to help maintain his BP. His heart failure deteriorated to NYHA functional Class III-IV. On (b) (6), he experienced circulatory collapse (cardiogenic shock) and hypoxia. He was intubated, received mechanical ventilation, and vasopressors. Study drug was permanently discontinued due to the event (last administration on 07-AUG-2013). On (b) (6) the patient died in the hospital, with heart failure or cardiogenic shock as the primary cause of death.
3	011717-710-008-118 LONG TERM Alirocumab 150Q2W South Africa	66/W/M	Cardiovascular CHD Cardiovascular procedure (I/P1)		562/532/on-study TEAE	Cardiovascular Coronary Procedure (Coronary artery disease)	History of non-FH, on atorva 20 mg at screening, LDL at baseline 107 mg/dL, history of MI. On Day 542 of the study (b) (6), the patient had a new adverse event of mild intensity, reported as coronary artery disease (single vessel) (Coronary Artery Disease), which progressed to severe intensity on (b) (6) (b) (6) No clinical signs and symptoms were present. An ECG was performed on (b) (6) (result was not available), followed by a diagnostic angiogram (Angiogram) on (Day 542 (b) (6) which revealed coronary artery disease (single vessel). The patient was scheduled to be hospitalized for rotablation. On (b) (6) an ECG showed an inferior infarct and right bundle branch block. On (b) (6) (b) (6) the patient was hospitalized for PCI (stent insertion). Cardiac enzymes including creatine kinase (CK), CK-MB, and troponin were not drawn. The patient underwent PCI on (b) (6) for coronary artery disease. The patient died during the procedure due to an unknown complication. No autopsy was performed. The time of death was not reported and the primary cause of death was reported as coronary procedure.

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
4	011717-826-001-080 LONG TERM Alirocumab 150Q2W United Kingdom	63/W/M	Not adjudicated		442/421/on-study TEAE	Cardiovascular Cardiovascular hemorrhage (Traumatic intracranial hemorrhage)	History of acute MI, coronary revascularization procedures, transluminal balloon angioplasty of coronary artery, ischemic heart disease, and other clinically significant CHD. On Day 442, the patient, who had a long-term (14 years) history of recurrent fainting episodes, experienced an extensive traumatic intracranial hemorrhage (traumatic intracranial hemorrhage) and died immediately following collapse. According to the Investigator the patient's sudden death was due to the head injury. However, the patient's clinical status 24 hours prior to death or specific circumstances surrounding his death, were unknown. The last injection of IMP (alirocumab) was on Day 421. As of the cut-off date for this report, this event was not yet adjudicated.
5	011717-826-009-186 LONG TERM Alirocumab 150Q2W United Kingdom	72/W/M	Cardiovascular Non-CHD Cardiovascular hemorrhage (I/P1)		387/379/on-study TEAE	Cardiovascular Other CV cause (Aortic aneurysm rupture)	History of non-FH, atorva 20 mg at screening. Baseline LDL at baseline 86 mg/dL, history of T2DM, HTN. On Day 386 of the study (b) (6) the patient had 2 new serious adverse events of severe intensity, reported as ruptured atherosclerotic abdominal aortic aneurysm (Aortic Aneurysm Rupture) and sudden blackout due to hypotension (Syncope), respectively. Patient was hospitalized and died the following day. The autopsy findings included massive retroperitoneal hemorrhage due to ruptured atherosclerotic abdominal aortic aneurysm in addition to severe systemic atherosclerosis and were assessed as natural causes of the patient's death.

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
6	011717-840-165-013 LONG TERM Alirocumab 150Q2W USA	61/W/M	Cardiovascular Non-CHD Cardiovascular hemorrhage (I/C)		296/281/on-study TEAE	Cardiovascular Cardiovascular hemorrhage (Aortic dissection, hemorrhagic stroke)	History of non-FH, rosuva 40 mg at screening. LDL at baseline 113 mg/dL. History of MI, aortic root aneurysm. On (b) (6) the patient was hospitalized for a CT angiogram of the chest, abdomen and pelvis; the procedure revealed type A aortic dissection (intensity severe) extending from the level of the aortic valve. The same day (b) (6) the patient was sent from radiology directly to the emergency department. Patient underwent emergent repair with aortic root replacement. In the immediate postoperative period, the patient experienced seizure-like activity, the longest duration of neurological symptoms was given as more than 24 hours and on the same day patient was diagnosed with hemorrhagic stroke (intensity severe) peri-procedural. The hemorrhage was intraventricular. On (b) (6) CT scan of head was done which revealed hemorrhage and edema. The patient ultimately underwent a right hemicraniectomy and clot extraction. Following that he never regained consciousness and continued to have seizures. After all narcotics had been weaned, he remained with a severe neurological deficit and after discussion with his family; he was made a no code, treated with comfort care and extubated. The patient did not recover from the event of aortic dissection. On (b) (6) (b) (6) the patient died due to hemorrhagic stroke and the underlying cause was reported to be type A aortic dissection and repair of aortic dissection.

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
7	011717-826-007-103 LONG TERM Alirocumab 150Q2W United Kingdom	64/W/M	Cardiovascular Non-CHD Stroke-Hemorrhagic (I/P1)		378/63/on-study post TEAE	Cardiovascular Stroke (Hemorrhagic stroke)	On Day 377 of the study (b) (6) and more than 10 months after the last IMP administration (during follow-up period), the patient had a new serious adverse event of severe intensity, reported as hemorrhagic stroke. The patient was admitted to hospital with Glasgow coma scale of 12/15 after sudden collapse. On (b) (6) CT head scan showed 'massive cerebral hemorrhagic stroke at left frontal lobe.' The neurosurgical team reviewed that patient was not suitable for intervention thus no procedures were undertaken. The patient rapidly deteriorated and died on (b) (6)
8	011717-826-007-168 LONG TERM Alirocumab 150Q2W	65/ /F	Non-cardiovascular Pulmonary (I/C)	Malignancy Worsening prior malignancy	335/169/on-study post TEAE	Non-cardiovascular (Metastatic lymphoma)	History of type 2 diabetes mellitus and hypertension, and Guillain-Barre syndrome (since 2005). On Day 169, the patient was reported to have metastatic lymphoma (metastases to lung, liver & kidney) (metastatic lymphoma). A CT scan revealed “right side lung mass”. She permanently discontinued alirocumab on Day 169 due to this event. She was hospitalized on a number of occasions for treatment and diagnostic procedures (Days 235, 272, 321). Approximately 5 months after this diagnosis, the patient contracted pneumonia viral while hospitalized. The outcome of the event was fatal. The patient died on Day 335. Interim death certificate report stated viral pneumonia, Epstein-Barr driven lymphoma, chronic demyelinating polyneuropathy confirmed as Guillain Barre Syndrome and treatment as the causes of the patient's death. Per adjudication, the primary cause of death was non-cardiovascular.
			Non-cardiovascular Pulmonary (I/C)	Malignancy Worsening prior malignancy	335/169/on-study post TEAE	Non-cardiovascular (Pneumonia viral)	

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
9	011717-826-008-024 LONG TERM Alirocumab 150Q2W United Kingdom	69/W/F	Cardiovascular CHD Sudden cardiac death (I/C)		152/15/on-study post TEAE	Cardiovascular Acute MI (Acute MI)	On Day 152 of the study (12-JAN-2013 and 137 days after the last study drug administration), the patient with a history of acute myocardial infarction (2010) had a new serious adverse event of severe intensity, reported as acute myocardial infarction. The primary cause of death was acute myocardial infarction. No autopsy was performed. According to the death certificate, the causes of death were acute myocardial infarction, severe coronary artery atheroma, chronic kidney disease, and obesity. The patient was not hospitalized at the time of death. According to the Investigator, the 'patient had cardiac arrest at home and the patient's husband was present at the death'.
10	011717-826-008-165 LONG TERM Alirocumab 150Q2W United Kingdom	67/W/M	Cardiovascular CHD Acute MI (I/P1)		72/1/on-study post TEAE	Cardiovascular Acute MI (Acute MI)	History of non-FH, TIA (2007), MI (1994). On Day 72 of the study (06-FEB-2013), the patient had a new serious adverse event of severe intensity, reported as acute MI. Prior to this event on 01-FEB-2013, the patient underwent an echocardiogram which showed severely reduced left ventricular systolic function and 'trace mitral regurgitation', with 'extremely guarded prognosis'. On 05-FEB-2013, the patient's condition was reported stable. On 06-FEB-2013, at 18.50, the patient had a fall in the bathroom and was found on the floor; the patient's head hit the sink and lost a tooth. The patient was checked for injury and assisted back to bed. The patient was agitated, alert, able to talk and move the limbs; and he denied any pains. Urinary incontinence was noted. The patient was given midazolam and morphine. No electrocardiogram was performed for the ischemic symptoms. The final diagnosis was an acute myocardial infarction. Subsequent functional status of the patient was unknown. The patient was placed on a palliative care pathway. The patient died on (b) (6)

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
11	011717-840-058-001 LONG TERM Alirocumab 150Q2W USA	57/W/M	Cardiovascular CHD Sudden cardiac death (I/C)		349/255/on-study post TEAE	Cardiovascular Other CV cause (Hypertensive heart disease)	History of HeFH, stenting for PAD 2012, HTN, T2DM, On Day 349 of the study (14-APR-2013), the patient, with a history of hypertension since 2009, had a new serious adverse event of severe intensity, reported as hypertensive cardiovascular disease. The patient had abnormal ECGs during screening on 10-APR-2012 (showing sinus rhythm and supraventricular extrasystoles) and during study on 16-OCT-2012 ('possible left anterior fascicular block and probable left ventricular hypertrophy'). But his vital signs and blood levels of creatine kinase and sodium were normal on 10-APR-2012 and 10-JAN-2013. No anti-hypertensive therapy adjustment was required since study inclusion. There was no malignant hypertension before and after study inclusion and patient's underlying hypertension had been well controlled. On (b) (6) the patient died unexpectedly at (b) (6) The patient was not hospitalized at the time of death; it occurred at a warehouse. There was no witness to the event. The patient's death was not expected. The patient was last seen alive on (b) (6) as reported by family. According to the Investigator, relevant circumstances that lead to death were *'subject was last seen on January 10, 2013 for study visit w 36 and was stable at this visit; subject status 24 hours prior to death is unknown; none the PI called and spoke to the medical examiner and he was the one who determined that the cause of death was hypertensive cardiovascular disease'*. No autopsy was done. No death certificate was available. The patient's death was adjudicated to be CHD death.
12	012492-124-401-002 FH I Alirocumab 75/150 Canada	64/W/M	Cardiovascular CHD Sudden cardiac death (I/C)		57/56/on-study TEAE	Cardiovascular Acute MI (Acute MI)	Patient with HeFH, history of coronary artery stenosis requiring stenting, HTN. On Day 57 of study "collapsed and was never reanimated". Previous death, had experienced mild adverse events of "left should pain on Day 12 and "chest pain" (not reported as of cardiac origin) on Day 29.

