FDA ADVISORY COMMITTEE BRIEFING DOCUMENT
PRALUENT^{TM} (alirocumab)

BLA 125559

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

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ABBREVIATIONS

ACC/AHA:	American College of Cardiology/American Heart Association
ACTH:	adrenocorticotropic hormone
ADA:	anti-drug antibody
AE:	adverse event
AEPM:	adverse events with prespecified monitoring
AESI:	adverse event of special interest
ALT:	alanine amino transferase
Apo A-1:	apolipoprotein A-1
Apo B:	apolipoprotein B
ASCVD:	atherosclerotic cardiovascular disease
BLA:	Biologics License Application
BMI:	body mass index
CEC:	Clinical Events Committee
CHD:	coronary heart disease
CHF:	congestive heart failure
CHMP:	Committee for Medicinal Products for Human Use
CI:	confidence interval
CMQ:	Company MedDRA Query
COPD:	chronic obstructive pulmonary disease
CPK:	creatinine phosphokinase
CTD:	Common Technical Document
CV:	cardiovascular
CVD:	cardiovascular disease
DMC:	data monitoring committee
e-CRF:	electronic-Case Report Form
ESC/EAS:	European Atherosclerosis Society/ European Society of Cardiology
FDA:	US Food and Drug Administration
FSH:	luteinizing hormone
GCP:	Good Clinical Practice
HCV:	hepatitis C virus
HDL-C:	high-density lipoprotein cholesterol
heFH:	heterozygous familial hypercholesterolemia
HLGT:	high-level group term
HLT:	high level term
HMG-CoA:	3-hydroxy-3-methyl-glutaryl-CoA
hoFH:	homozygous familial hypercholesterolemia
HR:	hazard ratio
hs-CRP:	high-sensitivity C-reactive protein
IMP:	investigational medicinal product
IND:	Investigational New Drug
ISS:	integrated summary of safety
ITT:	intention-to-treat
LDL:	low-density lipoprotein
LDL-C:	low-density lipoprotein cholesterol

LDLR:	low-density lipoprotein receptor
LH:	luteinizing hormone
LLN:	lower limit of normal
LMT:	lipid-modifying therapy
LOF:	loss of function
Lp (a):	lipoprotein (a)
mAb:	monoclonal antibody
MACE:	major adverse cardiac events
MAR:	missing at random
MI:	myocardial infarction
mITT:	modified intention-to-treat
MMRM:	mixed-effect model with repeated measures
MNAR:	missing not at random
MTD:	maximally tolerated dose
NAb	neutralizing antibodies
NCEP-ATP III:	National Cholesterol Education Program – Adult Treatment Panel III
non-FH:	non-familial hypercholesterolemia
non-HDL-C:	non-high-density lipoprotein cholesterol
PCSA:	potentially clinically significant abnormality
PCSK 9:	proprotein convertase subtilisin kexin type 9
PD:	pharmacodynamic
PFP:	pre-filled pen
PFS:	pre-filled syringe
PK:	pharmacokinetic
PMM:	pattern-mixture model
PO:	per os (by mouth)
POP PK:	population pharmacokinetic
PT:	preferred term
PY:	patient-year
Q2W:	every 2 weeks
Q4W:	every 4 weeks
QD:	once daily
SAE:	serious adverse event
SAP:	statistical analysis plan
SC:	subcutaneous
SE:	standard error
SOC:	system organ class
SMQ:	standardized MedDRA queries
SREBP-2:	sterol regulatory element-binding-protein-2
TEAE:	treatment-emergent adverse event
TGs:	triglycerides
Total-C:	total-cholesterol
ULN:	upper limit of normal
WHO:	World Health Organization

1.   EXECUTIVE SUMMARY

Alirocumab is a fully human monoclonal antibody (mAb) (IgG1 isotype) administered by subcutaneous injection that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK9) to reduce levels of low density lipoprotein cholesterol (LDL-C) and other atherogenic lipoproteins. Alirocumab is being co-developed by Sanofi and Regeneron.

PCSK9 binds to low density lipoprotein receptors (LDLR) at the surface of hepatocytes and thereby targets internalized LDLR for lysosomal degradation. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLR available to clear LDL particles, thereby lowering LDL-C. This new approach to harness the well-established mechanism of lowering LDL-C through increased expression of LDLR provides new therapeutic possibilities for patients who: 1) because of their cardiovascular risk or baseline LDL-C need additional LDL-C lowering on top of current therapies, or 2) are unable to take current therapy (i.e., statins) and therefore, not able to achieve the 50% LDL-C reduction recommended by current guidelines.

LDL-C lowering is a well-validated surrogate for cardiovascular benefit and has been accepted for drug approval by the US Food and Drug Administration (FDA) and other regulators world-wide. Numerous lines of animal, epidemiologic, genetic, and clinical data demonstrate the direct linear relationship of LDL-C levels to cardiovascular risk and that reductions of LDL-C by lifestyle changes or drugs reduce cardiovascular risk. Clinical trial data demonstrate that alirocumab provides clinically meaningful and statistically significant reductions in LDL-C together with changes in other lipid parameters related to cardiovascular risk. The extensive body of research demonstrating that cardiovascular risk reduction with LDL-C lowering by statins and more recently, ezetimibe, support that the robust reduction in lipids with alirocumab also will be associated with cardiovascular risk reduction. Studies of humans with functional mutations in their PCSK9 genes support the notion that LDL-C reduction by this pathway will be associated with cardiovascular benefit, as do animal atherosclerosis models utilizing PCSK9 blockade; an ongoing cardiovascular outcomes trial (OUTCOMES) will definitively address this prediction. The Sponsors therefore propose that, based on its LDL-C lowering efficacy, alirocumab be approved as an adjunct to diet for:

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

Approval is sought for the administration of alirocumab in combination with a statin, with or without other LMT; as monotherapy; or as add-on to other non-statin LMT, including in patients who cannot tolerate statins.