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
13	012492-124-401-009 FH I Alirocumab 75/150 Canada	51/W/M	Non-cardiovascular Pancreatic (I/C)	New malignancy	353/353/on-study TEAE	Non-cardiovascular (Pancreatic carcinoma metastatic)	Patient with HeFH. On Day 252 7.5 months afeter first IMP administration SAE of pancreatic carcinoma mestatic. Death adjudicated as metastatic pancreatic cancer on Day 353
14	012492-724-404-002 FH I Alirocumab 75/150 Spain	53/W/M	Cardiovascular CHD Acute MI (I/C)		240/239/on-study TEAE	Cardiovascular Acute MI (MI)	On Day 240 of the study, the patient had a new serious adverse event ofsevere intensity, reported as myocardial infarction. He developed oppressivechest pain radiating to left arm and profuse sweating, and reported to the emergency room, being hospitalized. At physical examination, the patient had normal general status, oriented, hydrated, normal color, pain score at 10, blood pressure at 156/107 mmHg and heart rate at 106 bpm. His cardiorespiratory auscultation was normal, and no lower limb edema was observed. ECG showed clinically significant abnormalities ('acute myocardial infarction with ST decreased.', 'ventricular tachycardia followed by ventricular bradycardia.' and 'exitus, asystole'). Blood samples for Troponin I assays were drawn. Troponin value was 0.05ng/mL (upper reference limit: 0.05, MI detection limit: 0.50). Blood samples for CK and CK-MB assays were drawn CK value was 118 IU/L (upper reference limit: 308). CK-MB value was 25 IU/L (upper reference limit: 25). There was no imaging evidence of new loss of viable myocardium and/or new regional wall motion abnormality. Intubation and CPR were performed for the event, but there was no response at any time
15	012492-840-424-002 FH I Alirocumab 75/150 USA	55/W/F	Non-cardiovascular Pulmonary (I/C)	New malignancy	140/99/on-study TEAE	Non-cardiovascular (Non-small cell lung cancer metastatic)	On Day 80,(11 weeks after 1st IMPadmin) SAE reported as non-small cell primary lung carcinoma with metastasis.
16	011568-840-870-003 COMBO I Alirocumab 75/150 USA	71/W/M	Non-cardiovascular Accidental (I/C)		254/239/on-study TEAE	Cardiovasular Other CV cause (Fall) Cardiovascular Other CV cause (Pulmonary embolism)	On Day 237 of the study (b) (6) the patient had 2 new serious adverse events of severe intensity, reported as left lower extremity thrombosis (Thrombosis) and accidental fall (Fall), respectively. The patient was seen at hospital after falling and injuring his left lower extremity (LLE). After this incident, there was progressive edema, pain,

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
						Cardiovascular Other CV cause (Thrombosis	erythema and ecchymosis. On Day 251 of the study the patient had a new serious adverse event of severe intensity, reported as pulmonary embolism (Pulmonary Embolism). On that day, an X-ray showed complete opacification of the left hemithorax that possibly could have corresponded to a pulmonary embolism. That patient received unspecified corrective treatment. Patient died in hospital, poss bly from thrombosis and pulmonary embolism.
17	011568-840-877-011 COMBO I Alirocumab 75/150 USA	52/AA/F	Cardiovascular CHD Acute MI (I/P1)		96/43/on-study TEAE	Cardiovascular Acute MI (Acute MI)	On Day 96 of the study the patient had a new serious adverse event of severe intensity, reported as acute myocardial infarction. Patient experienced acute chest pain and left arm pain for 15 minutes before emergency medical services (EMS) arrived. On the way to hospital she experienced a cardiac arrest and was intubated. The patient was hospitalized. Corrective treatment was given and included normal saline, magnesium, calcium chloride, vasopressin, epinephrine and sodium bicarbonate. Patient`s ECG (electrocardiogram) showed sinus tachycardia vital signs were reported as follows: blood pressure- 114/92 mmHg, pulse rate- 93 beats/minute, respiratory rate- 22 breaths/minute, and Glasgow coma score- 15. A repeat ECG (electrocardiogram) performed was abnormal showing sinus rhythm with complete heart block and wide QRS rhythm with fusion complexes, left axis deviation, right bundle branch block and ST elevation. She experienced second episode of cardiac arrest 40 minutes after her arrival in the emergency room. The patient underwent cardiopulmonary resuscitation; however, it was unsuccessful and she was pronounced dead due to cardiac arrest

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
18	011568-840-877-014 COMBO I Alirocumab 75/150 USA	43/W/M	Cardiovascular CHD Sudden cardiac death (I/P1 re-review)		298/170/on-study post TEAE	Cardiovascular Sudden cardiac death (Coronary artery disease)	History of MI, HTN The primary cause of death was sudden cardiac death. The patient was not hospitalized at the time of death. The patient's death was not witnessed. Autopsy was not performed. According to the Investigator, 'Patient's wife called stating subject has passed away in his sleep, pending records She states that her husband never went to the hospital, just directly to the funeral home She said that the medical examiner thinks it was a possible MI due to his history but no autopsy was performed'. The Investigator reported that the patient's last known clinical status within 24 hours prior to death was 'Patient was stable, passed away in sleep'. The patient's death was adjudicated to be CHD death.
19	011569-643-924-001 COMBO II Alirocumab 75/150 Russia	64/W/M	Cardiovascular CHD Sudden cardiac death (I/C)		125/113/on-study TEAE	Cardiovascular Sudden cardiac death (Sudden cardiac death)	On Day 125 of the study 4 months after first administration on IMP auto-injectors and IMP capsules and 12 days after the most recent administration of IMP auto-injectors, the patient had a new serious adverse event of severe intensity, reported as sudden cardiac death (Sudden Cardiac Death). On the morning of death, the patient measured his blood pressure which was high (values not reported) and he took the same drugs as usual at the same doses (perindopril, indapamide, isosorbide mononitrate, acetylsalicylic acid). The patient had malaise only without any complaints. Two hours later the patient remained unwell and an ambulance was called by his wife. An electrocardiogram (ECG) was performed and there was no change, blood pressure was within normal limits. There were no symptoms of visible deterioration. The patient went to bed. The same day the patient died in sleep. The primary cause of death was sudden cardiac death. The patient was not hospitalized at the time of death. The patient's death was neither expected nor witnessed. Autopsy was not performed. Autopsy was not performed. The patient's death was adjudicated to be CHD death.

	Pt. ID Study Treatment Country	Age (y)/ Race/ Sex/	Primary cause of death as per adjudication (Origin/Phase of final adjudication)	If other CV cause or other non CV cause	Study day of onset date as per adjudication/ study day of last injection/period	Primary cause of death per investigator (preferred term)	Summary
20	011569-710-913-003 COMBO II Alirocumab 75/150 South Africa	62/W/F	Cardiovascular CHD Sudden cardiac death (I/C)		261/253/on-study TEAE	Cardiovascular Sudden cardiac death (Cardiac arrest)	Patient on Day 110 had SAE of pneumonia and worsening of congestive cardiac failure. Patient recovered. On Day 261, On (b) (6) during an outpatient visit for cellulitis of legs with septic wounds, the patient complained about difficulty breathing. It was reported that the patient's face turned blue and the patient was rushed to emergency room. Cardiac arrest occurred and resuscitation efforts were unsuccessful.. No autopsy was performed and the primary cause of the death was the occurrence of sudden cardiac arrest.

I Investigator C committee (consensus review) P1 phase 1 review of adjudication
Source: Response to FDA IR submitted 17 December 2014 Module 5.3.5.1

Table 170. Summary of definitions and assessment for adverse events of special interest

Event	Studies	Definition/Guidance for management	Selection for analyses
Local injection site reactions (AESI)	Phase 3, DFI12361, PKD12910, POP12671, and BDR13362	Local injection site reactions related to the IMP injection and not deemed to be allergic were monitored as AESI without immediate notification. Investigators had to report the individual components and assess the severity of each of these individual components that comprised the local injection site reaction. Guidance was provided to the Investigators using a table outlining the criteria for severity. A specific electronic case report form (e-CRF) "Local injection site reaction complementary form" was to be completed.	Selected using e-CRF specific tick box on the AE page
	DFI11565, DFI11566, CL-1003	Local injection site reactions were to be reported on the AE form.	Selected using high-level term (HLT) "injection site reaction"
	Phase 1	Local injection site reactions were to be reported on the AE form.	Selected using HLT "injection site reactions" or "infusion site reactions". The terms included in this HLT were "Injection (infusion) site dermatitis", "Injection (infusion) site hypersensitivity", "Injection (infusion) site edema", "Injection (infusion) site rash", "Injection (infusion) site urticaria", "Injection (infusion) site eczema", "Injection site vasculitis" and "Injection site swelling". The term "Injection site joint swelling" was excluded.
General allergic events (AESI in phase 3 and DFI12361)	All phase (1/2/3)	Allergic events and/or local injection site reactions deemed to be allergic (or with an allergic component) that required consultation with another physician for further evaluation of hypersensitivity/ allergy were reported as AESI with immediate notification. Allergic events not referred for consultation with another physician were reported as AESI without immediate notification. Allergic events were to be reported on the "General allergic reaction and/or local injection site reaction complementary form" of the e-CRF.	"General allergic events, were selected using standardized MedDRA query (SMQ) "hypersensitivity" (broad and narrow) excluding the following PTs linked to local injection site reactions: infusion site dermatitis", "infusion site hypersensitivity", "infusion site rash", "infusion site urticaria", "injection site dermatitis", "injection site hypersensitivity", "injection site rash", "injection site urticaria", and "injection site vasculitis"). Of note, in phase 1 these events were monitored but the above analysis was not performed.

Event	Studies	Definition/Guidance for management	Selection for analyses
General allergic events or local allergic reactions at IMP injection site	All phase (1/2/3)	Patients were to be monitored at investigational sites for at least 30 minutes following the first injection. Allergic events with cutaneous involvement had to be evaluated by a dermatologist as soon as possible.	The union of "general allergic events and local allergic reactions at IMP injection site" was defined based on the above selection for general allergic events including PTs from the AE page for the phase 1 and 2 studies plus the following selection of PT from the symptoms complementary form for local injection site reaction : "injection site dermatitis", "injection site hypersensitivity", "injection site oedema", "injection site rash", "injection site urticaria", "injection site eczema", "injection site vasculitis", "injection site swelling", "infusion site dermatitis", "infusion site hypersensitivity", "infusion site oedema", "infusion site rash", "infusion site urticaria", "infusion site swelling". Of note, in phase 1 these events were monitored but the above analysis was not performed.
ALT increase (AESI or AEPM)	All phase 2/3	Routine monitoring of liver function tests was performed and abnormalities were reported based on drug-induced liver injury (DILI) recommendations. Abnormalities were to be reported as AESIs with immediate notification. Specific e-CRF screens were to be completed.	Alanine aminotransferase (ALT) ≥3 x ULN (if baseline ALT<ULN) or ALT ≥2 times the baseline value (if baseline ALT≥ULN) (including single elevations), selected using laboratory data.
	Phase 1 [d]	Routine monitoring of liver function tests was performed and abnormalities were reported based on DILI recommendations. Abnormalities were to be reported as AESIs with immediate notification. Specific e-CRF screens were to be completed.	ALT ≥2 x ULN

Event	Studies	Definition/Guidance for management	Selection for analyses
Hemolytic anemia (AESI in phase 3 and DFI12361)	Phase 3 and DFI12361	A decrease in hemoglobin ≥1.5 g/dL along with additional testing (reticulocytes, lactate dehydrogenase (LDH), indirect/total bilirubin, and haptoglobin measured by central laboratory) suggesting hemolysis was to be reported as AESI with immediate notification. A hematologist was to be consulted as needed. Specific e-CRF screens were to be completed.	e-CRF specific tick box on the AE page and confirmed final diagnosis provided in the AE complementary form
	DFI11565, DFI11566, CL-1003	No specific procedure was set up for the monitoring	Definition not applicable
	Phase 1 (BDR13362, PKD12910)	No specific procedure was set up for the monitoring	Definition not applicable
Selected neurologic events (AESI in phase 3 except MONO)	All phase 2/3	Neurologic events that required additional examinations/procedures and/or referral to a specialist were to be reported as AESI with immediate notification. Other neurologic events were AESI without immediate notification. Specific e-CRF screens were to be completed.	Neurologic events were selected based on SMQs "demyelination" (broad and narrow), "peripheral neuropathy" (broad and narrow), and "Guillain-Barré syndrome" (broad and narrow) excluding the following PTs "acute respiratory distress syndrome", "asthenia", "respiratory arrest", and "respiratory failure".
Neurocognitive events	All phase 1/2/3	No specific procedure was set up for the monitoring.	Neurocognitive events were selected using a CMQ as recommended by an external expert, based on the 5 following high level group terms (HLGTs): Deliria (incl. confusion), Cognitive and attention disorders and disturbances, Dementia and amnestic conditions, Disturbances in thinking and perception, Mental impairment disorders. A second grouping of terms for neurocognitive events was defined based on Regulatory Agency request, see 5.3.5.3 ISS/SCS SAP [Table 27]. This analysis was not done on phase 1 studies.

Event	Studies	Definition/Guidance for management	Selection for analyses
Ophthalmologic events (AESI in phase 3 except MONO)	All phase 2/3	Ophthalmologic events that required additional examinations/procedures and/or referral to a specialist were to be reported as AESI with immediate notification. Other ophthalmologic events were AESI without immediate notification.	Selection for analysis based on SMQs "optic nerve disorders" (broad and narrow), "retinal disorders" (narrow), and "corneal disorders" (narrow)
	Ophthalmologic substudy of LONG TERM (LTS11717)	Selected sites were asked to participate in the sub-study. Patients who signed the additional written informed consent for the sub-study underwent ophthalmologic assessments by ophthalmologists/ optometrists at the screening period. Patients deemed eligible for the sub-study underwent ophthalmologic assessments every 6 months during the 18-month double-blind treatment period. Ophthalmologic assessments included color vision testing, best corrected visual acuity, slit lamp ophthalmoscopy, dilated lens and fundus examination, optic disc and fundus photographs (if needed), and intraocular pressure, to be performed as per the usual practice of the ophthalmologist/optometrist and were not standardized across the sub-study sites. It was recommended that the same ophthalmologist/ optometrist perform the evaluations using the same methodology throughout the study. In case an optic nerve or fundus problem was identified, the ophthalmologist/optometrist had to further evaluate the patient, as appropriate, to determine the etiology. Additional evaluations may have included fluorescein angiography, standardized visual field testing, or optical coherence tomography as per the ophthalmologist's/optometrist's judgment.	For patients enrolled in the LONG TERM opthalmologic sub-study, an additional and broader selection of terms was used and presented in the CSR using SMQs "optic nerve disorders" (broad and narrow), "retinal disorders" (broad and narrow), and "corneal disorders" (broad and narrow).

Event	Studies	Definition/Guidance for management	Selection for analyses
Overdose with IMP (AESI or AEPM)	All phase 2/3	An overdose (accidental or intentional) was an event suspected by the Investigator or spontaneously reported by the patient and defined as at least twice the intended dose within the intended therapeutic interval (ie, 2 or more injections from the treatment kit administered in less than 7 calendar days). Cases of overdose with IMP "capsules" were also to be reported. Symptomatic overdose was to be reported as AESI with immediate notification. Asymptomatic overdose was to be reported as AESI without immediate notification. Specific e-CRF screens were to be completed. Patients were to be monitored and appropriate treatment instituted in case of symptomatic overdose.	Selected using HLT "Overdose" and "Overdose with IMP injection" specific tick box in the e-CRF.
Pregnancy (including male subject's partner) (AESI or AEPM)	All phase 2/3 and phase 1 (CL-902, CL-904, CL-1001)	Pregnancy was to be reported as AESI with immediate notification. Specific e-CRF screens were to be completed. The IMP had to be discontinued (in female patients only) and the follow-up of pregnancy was mandatory until the outcome was known.	Selected using Pregnancy and neonatal topics (SMQ) (MedDRA code: 20000185).

Event	Studies	Definition/Guidance for management	Selection for analyses
Muscle-related events (AESI)	ALTERNATIVE	Suspected or confirmed skeletal muscle related AEs were monitored as AESIs without immediate notification. Specific e-CRF was to be completed.	A specific analysis of muscle-related AEs was prespecified only in ALTERNATIVE (as defined in 5.3.5.1 Study CL-1119, see 1119-11-protocol-global [Appendix 3]). Skeletal muscle-related TEAEs were defined independently in 2 ways: 1) Skeletal muscle-related AEs, representing a broad selection of AEs, were recorded by tick box on the e-CRF, and 2) A more specific set of skeletal muscle-related AESIs were identified by CMQ for both the double-blind and open-label treatment periods. The PTs in this CMQ represent the AEs most commonly associated with skeletal muscle-related events in statin intolerant patients and were selected by a subject matter expert with extensive experience in the diagnosis and treatment of statin intolerant patients The MedDRA PTs used in the CMQ to identify these events included Myalgia, Muscle Spasms, Muscle Twitching, Muscle Tightness, Myofascial Spasm, Limb Discomfort, Musculoskeletal Discomfort, Musculoskeletal Pain, Pain in Extremity, Back Pain, Muscular Weakness, Musculoskeletal Stiffness, Muscle Contracture, Muscle Fatigue, and Muscle Contractions Involuntary. Analysis using the same CMQ was conducted on the placebo-controlled pool.

AESI = adverse event of special interest; AEPM = adverse event of pre-specified monitoring for DFI11565, DFI11566, CL-1003
a PKD12010, PKD12011, PKD12275, TDU12190, POP12671, BDR13362, PKD12910

Source: NDA 125559 ISS Table 2

Event	Studies	Selection for analyses
Hepatic disorder	All phase 2/3	SMQ "Hepatic disorder"
Diabetes mellitus	All phase 2/3	HLGT "Diabetes Complications", HLT "Diabetes Mellitus", and HLT "Carbohydrate tolerance analyses (incl diabetes)" excluding PT "Blood glucose decreased"

Table 171. FDA defined neurocognitive adverse events of interest

Adverse Event of Special Interest	Preferred Term or Lower Level Term
Neurocognitive disorders-FDA	Amnesia
	Amnestic disorder
	Anterograde amnesia
	Behavioral and psychiatric symptoms of dementia
	Change in sustained attention
	Cognitive deterioration
	Cognitive disorder
	Confusion
	Confusion aggravated
	Confusional state
	Delirium
	Dementia

Adverse Event of Special Interest	Preferred Term or Lower Level Term
	Dementia Alzheimer's type
	Dementia NOS
	Dementia NOS Aggravated
	Dementia of the Alzheimer's type NOS
	Dementia with Lewy Bodies
	Disorientation
	Disturbance in attention
	Executive dysfunction
	Frontotemporal dementia
	Global amnesia
	Illogical thinking
	Impaired reasoning
	Incoherent
	Judgement impaired
	Memory impairment
	Mental impairment
	Mental impairment NOS
	Mental state abnormal aggravated
	Mental status changes
	Mini mental status examination abnormal
	Presenile dementia
	Retrograde amnesia
	Senile amnesia
	Senile dementia NOS
	Short-term memory loss
	Thinking abnormal
	Thinking slowed
	Transient global amnesia
	Vascular dementia