The Phase 3 ODYSSEY program, consisted of ten double-blind studies: five 12- to 18-month placebo-controlled studies (N=3499) and five ezetimibe-controlled studies (N=1797) that varied from 6 months to 24 months in duration. All Phase 3 studies either completed or surpassed a prespecified time point for treatment duration. A total of 5296 patients with hypercholesterolemia or mixed dyslipidemia were studied (including 3188 randomized to

alirocumab). Three of the ten studies were conducted exclusively in patients with heterozygous familial hypercholesterolemia (heFH) and one exclusively in patients with a documented history of statin intolerance. Except for the 103 patients in the MONO (monotherapy) study and 43 of 310 patients in the ALTERNATIVE (statin intolerance) study, all patients in the Phase 3 program were at high or very high cardiovascular (CV) risk and all patients in the placebo-controlled studies were taking background lipid-modifying therapy (LMT) consisting of a maximally tolerated dose (MTD) of a high potency statin (atorvastatin, rosuvastatin, or simvastatin), with or without other LMTs. Of note, approximately 30% of all patients reported a history of diabetes mellitus. All patients were not at optimal LDL-C levels and required additional LDL-C reductions based on clinical treatment guidelines in effect at the time of study initiation.

Eight studies (N=2848 randomized), encompassing approximately half the patients in the Phase 3 program, were designed such that patients started treatment with 75 mg every 2 weeks (Q2W) alirocumab and were up-titrated at week 12 in a blinded manner to 150 mg Q2W if they had not reached their prespecified LDL-C goal at week 8. In the other two studies (N=2448 randomized), encompassing approximately the other half of the patients in the Phase 3 program, patients were treated with either placebo or alirocumab 150 mg Q2W for the entire study period. The primary efficacy endpoint in all studies was the percent reduction from baseline in LDL-C at Week 24 compared to placebo.

Superior efficacy of alirocumab versus control was demonstrated in each of the 10 Phase 3 studies. At Week 24, patients treated with alirocumab (on top of background therapy) achieved mean reductions in LDL-C which were significantly greater than those achieved with the addition of placebo or ezetimibe to background therapy. Averaged across the various studies, alirocumab use resulted in a mean -45.6 to -48.9% reduction in LDL-C from baseline to week 24 in studies that investigated the up-titration regimen and -60.4% in studies that solely investigated 150 mg Q2W dosing, whereas control rates were 0.5 to 4.2% (placebo) and -19.3 to -22.3% (ezetimibe). See Section 8.3.1 for additional information on the efficacy of up-titration.

In a prespecified key secondary analysis, both alirocumab doses also demonstrated significantly greater LDL-C reductions than controls over the first 12 weeks of treatment, prior to potential up-titration: -44.5% on the 75 mg Q2W dose pooled across Phase 3 placebo-controlled studies and -62.6% with the 150 mg Q2W dose. LDL-C reductions were sustained over the duration of treatment (up to 18 months) and were generally consistent across subgroups, regardless of type or dose of concomitantly used statin. In studies using the up-titration regimen, a majority of patients achieved pre-defined LDL-C goals of <70 mg/dL and/or <100 mg/dL (based on level of CV risk) on the 75 mg Q2W dose and did not require up-titration to 150 mg Q2W. Up-titration to the higher dose resulted in additional efficacy, particularly among patients taking statins.

The global double-blind safety database includes 3451 patient-years of exposure to 75 mg Q2W or 150 mg Q2W alirocumab and 1827 patient-years of exposure to double-blind control. This includes 2856 patients exposed to alirocumab for at least 24 weeks, 2408 patients exposed for at least 52 weeks, and 639 patients exposed for at least 76 weeks. The safety analyses demonstrate that alirocumab is well tolerated at both doses. There were 2 adverse events (AEs) that were more common in patients taking alirocumab: injection site reactionand pruritus. Almost all of these were mild in intensity, transient in nature, and did not necessitate treatment discontinuation. Rare allergic events leading to study discontinuation were observed, including

hypersensitivity, hypersensitivity vasculitis, and nummular eczema. These all resolved without clinical sequelae after discontinuation of alirocumab and, in some cases, with treatment with a short course of corticosteroids.

Alirocumab use was not associated with an increased risk of hepatic or muscle effects, types of adverse events noted in statin labeling. There do not appear to be meaningful effects on glycemic control. However, this effect of statins was not identified until recent analyses of large outcomes trials, so this topic will need to be readdressed in the cardiovascular outcomes trial. With regard to neurocognitive events, brain cholesterol is synthesized in situ by astrocytes and oligodendrocytes and is almost completely isolated from other pools of cholesterol in the body[1], and monoclonal antibodies are too large to cross the blood-brain barrier. There was no increase in neurocognitive events with alirocumab use compared to control in the safety pools, although an imbalance was seen in one analysis of neurocognitive events in the LONG TERM study the largest of the four 78-week, placebo-controlled studies included in the pooled data.   Overall, the data suggest that the incidence of neurocognitive events with alirocumab use is similar to control. However, there were only 29 patients with these events in the alirocumab groups combined across the safety pools, reflecting their low incidence rates. The OUTCOMES study is expected to provide sufficient data for more robust analyses of these rare events.

The benefit-risk profile of alirocumab is favorable. Alirocumab provides clinically meaningful mean reductions of LDL-C in patients not achieving adequate reductions with their existing statin or in patients unable or unwilling to take statins to achieve their LDL goals. In clinical studies, alirocumab also provided up to 63% mean reductions on top of statin therapy in patients with high cardiovascular risk who were not well controlled despite their current therapies, including those receiving a MTD of a highly-effective statin. This treatment effect is consistent with the >50% LDL-C reduction goal specified in the current guidelines for high-risk patient populations. The adverse reactions identified to date (injection site reaction and pruritus) were generally mild, transient and manageable; allergic events leading to discontinuation were rare. There were no meaningful effects on glycemic control or neurocognitive events in the large safety pools.

In a randomized, double-blind study of patients with a history of statin intolerance, alirocumab demonstrated greater efficacy than ezetimibe and a lower rate of muscle-related adverse events than with either statin or ezetimibe treatment. These data indicate that alirocumab is a valuable treatment for patients who are unable or unwilling to take a statin and support the proposed indication in this patient population. Although an 18,000-patient cardiovascular outcomes study is ongoing to assess the potential CV benefit of alirocumab, the Sponsors propose that alirocumab be approved now based on the robust clinical efficacy for patients not well-controlled despite their current therapies and the generally favorable safety data.

This briefing book summarizes the unmet medical needs of patients with primary hypercholesterolemia and the efficacy and safety information supporting the use of alirocumab to address these needs. The overall benefit-risk assessment derived from the clinical program supports the approval of alirocumab for the treatment of patients with primary hypercholesterolemia or mixed dyslipidemia including patients with type 2 diabetes mellitus.

1.1.   LDL-C and Risk of Cardiovascular Disease

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the Western world,[2,3] and an increasing burden in developing countries and in Asia.[4-6] Hypercholesterolemia constitutes a major risk factor for the development of atherosclerosis and consequently ASCVD, especially coronary heart disease (CHD).[7-9] Accumulation of cholesterol in the artery wall is one of the earliest signs of atherosclerosis (the fatty streak) and higher levels of accumulated cholesterol in more mature lesions is thought to increase the risk of plaque rupture, the pathophysiologic event that precipitates a clinical cardiovascular event.

LDL-C is identified as the primary target of lipid lowering and meets the criteria as a valid surrogate endpoint for CHD risk.[10-13] Multiple lines of evidence support this:

- Animal studies demonstrated that increases in LDL-C can initiate and progress atherosclerotic lesions and that lowering LDL-C in these models inhibits atherosclerotic progression.

- Numerous (human) epidemiological studies established that elevations in LDL-C results in increased risk for major cardiovascular events.

- Studies of human genetics demonstrate that mutations that influence LDL-C levels directly result in differences in cardiovascular risk. For example, loss-of-function mutations in the LDLR or apoB or gain-of-function mutations in PCSK9 can result in familial hypercholesterolemia and resultant premature CVD. Individuals carrying such gain-of-function mutations have extreme elevations in LDL-C from birth and, in the case of HoFH, can experience CV events by age 20, prior to other CHD risk factors being present, thus distinctly demonstrating the important role of LDL-C in progressing atherosclerosis that precipitates CV events.

- Complementing the data on human genetics, Mendelian randomization studies have demonstrated that loss-of-function mutations in genes that lower LDL-C levels (including PCSK9) result in lower rates of CHD in adulthood as compared to non-affected individuals. These data demonstrate that multiple genetic mechanisms of LDL-C lowering reduce CV risk.

- Finally, numerous clinical studies demonstrate that reducing LDL-C levels pharmacologically, mainly with statins, reduces the risk of CHD. These studies demonstrate both a strong direct relationship between the amount of LDL-C lowering and the degree of CVD risk reduction as well as between achieved LDL-C levels and incidence of CVD events. Recent data from the IMPROVE-IT study extend the benefits of lowering LDL-C to a non-statin agent, further supporting the principle linking LDL-C reductions to reductions in CV risk.[14]

Collective CV event trial data from both statin and non-statin lipid modifying therapies demonstrate that every 1 mmol/L (38.6 mg/dL) reduction in LDL-C results in an approximate 22% reduction in major CV events to mean LDL-C levels as low as approximately 50 mg/dL. Post-hoc analyses from these outcome studies extend this benefit to somewhat lower LDL-C levels (approximately 40 mg/dL). These data provide evidence for a direct relationship between LDL-C and cardiovascular events and further support that LDL-C lowering provides a well-validated surrogate for cardiovascular benefit. Accordingly, LDL-C reduction has been

accepted for drug approval by the FDA and other regulators world-wide. Public statements by FDA as recent as 2013 indicate that their position on LDL-C had not changed.[15]

1.2.   Unmet Need and Rationale for Product Development

Despite availability of statins and other LMTs, many individuals remain at high risk for ASCVD due to elevated LDL-C. Although guidelines for the management of dyslipidemias have evolved over time, treatment guidelines continue to recommend a treatment strategy based on patients' CV risk levels. European and US guidelines both recommend aggressive LDL-C goals in patients at high and very high CV risk:

- US: the most recent guidelines from American College of Cardiology/American Heart Association (ACC/AHA) recommend the use of high intensity statins in all high CV risk patients to achieve a ≥50% reduction in LDL-C, regardless of the baseline LDL-C level.[9] The National Lipid Association continues to recommend lowering LDL-C to specific target goals (LDL-C <100 mg/dL for patients at high CVD risk and <70 mg/dL for patients at very high CVD risk).[16]

- Europe: European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) recommend targeting an LDL-C goal <100 mg/dL for patients at high CVD risk and LDL-C goal <70 mg/dL or a ≥50% LDL-C reduction when the goal of <70 mg/dL cannot be reached for patients at very high CVD risk.[7,17]

Even when these guidelines are followed, current treatment options often do not provide sufficient efficacy for many patients to eliminate the excess cardiovascular risk attributable to their LDL-C level.[18] New, highly effective LMTs are most needed for patients requiring substantial reductions in their LDL-C level, such as patients with familial hypercholesterolemia or individuals at high risk of ASCVD.[19] In addition, patients unable to take a statin need new treatment options to achieve their LDL-C reduction goals.

1.3.   Mechanism of Action of Alirocumab

Alirocumab binds with high affinity and specificity to PCSK9. PCSK9 binds to the low-density lipoprotein receptors (LDLR) on the surface of hepatocytes and thereby promotes their degradation. LDLR are the major pathway through which cholesterol-rich LDL particles are cleared from circulation. When PCSK9 binds to cell surface LDLR, the LDLR, when subsequently internalized, is targeted for degradation instead of recycling to the cell surface. By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the number of LDLR available on the cell surface to clear LDL particles, thereby lowering LDL-C levels.

It is important to point out that alirocumab ultimately acts by regulating the same functional target as do statins – that is, both work by indirectly increasing the levels of LDLR surface expression on hepatocytes, and thus promoting LDL-C clearance. Their similar mechanism of action supports the possibility that blocking PCSK9 will not only lower LDL-C as do statins, but also similarly share the ability to reduce CV risk. Studies of humans with genetic mutations of their PCSK9 genes show that mutations which increase PCSK9 activity promote CV disease, whereas down-mutations are protective. Furthermore, PCSK9 blockade also shows benefit in animal models of atherosclerosis.

Although alirocumab lowers LDL-C as monotherapy, LDL-C lowering is greater in the presence of concomitant statin therapy. Statins inhibit HMG-CoA reductase and decrease cholesterol synthesis. This leads to an increase in cellular sterol regulatory element-binding-protein-2 (SREBP2) which up-regulates the transcription and ultimately, the surface expression of LDLR on hepatocytes. The SREBP-mediated increase in surface LDLR is one of the main mechanisms of LDL-C lowering by statins. SREBP2, however, also promotes the transcription and expression of PCSK9, which dampens the ability of statins to clear circulating LDL particles.[20] By inhibiting the binding of PCSK9 to LDLR, alirocumab increases the statin-induced increase in LDLR density on hepatocytes, maximizing their potential lipid-lowering efficacy. Ezetimibe and fibrates have qualitatively similar but quantitatively smaller effects on PCSK9 levels. Thus, this enhancement of the LDL-C lowering effect of alirocumab is also observed with ezetimibe and fibrates, but to a lesser degree.