Source: ISS SAP phase 2/3 Table 27

Table 172. Terms defining the musculoskeletal-related CMQ

Preferred Term	High Level Term	High Level Group Term
Myalgia	Muscle pains	Muscle disorders
Muscle spasms	Muscle related signs and symptoms NEC	Muscle disorders
Muscle twitching	Muscle related signs and symptoms NEC	Muscle disorders
Muscle tightness	Muscle related signs and symptoms NEC	Muscle disorders
Myofascial spasm	Muscle related signs and symptoms NEC	Muscle disorders
Limb discomfort and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort NEC	Musculoskeletal
Musculoskeletal discomfort and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort NEC	Musculoskeletal
Musculoskeletal pain and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort NEC	Musculoskeletal
Pain in extremity and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort NEC	Musculoskeletal
Back pain and connective tissue disorders	Musculoskeletal and connective tissue pain and discomfort NEC	Musculoskeletal
Muscular weakness	Muscle weakness conditions	Muscle disorders
Musculoskeletal stiffness	Musculoskeletal and connective tissue signs and symptoms NEC	Musculoskeletal and connective tissue disorders NEC
Muscle contracture	Musculoskeletal and connective tissue signs and symptoms NEC	Musculoskeletal and connective tissue disorders NEC
Muscle fatigue	Muscle related signs and symptoms NEC	Muscle disorders
Muscle contractions involuntary	Muscle related signs and symptoms NEC	Muscle disorders

Source: ALTERNATIVE protocol appendix 3

Table 173. Number (%) of TEAE by SOC experienced by placebo, alirocumab (all), alirocumab (≥ 25 mg/dL), alirocumab (2 LDL-C <25 mg/dL (safety population) – pool of placebo and ezetimibe-controlled studies

	Control N=1894		Alirocumab N=3340		Alirocumab LDL-C ≥ 25 mg/dL N=2544		Alirocumab 2 LDL-C <25 mg/dL N=796	
	n (%)	Per 100 pt/year	n (%)	Per 100 pt/year	n (%)	Per 100 pt/year	n (%)	Per 100 pt/year
Infections and infestations	687 (36.3)	49.1	1286 (38.5)	49.7	947 (37.2)	49.6	271 (34.0)	44.3
Neoplasms	48 (2.5)	2.5	85 (2.5)	2.4	59 (2.3)	2.3	22 (2.8)	2.8
Blood/lymphatic	46 (2.4)	2.4	72 (2.2)	2.0	55 (2.2)	2.1	13 (1.6)	1.6
Immune system	15 (0.8)	0.8	44 (1.3)	1.2	36 (1.4)	1.4	5 (0.6)	0.6
Endocrine	11 (0.6)	0.6	23 (0.7)	0.6	15 (0.6)	0.6	8 (1.0)	1.0
Psychiatric	110 (5.8)	5.9	171 (5.1)	4.9	137 (5.4)	5.4	28 (3.5)	3.6
Nervous system	283 (14.9)	16.4	497 (14.9)	15.4	384 (15.1)	16.3	82 (10.3)	11.0
Eye	71 (3.7)	3.8	152 (4.6)	4.4	103 (4.0)	4.0	42 (5.3)	5.4
Ear and labyrinth	53 (2.8)	2.8	56 (1.7)	1.6	44 (1.7)	1.7	11 (1.4)	1.4
Cardiac	159 (8.4)	8.7	275 (8.2)	8.0	212 (8.3)	8.5	53 (6.7)	6.9
Vascular disorders	134 (7.1)	7.3	211 (6.3)	6.1	164 (6.4)	6.5	32 (4.0)	4.1
Respiratory	172 (9.1)	9.5	325 (9.7)	9.6	242 (9.5)	9.8	62 (7.8)	8.1
GI	318 (16.8)	18.6	567 (17.0)	17.9	426 (16.7)	18.4	101 (12.7)	13.8
Hepatobiliary	24 (1.3)	1.3	38 (1.1)	1.1	28 (1.1)	1.1	9 (1.1)	1.1
Skin and subcutaneous	130 (6.9)	7.1	270 (8.1)	7.9	203 (8.0)	8.2	51 (6.4)	6.7
Musculoskeletal	478 (25.2)	29.8	808 (24.2)	27.1	605 (23.8)	27.6	168 (21.1)	24.6
Renal and urinary	84 (4.4)	4.5	128	3.6	98 (3.9)	3.8	25 (3.1)	3.2

			(3.8)					
Reproductive/breast	40 (2.1)	2.1	77 (2.3)	2.2	58 (2.3)	2.2	15 (1.9)	1.9
Congenital	4 (0.2)	0.2	9 (0.3)	0.3	6 (0.2)	0.2	3 (0.4)	0.4
General	282 (14.9)	16.3	504 (15.1)	15.8	395 (15.5)	17.0	81 (10.2)	10.9
Investigations	127 (6.7)	6.9	235 (7.0)	6.8	192 (7.5)	7.6	34 (4.3)	4.4
Injury, poisoning, procedural	242 (12.8)	13.8	428 (12.8)	13.0	329 (12.9)	13.7	80 (10.1)	10.7

Source: ISS Appendix 1.4.5.4 Pbo controlled studies: phase 3 (LONG TERM, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361). Eze controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE) Only TEAEs that occurred, worsened or became serous 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

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/s/

JULIE K GOLDEN
07/22/2015

MARY D ROBERTS
07/22/2015

JAMES P SMITH
07/22/2015

Consultative Review and Evaluation of Clinical Data

BLA (Supporting Document Number)	**125559 (SDN 1)**
Petitioner:	**Division of Metabolism and Endocrinology Products**
Sponsor:	**Sanofi-Aventis US, LLC**
Drug:	**Alirocumab injection (Praluent)**
Proposed Indication:	**Hyperlipidemia and mixed dyslipidemia**
Consultation Date:	**2015 February 3**
Date Received / Division:	**2015 February 3**
Date Review Completed:	**2015 April 21**
Materials Reviewed:	**BLA application, selected portions**
Reviewer:	**Kenneth Bergmann, MD**
Through:	**Gerald D. Podskalny, DO (TL)** **Eric Bastings, MD, Deputy Director** **DNP / ODE I / OND / CDER**

1. Summary and conclusion

Following review of information from the BLA for Praluent, this reviewer finds that there is no compelling evidence to support the notion that alirocumab, a human monoclonal antibody, is associated with a specific neurological adverse event or syndrome as a result of drug treatment. This is based upon review of the neurological cases identified by the sponsor as being of special interest and analysis of the adverse event data files provided by the sponsor. In brief:

- There do not appear to be any imbalances in either individual or groups of adverse events that would be suggestive of a disorder of peripheral myelin (peripheral neuropathy or polyradiculopathy).

- Genetic disorders that knock out the PCSK9 gene result in loss of the PCSK9 enzyme and profoundly lowered low-density lipoprotein cholesterol (LDL-C) levels. These mutations are not associated with neurological symptoms. This suggests that adverse events as a result of the proposed therapeutic mechanism of the drug are not likely.

Rarely occurring treatment emergent neurological syndromes or adverse events cannot be completely ruled out. Miller Fisher syndrome and transverse myelitis are so rare that a single case of either is unexpected in this clinical trial population. However, none of the cases are definitive, each is lacking in important supportive clinical or laboratory findings, and there appears to be no evidence supporting a particular biological pathway that would give alirocumab a propensity to cause such side-effects. We recommend that the review division consider classifying demyelinating adverse events as Adverse Events of Special Interest, and asking for enhanced investigation and reporting of such events.

Specific questions posed by the Division of Metabolism and Endocrinology Products (DMEP) are addressed in Section 6 of this review.

2. Introduction

The Division of Metabolism and Endocrinology Products is reviewing a BLA for alirocumab, a PCSK9 inhibitor, which has been developed for the treatment of hypercholesterolemia and mixed dyslipidemia in patients with or without background statin therapy.

Alirocumab is a fully human monoclonal antibody that binds with high affinity and specificity to the PCSK9 enzyme protein, thereby increasing the number of LDL receptors available to clear LDL particles, and subsequently reducing LDL-C levels significantly.

The occurrence of seven cases of serious adverse neurological events in alirocumab treated patients raises the concern about the possible relationship of these events to drug treatment. The Division of Neurology Products is asked to comment on the cases and to consider specific questions posed by DMEP.

Review Strategy

I considered the possibility that adverse neurological events may occur via biological pathways that are not mutually exclusive.

One potential path to adverse drug effects has to do with the actual physiological action of alirocumab to greatly reduce the levels of LDL-C. Because cholesterol is a necessary component of cell membranes and myelin, there is a theoretical concern that the very low levels of LDL-C observed with PCSK9 inhibition could result in myelin sheath-related disorders such as peripheral neuropathy or central demyelination. A counterargument is that intracellular *de novo* cholesterol synthesis should be unaffected and therefore low levels of LDL-C should not affect myelination. In this regard, clinical syndromes resulting from genetic disorders that result in loss of function of the PCSK9 gene (and its resulting encoded protein enzyme) illuminate the potential for neurological syndromes that could occur as a result of greatly reduced LDL-C or absent PCSK9.

Another potential mechanism for the development of adverse events has to do with the antigenic properties of monoclonal antibodies and the likelihood of developing a variety of immune-based clinical events. To this end, I analyzed the treatment emergent adverse events reported in the blinded controlled clinical trials in the alirocumab development program and reviewed case narratives pertaining to patients who developed neurological illness during drug administration. These results are compared to the sponsor's findings as well.

3. Loss of Function Mutations

Elevated levels of LDL-C lead to atherosclerosis via the accumulation of low-density lipoprotein particles in the subendothelial layer of arterial walls. These plasma LDL-C particles find their way there via hepatic LDL receptor - mediated endocytosis. Through studies of familial hypercholesterolemia, the *proprotein convertase subtilisin/kexin type 9* gene (*PCSK9*) was shown to code for a natural inducer of this LDL receptor - mediated degradation[1,2].

More than 160 PCSK9 allelic variations have been identified. Loss of function (LoF) gene mutations interrupt this natural endocytosis process and greatly lower circulating LDL-C. While the exact mechanism is unknown, allelic variations resulting in some loss of function of PCSK9 have resulted in clinically significantly reduced cardiovascular events[3]. These are not rare mutations and individuals with profound loss of PCSK9 function have also been described[4]. One woman who was a compound heterozygote for a PCSK9 LoF mutation had no detectable circulating PCSK9 and an extremely low level of LDL-C (14 mg/dl). She was healthy with no detectible clinical symptomatology and worked as an aerobics exercise instructor[5].