In all species tested (mice, hamsters, and cynomolgus monkeys), alirocumab reduced LDL-C levels and in an animal model, alirocumab reduced the overall burden of atherosclerosis.

1.4. Proposed Indication and Dosing Regimen

Indication

The intended population for alirocumab treatment are those patients who, by virtue of their underlying CV risk, require reductions in their LDL-C level beyond that attainable by a maximally tolerated dose of statin. The following is the indication proposed in the Sponsor's Biologics License Application (BLA):

"Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at increased risk for atherosclerotic cardiovascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to diet and other non-pharmacologic measures has been inadequate.

Alirocumab 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 LDL-C, Total-C, non-HDL-C, Apo B, TGs, and Lp(a), and to increase HDL-C and Apo A-1.

Alirocumab is indicated in combination with a statin, with or without other LMT.

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

Limitations of Use

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

Dosing Regimen

The usual starting dose for PRALUENT is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks.

The dose of PRALUENT can be individualized based on patient characteristics such as goal of therapy and response. Lipid levels can be assessed as early as 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dosage adjusted accordingly.

1.5.　　Overview of Clinical Development Program

The clinical development program was designed to assess the efficacy and safety of alirocumab for the treatment of patients with primary hypercholesterolemia or mixed dyslipidemia, as combination therapy with a statin, with or without other LMTs, or as monotherapy or add-on to non-statin LMTs, including in patients with statin intolerance.

The alirocumab program evaluated two doses to flexibly meet patient's needs based on their baseline LDL-C and their target LDL-C. Data from outcomes studies with other drugs that lower LDL-C indicate that there is a benefit to lowering mean LDL-C values to <50 mg/dL. Post-hoc analyses from these outcome studies extend this benefit to somewhat lower LDL-C levels (approximately 40 mg/dL). However, the benefit/risk for considerably lower values of LDL-C (eg., <25 mg/dL) is unknown. It was intended that by providing two doses of alirocumab, health care providers could more precisely target patients' individual goals.

The integrated efficacy database includes the ten Phase 3 clinical studies that have been completed or for which the primary double-blind treatment periods (first-step analysis) have been completed. All data which were available and validated at the time of the database lock (or interim database lock for ongoing studies) were included in the integrated efficacy database.

The integrated safety database includes these ten Phase 3 studies as well as the placebo and alirocumab 75 mg Q2W or 150 mg Q2W treatment arms from the four completed Phase 2 studies conducted in patients with familial and non-familial hypercholesterolemia. For the ongoing Phase 3 studies, the prespecified first-step analyses include all safety data up to each individual study cut-off date. The following safety pools were analyzed:

- **Placebo-controlled pool:** pool of 9 placebo-controlled Phase 2/3 studies, including the 4 Phase 2 studies, four 78-week Phase 3 studies (FH I, FH II, HIGH FH, and LONG TERM) and one 52-week Phase 3 study (COMBO I). All 5 Phase 3 studies utilized 2:1 randomization of patients to alirocumab or placebo, all had surpassed the 52-week landmark visit for the last patient enrolled, and all patients in the 5 Phase 3 studies were at high or very high CV risk. The placebo-controlled data are considered primary in our assessment of safety.

- **Ezetimibe-controlled pool:** pool of 5 ezetimibe-controlled Phase 3 studies, including studies with concomitant statin use (COMBO II, OPTIONS I, OPTIONS II) and without statin use (ALTERNATIVE, MONO). These studies varied in patient populations, use of statin, duration (2-year COMBO II study, 24-weeks for others) and randomization ratios. Accordingly, this pool is considered supportive.

- **Global pool:** the pool in which all the alirocumab 75 mg Q2W and 150 mg Q2W data from the Phase 2 and 3 studies above were combined into one treatment group and all the control (placebo/ezetimibe) data into a second group. The analysis plan pre-specified to use the global pool only for the analysis of injection site reactions, deaths, and AEs in patients with 2 consecutive LDL-C values <25 mg/dL. Because an independent and external CV event adjudication was not conducted in Phase 2 studies

a global subpool of Phase 3 studies was used to evaluate CV events. Similarly, anti-drug antibodies were assessed separately in the global pool of Phase 3 studies.

Key Aspects of the Phase 3 Clinical Program

The alirocumab Phase 3 clinical program was developed in consultation with the United States FDA and the European Committee for Medicinal Products for Human Use (CHMP)/Scientific Advice Working Party.

Collectively, the program was designed to contain key elements to provide a strong basis to characterize the efficacy and safety of alirocumab:

- The program was enriched with patients with high unmet medical need. Most of the Phase 3 patient population met strict definitions for high/very high CV risk (based on US and EU guidelines in effect at the time of clinical development plan finalization) and over 1200 patients had heFH.

- All 10 Phase 3 studies were at least 6 months in duration and 5 studies (LONG TERM, HIGH FH, FH I, FH II, and COMBO II) were at least 18 months in duration.

- The clinical studies had double-blind treatment periods ranging in length from 24 to 104 weeks; all patients in the 52-week or longer studies (approximately 80% of patients in the Phase 3 population) had at least 52 weeks of treatment at the time of database lock for the BLA.

- The enrichment for high/very high CV risk patients with long-term double-blind assessment provided a sufficient number of CV events to assess safety.

- The 10 Phase 3 clinical studies supporting efficacy incorporated 2 dosing regimens with distinct levels of efficacy to provide health care providers with the flexibility to tailor dosing based upon individual patient needs.

  - A 75 mg Q2W dose was selected based on Phase 2 data to provide approximately 50% LDL-C lowering from baseline. The 50% target was based on:

    - treatment guidelines that recommend patients achieve a minimum of 50% reduction in LDL-C in addition to achieving certain targets, and

    - the demonstrated benefit from aggressive (>50%) LDL-C lowering in outcomes studies.

  - A 150 mg Q2W dose was selected based on the anticipated maximal 60-65% LDL-C lowering from baseline.

- Patients with a history of statin intolerance were identified as an important population to study. The ALTERNATIVE study examined the efficacy and safety of alirocumab in these patients and, at the recommendation of FDA, included a statin re-challenge arm as a calibrator.

Additionally, the ODYSSEY OUTCOMES study is ongoing and will consist of 18,000 patients with recent acute coronary syndrome on a background of high intensity statin randomized 1:1 to alirocumab or placebo.

1.6.   Study Designs

1.6.1.   Overview

The Phase 3 program randomized 5296 patients. The majority of patients in the Phase 3 program in both alirocumab and control arms were on MTD of a potent statin (atorvastatin, rosuvastatin, or simvastatin) with or without other LMTs. Patients included in the program were primarily from 3 core patient populations who, based on guidelines at the time of study initiation, had significant unmet medical need due to their inability to achieve their LDL-C goal on maximally tolerated therapy: (1) heFH patients; (2) non-FH patients at high/very high CV risk, including patients with mixed dyslipidemia and diabetic patients who may have additional factors for cardiovascular risk; (3) patients with a history of intolerance to statins due to muscle-related adverse effects. All patients in these studies were in need of LDL-C lowering as evidenced by these CV risk levels and baseline LDL-C values considered to be at levels associated with excess cardiovascular risk. The different studies enrolled patients with a range of mean baseline LDL-C values allowing evaluation of highly intensive and less intensive strategies for LDL-C lowering. A brief overview of the studies is presented in Table 1.

The integrated efficacy database includes the ten Phase 3 clinical studies that had either been completed (COMBO I, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO) or for which the primary double-blind treatment period (first-step analysis) had been completed (FH I, FH II, HIGH FH, COMBO II, and LONG TERM, Table 1) at the time of the data cut-off for the BLA.

Table 1:   Overview of Phase 3 Studies

Study	Treatment Arm(s) (N)	Duration of Study	Baseline LDL-C (mg/dL)	Patient Population	Status of the Study at BLA Cut-off Date
Combination Therapy with Statins					
FIXED-DOSE STUDIES[a]					
Alirocumab 150 mg vs Placebo					
LONG TERM	Al (1530), P (780)	18 months	122.4	heFH patients, very high CV risk patients	Ongoing[c]; All patients completed at least 1 year and >600 completed 18 months
HIGH FH	Al (71), P (35)	18 months	197.8	heFH patients	Ongoing; All patients completed at least 1 year
UP-TITRATION STUDIES[b]					
Alirocumab 75mg /150 mg vs Placebo					
COMBO I	Al (205), P (106)	12 months	102.2	Very high CV risk patients	Completed
FH I	Al (322), P (163)	18 months	144.6	heFH patients	Ongoing[c]; All patients completed at least 1 year
FH II	Al (166), P (81)	18 months	134.4	heFH patients	Ongoing; All patients completed at least 1 year
Alirocumab 75mg /150 mg vs Ezetimibe					
COMBO II	Al (467), E (240)	24 months	107.3	Very high CV risk patients	Ongoing; All patients completed at least 1 year
OPTIONS I	*At 20mg*: Al (55), E (53), At[d] (53); *At 40mg*: Al (46), E (46), At[d] (47), R (45)	6 months	105.1	High/very high CV risk patients	Completed
OPTIONS II	*R 10mg*: Al (48), E (47), R[d] (48); *R 20mg*: Al (53), E (50), R[d] (52)	6 months	111.3	High/very high CV risk patients	Completed
Monotherapy					
Alirocumab 75mg /150 mg[b] **vs Ezetimibe**					
ALTERNATIVE	Al (126), E (122), At (62)	6 months[e]	191.3	Statin-intolerant and moderate/high/ very high CV risk patients	Ongoing open-label extension; All patients completed at least 6 months
MONO	Al (52), E (51)	6 months	139.7	Moderate CV risk patients	Completed

Al: alirocumab, At: atorvastatin, CV: cardiovascular, E: ezetimibe, heFH: heterozygous familial hypercholesterolemia, P: placebo, R: rosuvastatin

[a] Patients received alirocumab 150 mg throughout the study.

[b] Patients were up-titrated in a blinded manner from 75 mg to 150 mg at Week 12 based on Week 8 LDL-C levels.

[c] Study completed after BLA submission. Complete study data provided to FDA in the 4-month safety update.

[d] Denotes titration arm.

[e] The 6-month double-blind treatment period is complete. An open-label extension is ongoing.

1.6.2.   Study Periods and Dosing

The Phase 3 clinical study designs were similar and usually included the following treatment periods:

Screening period: assessed the baseline status for eligibility and trained eligible patients or care-givers on injection of study medication.

Double-blind treatment period of 24 to 104 weeks: the four 24-week studies are complete. Six studies (N=4219) with 80% of the Phase 3 study populations were analyzed after achieving a prespecified time point at Week 52 (for all patients) or Week 78 (for >600 patients).

- Eight studies (N=2848) initiated alirocumab at 75 mg Q2W with a blinded increase to 150 mg Q2W at Week 12 (referred to as 75/150 mg Q2W hereafter) for patients who had not achieved their pre-specified LDL-C goals at their week 8 visit. LDL-C goals were based on their baseline level of CV risk (either <70 mg/dL or <100 mg/dL for patients at very high or high CV risk, respectively). Any dose increase was determined by a computer algorithm which assigned the appropriate study kit for the patient. No Sponsor personnel or investigators were provided the laboratory efficacy data during the course of the study. This up-titration scheme was designed to test the 75/150 mg Q2W dosing strategy to reduce LDL-C levels below a specific goal.

- Two studies (N=2448) initiated and maintained patients on a 150 mg Q2W dosing regimen. The LONG TERM study (N=2341) was designed to provide a substantial fraction of the safety data at the maximum proposed alirocumab dose as well as sufficient numbers of patients with low LDL-C levels (defined as <25 and <15 mg/dL) to support subgroup analyses of the safety of low LDL-C. The HIGH FH study was designed in recognition that the maximal efficacious dose would be required to get LDL-C below treatment goals when baseline LDL-C levels are very high.

Open-label extension study/period or a follow-up period of 8 weeks duration: the 8-week follow-up period after the end of treatment visit was selected to allow alirocumab serum concentrations to decline well below levels that could be measured.

1.6.3.   Study Populations

Overall, 5138 patients (97.0%) were at high/very high CV risk, including 64.1% with a history of CHD. The definition of CV risk and corresponding LDL-C targets were based on US and EU guidelines in effect at the time of clinical development plan finalization.[7,17,21] European Society of Cardiology and the European Atherosclerosis Society (ESC/EAS) 2011 guidelines[7] and 2012 update[17] were used to delineate high and very high CV risk.

Three studies (FH I, FH II, and HIGH FH) exclusively enrolled heFH patients (N=795). Patients with heFH were included in several other studies including a stratum of LONG TERM in which they represented approximately 18% (N=415) of the overall population.