LoF mutations of PCSK9 have not been clinically linked to neurological dysfunction.

4. Treatment emergent adverse events

Patients in double blind, placebo or active control trials that developed treatment emergent adverse events in the course of the development program are considered in this section. The tables presented in this section were created by the reviewer using information and datasets provided by the Sponsor.

Exposure to alirocumab

The trials that contributed to this section are as follows (source: ADSL):

Trial	Duration (weeks)	Control	N receiving alirocumab	Total N	Trial contribution to total
DFI11566	8	Placebo	61	92	2%
DFI11565	12	Placebo	151	183	3%
DFI12361	12	Placebo	75	100	2%
R727-CL-1003	12	Placebo	62	77	1%
EFC11716	24	Ezetimibe	52	103	2%
R727-CL-1110	24	Ezetimibe	104	355	6%
R727-CL-1118	24	Ezetimibe or Rosuvastatin	103	305	5%
R727-CL-1119	24	Ezetimibe or Atorvastatin	126	314	5%
EFC11568	52	Placebo	207	316	5%
EFC12492	78	Placebo	322	486	8%
EFC12732	78	Placebo	72	107	2%
LTS11717	78	Placebo	1550	2345	41%
R727-CL-1112	78	Placebo	167	249	4%
EFC11569	104	Ezetimibe	479	720	13%
Total			3531	5752	100%

Most patients had more than 52 weeks' exposure to alirocumab (some of these persons were treated in studies that were uncontrolled and those do not contribute patients to the analysis of adverse events in this review):

Alirocumab Exposure	N	Percent of total
0 -24 weeks	697	18
24 - 52 weeks	464	13
> 52 weeks	2420	69
Total	3581	100

The proposed dose for alirocumab is 75 mg or 150 mg administered subcutaneously (sc) once every 2 weeks (Q2W). The lower dose of 75 mg Q2W was administered to 1560 patients mostly in studies of 12 weeks or less. About 30% of these patients went on to titrate to the full dose of 150 mg sc Q2W. The higher dose of alirocumab was used as the starting dose in 1622 patients. In early blinded studies of alirocumab other doses, both higher and lower, were used in a small number of patients.

The study population in both pools consisted of patients with considerable risk for cardiovascular morbidity. The majority of patients had hypertension (70%), type 2 diabetes (30%), and a history of coronary heart disease (roughly two thirds of patients). Almost 20% were current smokers.

TEAE

The sources of data for the tabulation of treatment emergent adverse events were the Sponsor's data sets, ADSL and ADAE. Neurological adverse events were experienced by 942 patients in the blinded, controlled Phase 2 and 3 trials:

Arm	Patients with any Neurological AE	% patients in arm	Number of neurological AEs	Mode (Range)
Placebo or Active Control	379	17%	805	1 (1-18)
Alirocumab	563	16%	1258	1 (1-12)
Total	942		2063	

There were 1615 unique Preferred Terms used to describe TEAE. All PTs in all SOCs were inspected for similarity of coded events. The rationale for this is that verbatim terms describing neurological symptoms may be translated to closely related Preferred Terms in different SOCs. As example, using the common verbatim description of dizziness, it may be translated to *labyrinthitis* (SOC *Infections and Infestations*), *vertigo* (SOC *Ear and Labyrinth Disorders*), and to *dizziness, dizziness exertional, or dizziness postural* (SOC *Nervous System Disorders*).

For the sake of readability, the tabular presentation for adverse events for the Nervous System Disorders SOC is presented later this review. In brief, there appears to be no disparity between active and control treatments in the occurrence of any particular treatment emergent adverse event.

Peripheral Neuropathy

Because of the theoretical concern that alirocumab's mechanism of action could interfere with peripheral myelin and result in a neuropathy, I created a custom query using the adverse events that did occur in the trials and that could indicate any kind of peripheral nerve dysfunction. These were grouped together and a headcount performed.

Preferred Terms that were reported in the Phase 2 and 3 trials suggesting possible peripheral neuropathy are:

TEAE suggesting neuropathy (Preferred Term)	Placebo or Active Control (N= 2221)	Alirocumab (N=3531)	% Placebo or Active Control	% Alirocumab
Paraesthesia	17	32	0.8	0.9
Hypoaesthesia	13	26	0.6	0.7
Carpal tunnel syndrome	11	12	0.5	0.3
Diabetic neuropathy	3	9	0.1	0.3
Decreased vibratory sense	7	7	0.3	0.2
Burning sensation	2	5	0.1	0.1
Neuropathy peripheral	9	5	0.4	0.1
Neuralgia	3	4	0.1	0.1
Polyneuropathy	0	2	0.0	0.1
Sensory disturbance	0	2	0.0	0.1
Hyporeflexia	1	1	0.0	0.0
Peripheral nerve palsy	0	1	0.0	0.0
Polyneuropathy idiopathic progressive	0	1	0.0	0.0
Diabetic autonomic neuropathy	1	0	0.0	0.0
Neuritis	1	0	0.0	0.0
Sensory loss	1	0	0.0	0.0

These events in total were coded 222 times and represent 167 different patients. The numbers of individual patients that this represents (taking into account that the same patient may have collections of symptoms coded by different PTs at different visits in the end) is represented in the following contingency table:

	Any neuropathy PTs		
	Yes	No	Total
Alirocumab	103	3428	3531
Placebo or active control	64	2157	2221

Total	167	5585	5752

The probability that the differences have meaning is not significant (Likelihood Ratio and Pearson $\psi^2 > 0.94$).

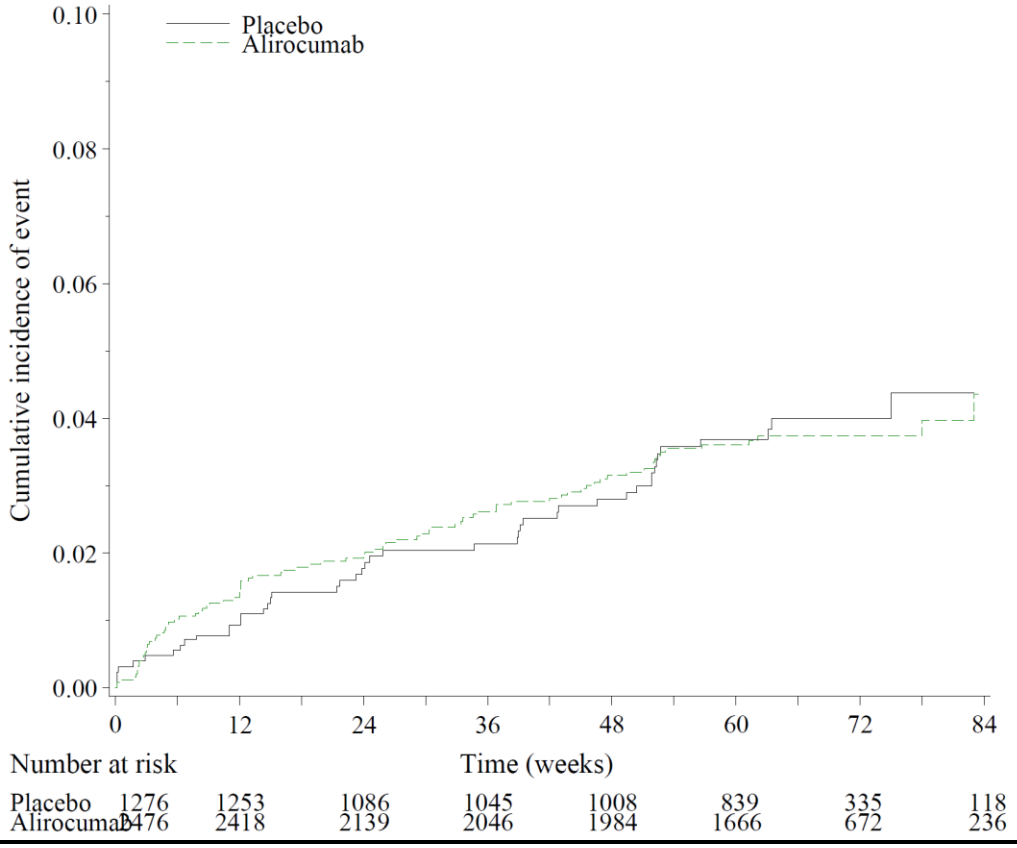
Fatigue is also a commonly experienced but non-specific general symptom of neurological illness. A similar analysis was performed for related PTs. There was no difference between the active and control arms.

System Organ Class	AEDECOD	Placebo or Active Control	Alirocumab	% Placebo or Active Control	% Alirocumab
General disorders and administration site conditions	Asthenia	24	22	1.1	0.6
General disorders and administration site conditions	Fatigue	67	104	3.0	2.9
General disorders and administration site conditions	Malaise	9	16	0.4	0.5
Nervous system disorders	Lethargy	5	15	0.2	0.4

The Sponsor performed both broad and narrow Standard MedDRA Queries (SMQs) for demyelination, Guillain-Barre syndrome, and peripheral neuropathy. They noted that some small differences occurred among the arms (confirmed for peripheral neuropathy above) but as a group these did not demonstrate meaningful differences by treatment arm. These SMQs identified individuals by casting a large net and those cases were inspected more closely by the Sponsor. None of the targeted syndromes of special interest were identified with the exception of the cases discussed below. I agree with the Sponsor's assessment of cases identified by SMQs and that they did not rise to a level of clinical suspicion that suggested a syndromic diagnosis.

There is no temporal relationship between the development of neurological adverse events and the duration of treatment (Sponsor's ISS, p130):

Figure 7 - Study-adjusted Kaplan-Meier cumulative incidence curve for time to first Neurologic events during TEAE period (Safety population) - Pool of placebo-controlled studies



5. Case Narratives

No neurological fatalities occurred in the development program. The serious adverse event cases of neurological clinical interest are briefly described below. (The verbatim synopses of the Sponsor's narratives in this section [ISS, pages 131-133] are contributed by Dr. Mary Roberts, DMEP reviewer for this BLA.)

There were 7 patients (0.2%) treated with alirocumab who experienced serious neurologic events compared with 2 patients (0.1%) in the placebo /active control group. Of these events, 4, all occurring in alirocumab-treated patients, are notable (optic neuritis, Miller-Fisher syndrome, demyelination, and transverse myelitis). Narratives were submitted by the sponsor for all nine patients and are the basis of my comments.