Overall, 2025 patients (38.2%) had mixed dyslipidemia (baseline TGs ≥150 mg/dL) and 1629 patients (30.8%) reported a history of type 2 diabetes mellitus. The mean LDL-C levels at

baseline varied across the studies between approximately 100 mg/dL and 200 mg/dL depending on the population enrolled.

The majority of patients in the program were enrolled in studies where patients were on background statin therapy with or without additional concomitant use of other LMTs. Approximately 80% of the patients (N=4219) were receiving a MTD of a potent statin at randomization. Four studies included patients not on MTD of statins. The OPTIONS I and OPTIONS II studies enrolled patients who were not adequately controlled on non-maximal doses of statins. Two studies were conducted with patients not receiving concomitant statins: ALTERNATIVE (patients with a history of statin intolerance) and MONO (as monotherapy in patients at moderate CV risk).

1.6.4.   Study Endpoints

In all studies the primary efficacy endpoint was the percent change in calculated LDL-C from baseline to Week 24. Patients who had discontinued study therapy were encouraged to return for all study visits. The primary analyses were conducted using an ITT approach with mixed-effects models with repeated measures (MMRM) which included all lipid data regardless of adherence to therapy. Analyses were also conducted using the on-treatment approach which included all lipid data when patients were adherent to treatment. Sensitivity analyses examined the effect of non-random data missingness.

Secondary efficacy endpoints in all Phase 3 studies included LDL-C at other time points (Week 12 and Week 52 if appropriate), the proportion of patients achieving pre-specified LDL-C treatment goals, and other lipid parameters, including total-C, non-HDL-C, apo B, TGs, and Lp(a), HDL-C and Apo A-1. A hierarchical testing procedure was employed to control the type I error rate for secondary endpoints at the 0.05 level. In the OPTIONS studies, alpha was split amongst the different comparators.

1.7. Overview of Efficacy of Alirocumab in Phase 3

Summary

- All studies met the primary efficacy endpoint demonstrating superior mean percent reduction from baseline in LDL-C at Week 24 by the addition of alirocumab to baseline therapy as compared to the addition of placebo or ezetimibe. LS mean percent changes in LDL-C from baseline to Week 24 were
  - In the placebo-controlled studies:
    - -48.6% with 75 mg with potential up-titration to 150 mg Q2W
    - -60.4% with 150 mg Q2W continuous dosing
  - In the ezetimibe-controlled studies:
    - -45.6 to -48.9% with 75 mg with potential up-titration to 150 mg Q2W
- At Week 12, the LS mean percent changes in LDL-C from baseline were:
  - -44.5 to -49.2% with 75 mg Q2W prior to potential up-titration to 150 mg Q2W
  - -62.6% with 150 mg Q2W continuous dosing
- The lipid-lowering effect of alirocumab was observed within 15 days after the first dose reaching maximum effect at approximately 4 weeks and was sustained throughout the treatment period.
- Most patients achieved their LDL-C goal on 75 mg dosing (73.7%) and did not require up-titration. Up-titration was associated with an additional 14.2% mean reduction in patients on a background statin and an additional 3.1% mean reduction in patients not on a background statin.
- LDL-C reductions observed with 75 mg and 150 mg Q2W doses allow for initial dose selection to be individualized, taking into account baseline LDL-C levels and CV risk status, and the goal of therapy.   Dose can be adjusted based on treatment goals and patient response to treatment. No dose adjustments are required in any sub-population beyond those potentially needed across all populations to titrate to target LDL-C.
- Reductions in LDL-C were sustained through 52 weeks. More than 80% of the Phase 3 population enrolled in studies with a minimum 52-week double-blind period.
- Similar LDL-C lowering efficacy (compared to baseline and compared to controls) was observed in heFH and non-FH populations, in patients with mixed dyslipidemia and diabetes regardless of baseline LDL-C, and in other sub-groups of interest.
- In general, treatment with alirocumab also resulted in significantly greater reductions in Total-C, non-HDL-C, Apo B, and Lp(a) as compared to placebo or ezetimibe, whether or not patients were concomitantly being treated with a statin.
- Alirocumab reduced TGs and increased HDL-C and Apo A-1 as compared to placebo.

1.7.1. Primary Efficacy Endpoint: Percent Change in LDL-C at Week 24

All ten Phase 3 studies met the primary efficacy endpoint, demonstrating superiority of alirocumab over placebo and ezetimibe controls in the percent change in LDL-C at Week 24 in the ITT population (Figure 1).

Six studies (FH I, FH II, COMBO I, COMBO II, OPTIONS I, and OPTIONS II) examined the up-titration scheme with alirocumab on top of statins with or without other LMTs. Two studies (LONG TERM and HIGH FH) used 150 mg Q2W among patients insufficiently controlled on statins with or without another LMT. The LONG TERM study included patients with and without heFH while the HIGH FH study exclusively included patients with heFH.

Finally, two ezetimibe-controlled studies (MONO and ALTERNATIVE) assessed the efficacy of alirocumab 75/150 mg Q2W in non-statin-treated patients. The MONO study enrolled patients who were on diet alone. In the ALTERNATIVE study which included patients with a history of statin intolerance, 43.3% received LMTs other than statin or ezetimibe as background therapy.

All 10 studies showed a statistically significant effect of alirocumab compared to at least one of the comparators for the primary efficacy endpoint. A summary of the week 24 primary efficacy endpoint data for all ten trials can be seen in Figure 1. All treatment differences between alirocumab and the comparators (placebo or ezetimibe) were highly statistically significant in the trials except for two treatment comparisons in OPTIONS II, where the smaller sample size was associated with more variability (Figure 12).

Figure 1:   Percent Change from Baseline in Calculated LDL-C at Week 24 in Phase 3 Studies

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	P-value	N Patients	
	Control	Alirocumab	Alirocumab - Control		Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	0.8 (1.0)	-61.0 (0.7)		<0.0001	780	1530
HIGH FH	-6.6 (4.9)	-45.7 (3.5)		<0.0001	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-2.3 (2.7)	-48.2 (1.9)		<0.0001	106	205
FH I	9.1 (2.2)	-48.8 (1.6)		<0.0001	163	322
FH II	2.8 (2.8)	-48.7 (1.9)		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-20.7 (1.9)	-50.6 (1.4)		<0.0001	240	467
OPTIONS I	-21.4 (3.3)	-48.5 (3.2)		<0.0001	99	101
OPTIONS II	-11.6 (4.4)	-42.7 (4.3)		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-14.6 (2.2)	-45.0 (2.2)		<0.0001	122	126
MONO	-15.6 (3.1)	-47.2 (3.0)		<0.0001	51	52

-80 -60 -40 -20   0   20 40 60 80

← Favors alirocumab   Favors control →

Note: OPTIONS I and OPTIONS II are pooled results across study arms.