Alirocumab-treated

- Optic neuritis (serious) Pt #. 011717-840-202-001:

This 66-year-old male patient with over-the-counter readers without distance correction, and history of severe vasculitis affecting the skin on the right upper limb (biopsy result unknown) and blurred vision over the last 2 years, was receiving atorvastatin 40 mg/day for 5 months before alirocumab initiation, fenofibrate 135 mg/day for 4 years, and levothyroxine, in addition to multiple CV drugs. He was diagnosed with retrobulbar optic

neuritis of the right eye (PT optic neuritis) on Day 34. Right eye pain and blurriness in right lower quadrant with perception of a "grey film" over the total inferior visual field which worsened when looking to the side (with or without glasses) was noted. Retinal Nerve Fiber Layer/ Optic Nerve Head revealed optic nerve cupping which appeared non-glaucomatous in both eyes. MRI of the brain showed enhancement of right optic nerve and the surrounding fat consistent with optic neuritis, right maxillary sinusitis, and was said to rule out tumor, cerebrovascular accident, and multiple sclerosis. Alirocumab was discontinued and after 1 month of prednisolone (20 mg 3 times daily) treatment, an 85% to 90% improvement was observed. Full recovery was reported 2 months later. The Investigator concluded that the event was related to pre-existing vasculitis and was not related to the investigational drug, to statin, or to other lipid modifying therapy (LMT). An academic neuro-ophthalmologist consultant to the Sponsor considered the case to be optic perineuritis, which is commonly due to vasculitis and a more consistent diagnosis with the described MRI findings in patients of this age, thus agreeing with the overall impression of the Investigator but not the specific MedDRA term. Of note, this patient did not experience 2 consecutive LDL-C values <25 mg/dL and his lowest values of LDL-C occurred at Weeks 4 and 8 (36 mg/dL and 30 mg/dL respectively). Vitamin E levels remained normal throughout the study. This patient had pre-existing positive antidrug antibody (ADA) status.

Reviewer comment: Review of this narrative indicates this patient developed "severe vasculitis" ((b) (6) and suffered a "general allergic reaction" (July, 2012) prior to entering the trial (February, 2013). The patient's eye symptoms (pain, blurred and greying of vision) developed and worsened over a month's time leading to the MRI examination. He was treated with steroids and promptly recovered. No details of the previous vasculitis were supplied. A comprehensive serological examination for usual causes of vasculitis was unrevealing. It is likeliest that this is part of the patient's vasculitic diathesis.

- Miller-Fisher syndrome (serious) Pt # 011717-826-010-268:

A 47-year-old male patient, with a history of drug allergy, on simvastatin 40 mg/day for 6 years, reported diplopia on Day 190 which had been preceded by nausea and diarrhea suggestive of an infectious gastroenteritis, and "some weight loss". His condition continued to deteriorate leading to hospitalization on Day 197. He suffered from neuropathic pain due to a post-surgery scar. On admission, mild distal weakness, areflexia (upper and lower extremities) and 6th cranial nerve palsy (external ophthalmoplegia, subtle ptosis of right eyelid) were noted. CT and MRI of the brain were normal. Miller-Fisher syndrome was diagnosed. The patient received gammaglobulin treatment. Cerebrospinal fluid revealed normal glucose, protein and cells. Antibodies to GQ1b were not detected. Neurological picture resolved 1 month after first symptoms; while diplopia persisted for 7 months until recovery. Multiple tests, including complete blood count, C-reactive protein, renal and liver tests, serum angiotensin converting enzyme (ACE), anti-neutrophil cytoplasmic antibody (ANCA) screen, Lyme serology, syphilis, human immunodeficiency virus (HIV) serology, anti-myelin-associated glycoprotein (MAG) antibodies, anti-ganglioside antibodies, serum immunoglobulins were all normal, with the exception of slight transitory lymphocytosis. Alirocumab was

permanently discontinued due to the event. The Investigator considered the event to be related to the investigational and not related to statin or to other LMT. Of note, the patient had low LDL-C reaching 2 consecutive values <25 mg/dL. The lowest value of LDL-C, reached by this patient at Week 24 (Day 168) was 1.5 mg/dL. Vitamin E levels of this patient remained normal throughout the study. A transient positive ADA response (titer: 480) was observed at Week 4, not associated with a neutralizing activity. ADA negative responses were observed at all other evaluated time points.

Reviewer comment: Review of this patient's narrative reveals that his neurological syndrome began 6 months following the detection of antidrug antibodies (June 28 and January 18, 2013, respectively). The patient has a sub-acute progressive illness beginning with diplopia and progressing to ophthalmoplegia, ptosis, areflexia, with mild distal hand weakness over a few weeks' time. CSF examination was normal without elevated protein. GQ1b antibodies were not present but these are typically representative of severe disease. He was treated with gammaglobulin about 10 days into his illness. MRI remained normal. He improved with residual diplopia. The patient's treatment with alirocumab was ended a week before his diagnosis after 196 days of treatment.

Of interest, the gastrointestinal symptoms reported in the sponsor's synopsis above do not appear in the narrative in the clinical study report. Ataxia, a clinical symptom of MF syndrome was not described, and protein in the CSF was not elevated as it usually is. Nevertheless the syndrome is consistent with a very mild myeloradiculopathy centered in the brainstem. Improvement following globulins supports that diagnosis. No alternative diagnosis is suggested by the events.

- Demyelination (serious) Pt # 011717-380-002-004:

A 57-year-old female patient with anxiety and depression, treated with rosuvastatin 5 mg/day for 8 months at alirocumab initiation, complained of walking difficulty, lower limb weakness and tingling in toes, persisting after rosuvastatin withdrawal, on Day 64. Electromyogram (EMG) was negative. The event was not diagnosed until neurological examination performed 11 months later, MRI of the brain showed multiple lesions of supratentorial and subtentorial white matter and cervical spine cord. Autoimmune screening was normal. Cerebrospinal fluid revealed presence of oligoclonal bands with intrathecal IgG synthesis. Reduced amplitude of the brainstem auditory-evoked response (BAER) and delayed and reduced potential of evoked somesthetic response (PESS) on the left side and the MRI findings led to the diagnosis of demyelinating disease of central nervous system, and suspicion of multiple sclerosis. High dose corticosteroid therapy for 3 days resulted in noticeable improvement. The patient recovered with sequelae, reported as ongoing constant myalgia of the lower limbs. The Investigator considered the event to be possibly related to the investigational drug and to statin, and not related to other LMT. No action was taken with the investigational drug. Long-term immunomodulatory therapy and neurological check-up were planned. This patient did not show 2 consecutive LDL-C values <25 mg/dL and the lowest value of LDL-C reached was 44 mg/dL at Week 4. The patient had ADA negative responses at all evaluated time points.

Reviewer comment:
The clinical syndrome with laboratory support (MRI with brain and cervical cord lesions and CSF oligoclonal bands) is most consistent with a demyelinating disorder. While generally occurring at a younger age, it is not rare to have the illness discovered after more overt symptomatology develops in later life. The patient improved somewhat after intravenous corticosteroid treatment. Alirocumab was continued for a month after the event started and some improvement in the clinical syndrome had already occurred.

- Myelitis transverse (serious) Pt # 011569-840-974-004:

A 75-year-old female patient on simvastatin 40 mg/day for over 15 years and with relevant medical history of hypothyroidism, obesity, depression and arthritis, experienced myelitis transverse on Day 64. She was hospitalized for dizziness, impaired balance, left abdominal pain, left-sided numbness, left back pain and weakness of the left lower extremity. Initial diagnosis was stroke of the spinal cord. MRI of the thoracic spine showed increased spinal cord signal, and slight expansion at T6-T9 level, and was considered more consistent with a diagnosis of transverse myelitis. Cerebrospinal fluid by lumbar puncture was acellular with normal proteins and without oligoclonal bands. Pulse steroids led to rapid improvement and a discharge within 10 days. Alirocumab was discontinued. On consecutive evaluations up to 9 months after discharge left lower extremity spasticity was persisting with presence of MRI spine lesion at T6-T8 level. CT of the brain did not show an active process at the time of event. The patient used a walker and received baclofen 10 mg 3 times a day and diazepam. Two brain MRI findings were available at 6 and 7 months post-event onset, respectively. The first MRI concluded generalized cerebral volume loss and mild degree of chronic small vessel ischemic disease, while the second was said to show several small areas of white matter involvement around the corpus callosum posteriorly and one such area in the splenium of the corpus callosum. This case is still under investigation and efforts are being made to obtain the original MRI images. The patient had not had 2 consecutive LDL-C values <25 mg/dL. The lowest value of LDL-C occurred at Week 8 and was 44 mg/dL. ADA status was negative at baseline while no other values were available.

Reviewer comment: The clinical description and findings on clinical examination could indicate a mild transverse myelitis process but they are also consistent with a spinal cord stroke. This level of the cord is typical for ischemia and the MRI demonstrates a patchy multilevel lesion as is often the case in spinal cord stroke. The normal CSF laboratory tests would also support a vascular etiology. Nevertheless it is not possible to say that either syndrome is related to the investigational drug which was discontinued at the start of the clinical event.

- Sensory disturbance (serious) Pt # 011569-208-914-009:

A 57-year-old male patient woke up tired with new onset of tingling in hands and feet on Day 289. The patient was admitted for laboratory tests and neurological examination, with no final diagnosis made. The symptoms disappeared within 2 days. The lowest value of LDL-C of 25 mg/dL occurred at Week 4. The patient's ADA status was negative throughout the study participation.

Reviewer comment: It is not clear what two days of distal limb paresthesias represent in this patient. The patient's medical history reports ">2 standard drinks containing alcohol at least daily." The description of the altered sensation is unusual: "tingling feeling and felt as if water was running on the skin." It was not accompanied by any findings on physical examination. The patient recovered spontaneously and continued on treatment.

- In the alirocumab group, 2 additional serious neurological events were reported: a bilateral lower extremity profound weakness (PT: muscular weakness) mild in intensity on Day 242 (Pt #. 011568-840-894-001) and ataxia due to combination of dehydration and Lyrica (PT: ataxia) severe in intensity on Day 33 (Pt #. 011717-124-006-008). Both events recovered. No action was taken with alirocumab.