Sensitivity Analyses

For each study, sensitivity analyses of the primary efficacy endpoint were employed to address the potential impact of missing data. In large measure due to the efforts to keep missing data to a minimum, the method of analysis, including analyses assuming missingness was not at random (MNAR), had no impact on the overall interpretation and had minimal impact on any quantitative interpretations (see Section 8.2.4 for details).

1.7.2. Other Efficacy Measures

Summary of Mean Percent Change in LDL-C at Week 12 and 24: Comparative Efficacy of 75 mg and 150 mg doses

Table 2 summarizes the mean percent change from baseline in LDL-C with alirocumab at Week 12 (before up-titration so as to provide the efficacy of the 75 mg dose separate from that of the 150 mg dose) and at Week 24 (primary endpoint) based on ITT analyses across pooled Phase 3 placebo-controlled studies. The similarity among these studies provides the ability to compare the efficacy of the 75 mg and 150 mg Q2W doses prior to potential up-titration at Week 12. The pooled least squares (LS) mean percent changes in LDL-C from baseline to Week 12 were -44.5% with 75 mg Q2W and -62.6% with 150 mg Q2W (Table 2). Across the pooled 5 Phase 3 ezetimibe-controlled studies, the LS mean percent changes in LDL-C from baseline to Week 12 were -49.2% and -47.4% with 75 mg Q2W (alirocumab with and without background statin, respectively; see Table 11).

It was noted that the 150 mg dose produced more profound lipid lowering in the large LONG TERM study than in the small HIGH FH study; we presumed this might reflect chance due to the small sample size in HIGH FH. To pursue this, we examined the effects on the subset of heFH patients in the LONG TERM study, corresponding to those in the small HIGH FH study. In this subset of LONG TERM patients, alirocumab resulted in a -56.3% reduction in LDL-C compared to a 7.0% increase in the control patients. Thus, heFH patients appear to respond as well to alirocumab as other patients with elevated baseline LDL-C.

Table 2: **LS Mean Percent Change from Baseline in LDL-C at Week 12 (before up-titration) and Week 24 in Pooled Analyses of Phase 3 Placebo-controlled Studies in Patients on Background Statin**

Dose	Alirocumab (Additive Effect Beyond Statin)	Placebo (Additive Effect Beyond Statin)
Week 12 (secondary endpoint, before up-titration)		
75 mg[a]	-44.5 %	4.1 %
150 mg[b]	-62.6 %	1.1 %
Week 24 (primary endpoint)		
75/150 mg (up-titration studies) [a,c]	-48.6 %	4.2 %
150 mg[b]	-60.4%	0.5 %

[a] Based on pooled analyses of up-titration studies (COMBO I, FH I, and FH II). N=693 in the alirocumab group, N=350 in the placebo group.

[b] Based on pooled analyses of studies using the 150 mg Q2W dose (LONG TERM and HIGH FH). N=1601 in the alirocumab group, N=815 in the placebo group.

[c] Dose was up-titrated to 150 mg Q2W in 228 (34.5%) patients treated beyond 12 weeks.

Effects of Up-Titration

Patients who up-titrated to 150 mg Q2W (34.5% of patients) had a higher mean baseline LDL-C than patients who did not require up-titration. In the Phase 3 studies, patients on a background statin who up-titrated achieved an additional 14% mean reduction in LDL-C with 58.4% of these patients achieving at least an additional 10% LDL-C reduction. Among patients not on a

background statin, up-titration resulted in an additional 3% mean LDL-C reduction with approximately 25% of patients achieving an additional 10% LDL-C lowering.

LDL-C Treatment Goals

Regardless of the definition for the LDL-C treatment goal per the various therapeutic guidelines, a significantly greater proportion of patients receiving alirocumab achieved their goal LDL-C compared to patients in either placebo or ezetimibe control groups in nearly all treatment comparisons (see Section 8.3.2 for details and additional treatment goal definitions).

Other Lipid Parameters

In general, favorable effects of alirocumab on non-HDL-C, Apo B, Total-C, Lp(a), fasting TGs, HDL-C, and Apo A-1, based on pre-specified secondary endpoints were observed in most studies. Details can be found in Section 8.3.

1.7.3. Subgroup Analyses

In the 10 Phase 3 studies, alirocumab demonstrated consistent LDL-C reductions across age, body mass index (BMI), race, ethnicity, prior history of myocardial infarction or ischemic stroke, diabetes mellitus, moderate chronic kidney disease, free and total PCSK9 levels, baseline lipid levels, and in patients with and without heFH and mixed dyslipidemia.

Although qualitative efficacy of alirocumab compared to control, as measured by mean percent reductions in LDL-C, was observed in both men and women, a quantitative interaction for sex was present in 5 of the 10 studies, with an approximate 10% greater LDL-C-lowering in males relative to females. This difference in pharmacodynamics is not explained by differences in exposure as a slightly higher alirocumab exposure was observed for females compared to males. While the physiologic explanation for the quantitative difference in efficacy is presently not known, it should be emphasized that the qualitative efficacy in LDL-C lowering for both alirocumab dosing regimens compared to control(s) was statistically significant and clinically meaningful in both sexes.

Subgroup analyses by the 4 dose levels at randomization for each of the statins allowed as background therapy in the studies (atorvastatin, rosuvastatin, and simvastatin) showed consistent reductions in LDL-C with alirocumab regardless of the statin dose.

1.7.4. Maintenance of Effect Over the Treatment Period

In six of the 10 Phase 3 studies, representing approximately 80% of the Phase 3 population (N=4219), patients were studied for at least 52 weeks. The effect of alirocumab on LDL-C was well maintained over time in all studies. Change in LDL-C through Week 52 in the ITT populations in the LONG TERM and HIGH FH studies, which used continuous 150 mg Q2W dosing, is shown in Figure 2. Similar maintenance of effect was seen with the 75/150 mg Q2W dosing (see Figure 16).