Reviewer comment: Patient #011568-840-894-001 (M/70) had a history of Type 2 diabetes mellitus, chronic lower limb venous stasis, claudication, degenerative joint disease of both knees, and right ankle fracture with operative repair (fusion). On Day 242 he reported a new event of "bilateral lower extremity chronic pain" and weakness sufficient to prevent him from transferring from his wheelchair. He lived alone and this provided the opportunity for transfer to a nursing home. There was no observed change in the patient's physical examination.

Patient #011717-124-006-008 (F/65) had a history of diabetes, stroke, and chronic low back pain. After 529 days of treatment she suffered ataxia associated with dehydration, acute renal failure, intermittent hallucinations, tremor, and confusional state. She returned to "normal" after hydration and left the hospital against medical advice.

Control-treated (placebo or active control)
Two patients in control groups had neurological adverse events considered to be serious:

One patient (Pt # 001118-826-860-003) experienced a serious and severe TEAE of paresthesia. It occurred on Day 136 and was limited to the right arm. It lasted for 42 days and did not lead to the investigational drug discontinuation. No final diagnosis was provided. The event was considered not related to the investigational drug by the investigator.

A patient on placebo (Pt # 012492-840-430-009) was reported to have a serious change in gait. This 78-year-old male experienced gait disturbance on Day 363, lasting for 4 days. This event was not considered study-drug related and did not lead to treatment discontinuation.

Reviewer comment: In the first case, an upper extremity event such as this suggests a possible cervical radiculopathy. Gait disturbance is generally multifactorial and insufficient information was provided by the Sponsor to suggest a definitive diagnosis in the second case. In either case, they resolved spontaneously without a change in treatment.

6. DMEP questions

DMEP posed the following questions:

1. The sponsor makes a point of redefining the case of optic neuritis to optic perineuritis. We understand this may be an important distinction as optic neuritis is associated with demyelinating conditions such as multiple sclerosis whereas perineuritis is not. Would you agree that this case is more consistent with a perineuritis related to the patient's history of vasculitis?

Reviewer response: On face, this would seem to be a reasonable assessment by the Sponsor, but in my opinion the history of previous (pre-trial) vasculitis is more important in the determination of the etiology of the ophthalmological event. It is much more likely that the patient has a single syndrome as opposed to two diseases. Of interest, one epidemiologic survey reports that the prevalence of primary systemic vasculitis is about 14.5 per 100,000 or 1 in 6897 people – well within the ballpark of having such a patient in this trial population[6].

2. How concerning is it that a case of Miller Fisher syndrome was identified in a safety database of this size and patient population? Do you think there is any clinical relevance to either the presence of anti-drug antibodies or low LDL-C or both and this particular case?

Reviewer response: While this may not completely inform a decision about the significance of a single case of GBS, the estimated prevalence of Guillain-Barre Syndrome (of which Miller Fisher Syndrome is a variant) is about 72 per 100,000 or 1 in 1389.[6] The incidence is much less, estimated at 2 -3 / 100, 000 above the age of 50[7]. Given the paucity of autoimmune phenomena (outside of injection site reactions) related to alirocumab, my intuition is that it is unrelated to alirocumab treatment. There is no clear scientific basis to link alirocumab antidrug antibodies (most of which are neutralizing antibodies) to myelin sheath cross reactivity that could then result in a polyradicular autoimmune syndrome.

The LoF mutation cases suggest that this is unrelated to low LDL-C levels.

3. How concerning is it that a case of idiopathic transverse myelitis was identified in a safety database of this size and patient population?

Reviewer response: I am unconvinced that this represents a case of transverse myelitis as opposed to an ischemic event of the spinal cord. The patient's vasculopathic history, clinical presentation, course, and laboratory findings suggest the latter. If it is indeed myelitis, a single case provides insufficient basis for an opinion.

While these three cases do not rise to a level of diagnostic certainly, taken as a group they could represent demyelination in the central nervous system 6 to 12 months after starting alirocumab. Individually these are rare events and, given the size of the population in which they have occurred, it is concerning. On the other hand, none of the cases is

definitive, each is lacking in important supportive clinical or laboratory detail, and all are considered central immune processes. These would not be predicted by the mechanism of action of the drug, nor the peripheral immune response generated by it. The lack of any peripheral neuropathic symptoms suggestive of demyelination is worthy of note.

4. What would be the expected time to onset of symptoms for a drug-related demyelination disorder?

Reviewer response: The answer to this question depends upon the proposed mechanism by which myelin is disrupted. The time course for the development of demyelination in people with post infectious peripheral polyradiculopathy is about three weeks after the immune trigger. The time course leading to the typical presentation of ascending paralysis in animal models of experimental autoimmune encephalomyelitis following immunization in the periphery is similar.

Most drug induced neuropathies result from a dying back of axons in which longer nerves are most susceptible. However there are immune based neuropathies that presume a triggering event. Medication induced demyelinating neuropathies presumably mimic this mechanism. The onset of neuropathy depends upon a variety of factors; age, dose, schedule of administration, and individual genetic factors. The onset of these neuropathies may occur after as little as two months to a year or more[8].

An example of a specific drug-induced demyelinating neuropathy is that produced by amiodarone, which may result from interference with oligodendrocytes (the source of peripheral myelin) through inhibition of lysosomal sphingomyelinases. Of note, optic neuropathy (not vasculitis) has been associated this agent.[9]

5. The sponsor contends low levels of serum LDL-C should not contribute to central nervous system (CNS) dysfunction because all cholesterol used by the CNS is synthesized within the CNS and is not derived from LDL-C or other serum cholesterol. Do you agree that the marked effects of alirocumab on lipid metabolism would not be expected to affect the CNS or PNS? Are you aware of any other reasons to suspect that alirocumab could cause or contribute to neurological adverse events?

Reviewer response: While I do not necessarily endorse the Sponsor's tautological reasoning as to why low levels of serum LDL-C do not contribute to adverse drug effects, it would appear that the clinical literature from families with a variety of LoF mutations of PCSK9 support its observed lack of neurological sequelae.

7. Treatment emergent adverse events

Treatment Emergent Adverse Events in Phase 2 and 3 blinded, controlled trials (counts by patient; a blank space indicate no patient with that Preferred Term) for the System Organ Class (SOC) Nervous System Disorders.

AEDECOD (Preferred Term)	Placebo or Active Control (N=2221)	Alirocumab (N=3531)	% Placebo or Active Control	% Alirocumab
Headache	113	171	5.1	4.8
Dizziness	87	109	3.9	3.1
Paraesthesia	17	32	0.8	0.9
Sciatica	17	31	0.8	0.9
Hypoaesthesia	13	26	0.6	0.7
Syncope	21	24	0.9	0.7
Lethargy	5	15	0.2	0.4
Migraine	13	13	0.6	0.4
Carpal tunnel syndrome	11	12	0.5	0.3
Presyncope	3	10	0.1	0.3
Diabetic neuropathy	3	9	0.1	0.3
Memory impairment	2	8	0.1	0.2
Nerve compression	1	7	0.0	0.2
Decreased vibratory sense	7	7	0.3	0.2
Dizziness postural	2	7	0.1	0.2
Transient ischaemic attack	2	7	0.1	0.2
Carotid artery stenosis	5	7	0.2	0.2
Cerebrovascular accident		7		0.2
Ischaemic stroke	2	7	0.1	0.2
Amnesia	4	6	0.2	0.2
Tremor	7	6	0.3	0.2
Burning sensation	2	5	0.1	0.1
Neuropathy peripheral	9	5	0.4	0.1
Somnolence	3	5	0.1	0.1
Carotid arteriosclerosis	2	5	0.1	0.1
Neuralgia	3	4	0.1	0.1
Restless legs syndrome	3	4	0.1	0.1
Dysgeusia	1	3	0.0	0.1
Convulsion	1	3	0.0	0.1
Loss of consciousness	1	3	0.0	0.1
Radiculitis		3		0.1
Tension headache	1	3	0.0	0.1
Dysarthria	2	3	0.1	0.1
Sinus headache	4	3	0.2	0.1
Haemorrhagic stroke	1	3	0.0	0.1
Ageusia		2		0.1
Balance disorder	4	2	0.2	0.1
Brain injury		2		0.1

Disturbance in attention	3	2	0.1	0.1
Facial paresis		2		0.1
Hypersomnia		2		0.1
Intention tremor	1	2	0.0	0.1
Lumbar radiculopathy		2		0.1
Migraine with aura	1	2	0.0	0.1
Parkinson's disease		2		0.1
Polyneuropathy		2		0.1
Radicular pain	1	2	0.0	0.1
Sensory disturbance		2		0.1
Trigeminal neuralgia		2		0.1
Ulnar nerve palsy		2		0.1
Vibratory sense increased		2		0.1
Intracranial aneurysm		2		0.1
Lacunar infarction	2	2	0.1	0.1
Hemianopia		1		0.0
Miller Fisher syndrome		1		0.0
Optic neuritis		1		0.0
Ataxia		1		0.0
Myelitis transverse		1		0.0
Post-traumatic headache	2	1	0.1	0.0
Cervicobrachial syndrome		1		0.0
Cervicogenic headache		1		0.0
Hypotonia		1		0.0
Arnold-Chiari malformation		1		0.0
Cerebral atrophy		1		0.0
Cerebrosclerosis		1		0.0
Cervical radiculopathy	1	1	0.0	0.0
Cubital tunnel syndrome	1	1	0.0	0.0
Demyelination		1		0.0
Essential tremor		1		0.0
Excessive ocular convergence		1		0.0
Extensor plantar response		1		0.0
Facial spasm		1		0.0
Head discomfort		1		0.0
Hemiparesis		1		0.0
Hyporeflexia	1	1	0.0	0.0
Mononeuritis		1		0.0
Monoplegia		1		0.0
Myoclonus		1		0.0
Nervous system disorder		1		0.0

Neuroma	1	1	0.0	0.0
Oral dysaesthesia		1		0.0
Paresis		1		0.0
Peripheral nerve palsy		1		0.0
Polyneuropathy idiopathic progressive		1		0.0
Quadriparesis		1		0.0
Radicular syndrome		1		0.0
Radiculitis cervical		1		0.0
Radiculopathy		1		0.0
Transient global amnesia	2	1	0.1	0.0
VIIth nerve paralysis		1		0.0
Dementia	2	1	0.1	0.0
Dementia Alzheimer's type	1	1	0.0	0.0
Frontotemporal dementia		1		0.0
Basal ganglia haemorrhage		1		0.0
Brain stem infarction		1		0.0
Brain stem ischaemia		1		0.0
Cerebellar infarction		1		0.0
Cerebral artery occlusion		1		0.0
Hypertensive encephalopathy		1		0.0
Vertebral artery occlusion		1		0.0
Hypogeusia	1		0.0	
Diabetic autonomic neuropathy	1		0.0	
Hypoglycaemic coma	1		0.0	
Hypoglycaemic unconsciousness	1		0.0	
Metabolic encephalopathy	1		0.0	
Areflexia	1		0.0	
Complex regional pain syndrome	1		0.0	
Dizziness exertional	1		0.0	
Epilepsy	1		0.0	
Facet joint syndrome	1		0.0	
Grand mal convulsion	1		0.0	
Mononeuropathy	1		0.0	
Muscle contractions involuntary	2		0.1	
Myoclonic epilepsy	1		0.0	
Neuritis	1		0.0	
Post herpetic neuralgia	1		0.0	
Pyramidal tract syndrome	1		0.0	
Sensory loss	1		0.0	
Spinal cord infection	1		0.0	

Subdural haematoma	1		0.0	
Vocal cord paresis	1		0.0	
Altered state of consciousness	1		0.0	
Carotid artery disease	1		0.0	
Carotid artery occlusion	1		0.0	
Cerebral infarction	2		0.1	

8. Literature Citations

[1] Poirier S and Mayer G, The biology of PCSK9 from the endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density lipoprotein cholesterol. Drug Design, Development and Therapy 2013; 7: 1135–1148 dx.doi.org/10.2147/DDDT.S36984

[2] Lambert G, et al. Molecular basis of PCSK9 function. Atherosclerosis 2009; 209: 1–7 dx.doi.org/10.1016/j.atherosclerosis.2008.06.010

[3] Cohen, JC, et al. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med 2006; 354: 1264-72.

[4] http://omim.org/entry/607786

[5] Zhao Z et al. Molecular characterization of loss of function mutations in PCSK9 and identification of a compound heterozygote. Am J Hum Genet 2006;79: 514–23

[6] Hayter, SM, Cook, MC. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. Autoimmunity Reviews 2012; 11: 754 -765 http://dx.doi.org/10.1016/j.autrev.2012.02.001

[7] Dimachkie, MM , Barohn, RJ. Guillain-Barre Syndrome and variants. Neurol Clin. 2013; 31(2): 491–510. doi:10.1016/j.ncl.2013.01.005

[8] Stubgen, J-P. Drug-induced dysimmune demyelinating neuropathies. J Neurol Sci 2011; 307:1-8 http://dx.doi.org/10.1016/j.jns.2011.05.010

[9] Passman RS, et al. Amiodarone-associated optic neuropathy: a critical review. Am J Med. 2012; 125(5): 447–453. doi:10.1016/j.amjmed.2011.09.020

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

/s/

KENNETH J BERGMANN
04/23/2015

GERALD D PODSKALNY
04/24/2015

ERIC P BASTINGS
04/28/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

BLA Number: 125559 **Applicant: Sanofi-aventis** **Stamp Date: 11/24/2014**

Drug Name: alirocumab **BLA Type: priority**

On initial overview of the BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			The ISE includes supporting tables and figures. The textual summary and discussions of the results for efficacy data are presented in Module 2.7.3 Summary of Clinical Efficacy
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Included in Module 2.5 Clinical Overview (Section 6)
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			x	BLA 351(a)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: DFI11565	x			

	Content Parameter	Yes	No	NA	Comment
	Study Title: A randomized, double-blind, parallel-group, placebo-controlled, multicenter study evaluating the efficacy and safety of five doses and two dose regimens of SAR236553 over 12 weeks in patients with primary hypercholesterolemia and LDL-cholesterol ≥ 100 mg/dL on ongoing stable atorvastatin therapy Sample Size: 183 Arms: 6 Location in submission: 5.3.5.1 Study Number: R727-CL-1003 Study Title: A randomized, double-blind, placebo-controlled, 12-week study of the safety and efficacy of REGN727 in patients with heterozygous familial hypercholesterolemia Sample Size: 77 Arms: 5 Location in submission: 5.3.5.1 Study Number: DFI12361 Study Title: A multicenter, randomized, double-blind, parallel-group, placebo-controlled study evaluating the efficacy and safety of three doses of alirocumab over 12 weeks in patients with primary hypercholesterolemia and LDL-cholesterol ≥ 100 mg/dL on ongoing stable atorvastatin therapy Sample Size: 100 (Japan only) Arms: 4 Location in submission: 5.3.5.4				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: COMBO I (EFC11568) Pivotal Study #2: OPTIONS I (R727-CL-1110) Pivotal Study #3: OPTIONS II (R727-CL-1118) Pivotal Study #4: ALTERNATIVE (R727-CL-1119) Pivotal Study #5: MONO (EFC11716) Pivotal Study #6: FH I (EFC12492) Pivotal Study #7: FH II (R727-CL-1112) Pivotal Study #8: HIGH FH (EFC12732) Pivotal Study #9: COMBO II (EFC11569) Pivotal Study #10: LONG TERM (LTS11717)	x			All studies were conducted in support of hypercholesterolemia indication in patients unable to achieve their LDL-C goals. (b) (4) regarding differences in patient populations (e.g., familial hypercholesterolemia, high CV risk, statin intolerance, etc.) will be considered at the time of review.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			Mean percent LDL-C change from baseline (at week 24) was agreed upon at EOP2 as a reasonable endpoint, with the understanding that if there are safety concerns that preclude confidence in LDL-C as a surrogate for CV risk, a CV outcomes trial could be required prior to approval. This is a review issue, however, not a filing issue.
20.	Has the application submitted a rationale for assuming the	x			Module 2.5 Clinical

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data to U.S. population/practice of medicine in the submission?				Overview (section 1.3); Module 2.7.3 Clinical Summary of Efficacy (section 3.3.2.2, LDL-C results by region)
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		x		EOP2 meeting agreement no TQT study needed. Division requested categorical analysis of ECG findings in LTS11717 to be submitted – all elements of requested submission not located. However, not a filing issue –plan to issue an information request.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			x	Product is not licensed or marketed, therefore no post-market information available
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			2408 alirocumab-treated patients for at least 52 weeks; 639 alirocumab-treated patients for at least 76 weeks In one Phase 3 trial LONG-TERM; 543 patients treated with 150 mg Q2W for ≥76 weeks
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			MedDRA v 17.0
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver request: (b) (4) [redacted] Deferral request: (b) (4) [redacted]
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			Waiver request: Module 5.3.5.3
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	Studies conducted in Japan were considered supportive
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
37.	Are all datasets to support the critical safety analyses available and complete?	x			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			LDL-C is calculated using the Friedewald equation. Data points utilized in this equation (TC, HDL-C, TG) were provided for each patient.
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			Module 2.5 Clinical Overview

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____Yes___

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

- Not applicable

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Information requests

1. Please submit or provide the location of the following analysis that was requested in the EOP2 meeting written comments.

   You should perform a categorical analysis and submit it to the BLA. The analysis should include the number and percentage of individuals with:

   - **Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as the number and percentage of individuals with change from baseline >30 ms and >60 ms.**
   - **PR changes from baseline ≥50% if absolute baseline value was < 200 ms and ≥25% if absolute baseline value was >200 ms.**
   - **QRS changes from baseline ≥50% if absolute baseline value was <100 ms and ≥25% if absolute baseline value was >100 ms.**
   - **Number and percentage of individuals with abnormal ECG findings.**
   - **Number and percentage of individuals with AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia, e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death**

2. Please submit or provide the location of the assessment of skeletal muscle related withdrawal rates between alirocumab and ezetimibe in the ezetimibe-controlled pool referred to in the EOP2 meeting minutes.

3. Please submit or provide the location of non-fatal SAEs summarized in tabular form by SOC and preferred term in the placebo-controlled and ezetimibe-controlled pools.

4. We note in LONG TERM there were 5 patients with the preferred term "amnesia" (840-204-002, 840-083-004, 710-009-013, 826-006-080, and 124-006-008). Only two of these patients have narratives describing this event (840-083-004 and 124-006-008). Please submit narratives for the other 3 patients and clarify why they were not included in the original application.

5. For each phase 3 trial, utilizing the ITT analysis, fill in the mock table for the following targets (the right 2 columns will only be applicable in the trials that utilized alirocumab up-titration; studies that have more than one comparator should have those data presented in separate comparator columns):

   1. Among very high risk patients only, LDL-C < 70 mg/dL
   2. Among moderate-to-high risk patients only, LDL-C < 100 mg/dL

3. LDL-C < 70 mg/dL among very high risk patients or LDL-C < 100 mg/dL among moderate to high CV risk patients
4. Among very high risk patients only, LDL-C < 70 mg/dL and/or ≥ 50% reduction in LDL-C
5. LDL-C reduction ≥ 50% (all pts)
6. LDL-C reduction ≥ 50% (very high risk pts only)

Time		Comparator N=	Alirocumab		
			All N=	Up-titrate: No (75 mg) N=	Up-titrate: Yes (75/150 mg) N=
Week 12	Observed	n (%)	n (%)	n (%)	n (%)
	Missing	N	N	N	N
Week 24	Observed				
	Missing				
Week 52*	Observed				
	Missing				

*if applicable

6. Clarify why the dose change at week 12 was based on week 8 data (as opposed to week 10 or week 12 data, for example). Clarify how missing data from week 8 would be handled with respect to a dosing decision at week 12.

Review Issue

7. As we have stated previously, it will be a review issue whether alirocumab could be approved based on effects on lipid parameters such as LDL-C before cardiovascular (CV) outcomes data are available. Uncertainty is greater with regard to net clinical benefit when benefit of a drug is assessed solely by effects on a biomarker, regardless of whether the biomarker is considered a valid surrogate endpoint for a given patient population.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

JULIE K GOLDEN
01/08/2015

MARY D ROBERTS
01/08/2015

JAMES P SMITH
01/08/2015