Figure 2: **LS Mean (95% CI) Calculated LDL-C Percent Change from Baseline over Time in ITT Population with 150 mg Q2W Dosing in Pooled LONG TERM and HIGH FH Studies**
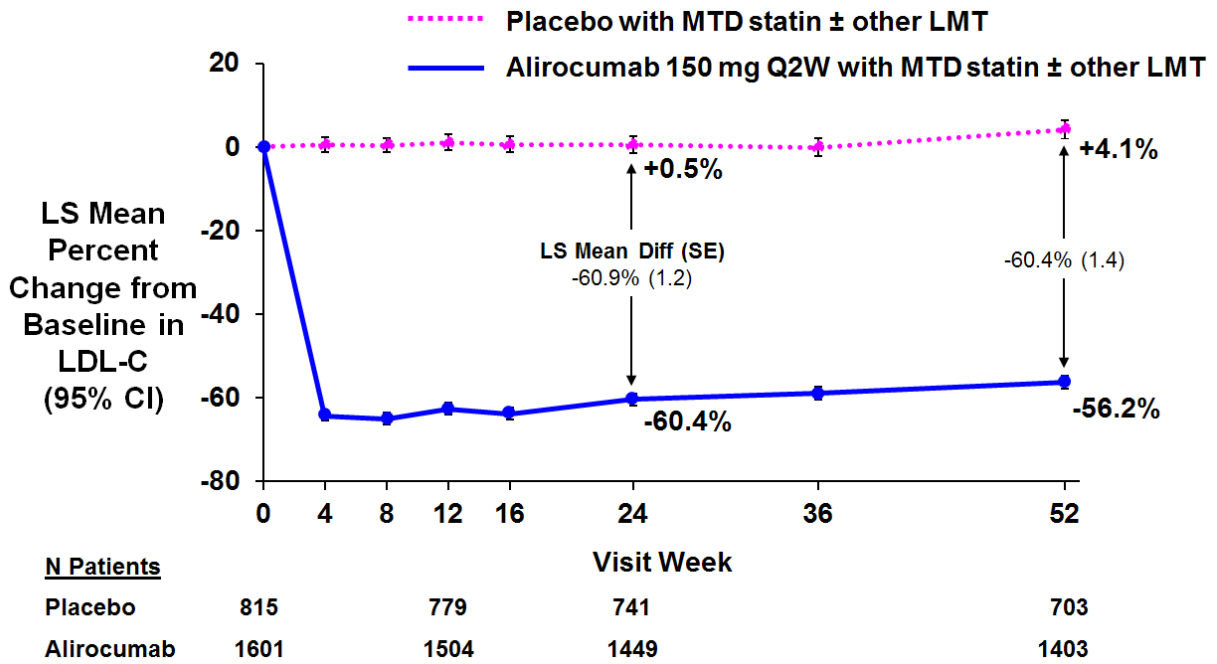
1.8. Overview of Safety

Summary

- The safety profile of alirocumab in the Phase 3 program supports a positive benefit-risk assessment.

- No dose-related signals in safety were identified.

- In total, 5234 patients from alirocumab (75 mg or 150 mg Q2W), ezetimibe and placebo groups were included in the safety pool of double-blind Phase 2/3 studies. A total of 3340 patients were exposed to alirocumab, with 2408 treated for at least 1 year and 639 for at least 18 months for a cumulative exposure to alirocumab of 3451 patient-years.

- The rates of treatment emergent AEs (TEAEs), treatment-emergent SAEs, or TEAEs leading to permanent discontinuation were similar between the alirocumab and placebo/ezetimibe groups.

- Among the common TEAEs, injection site reactions (HLT) (7.3% vs 5.2%) and pruritus (1.1% vs 0.4%) were identified as more common in patients taking alirocumab than control in multiple analyses.

- The rates of neurologic events, neurocognitive events, hepatic disorders, and clinically-meaningful changes in glycemic control were generally similar to placebo and ezetimibe in the pooled data.

- Discontinuations due to rare allergic events such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported with alirocumab. The adverse events all resolved after discontinuation of therapy and, in some cases, a short course of topical or systemic corticosteroids.

- Studies were designed to have sufficient numbers of patients with low LDL-C values to support subgroup analyses. No adverse effects were identified in patients with 2 consecutive LDL-C values <25 mg/dL (n=796) or <15 mg/dL (n=288).

- In patients with documented statin intolerance, there were fewer skeletal muscle-related TEAEs in the alirocumab arm than the statin arm.

- All-cause mortality was 0.6% in the pooled alirocumab data and 0.9% in the pooled control data. The primary cause of death (per adjudication) was CV events in the majority of these patients. There were no deaths in Phase 1 or 2 studies.

- In a pre-specified analysis of Major Adverse Cardiac Events (MACE) in the global pool of Phase 3 studies, the hazard ratio was 0.82 (95% CI: 0.54 to 1.25). For a broader endpoint that included CHF and revascularizations that also had been prespecified, the hazard ratio was 1.07 (95% CI: 0.78 to 1.46). In a post-hoc analysis of MACE in the largest study (LONG TERM), the hazard ratio was 0.52 (95% CI 0.31 to 0.90). A large ongoing study (OUTCOMES) is powered to investigate the potential benefit of alirocumab on CV mortality and morbidity.

1.8.1.   Safety Population

The pre-specified safety analyses contain all placebo- or ezetimibe-controlled safety data from the 10 Phase 3 trials and 4 Phase 2 trials described earlier through the BLA cut-off date of 31 August 2014.

The two main pools, based on the control group (placebo or ezetimibe) were considered for the analysis of all safety parameters and for signal detection. The alirocumab 75 mg Q2W and 150 mg Q2W dosing regimens were aggregated. The rationale for aggregating across doses was suggested by the completed Phase 2 studies showing no dose-related safety signals and was confirmed by the absence of dose-related trends in the Phase 3 studies.

In addition, a global pool of all studies was used to evaluate selected safety topics: deaths, injection site reactions, and AEs in patients with 2 consecutive LDL-C values <25 mg/dL or <15 mg/dL. Because independent, external CV event adjudication was not conducted in Phase 2 studies, a global subpool of Phase 3 studies was used to evaluate CV events.

1.8.2.   Safety Evaluation Plan

The analyses of safety data were based on a pre-specified statistical analysis plan (SAP) to identify possible signals in the study data and differentiate these from AEs typical for a population of patients at high or very high risk for future CV events and already taking LMT including maximally tolerated doses of statins.

This safety statistical analysis plan considered different tiers of AEs. Common adverse events were adverse events for which there were no pre-specified hypotheses. Each adverse event term was screened separately using the Cox model; those whose 95% CI of the hazard ratio excluded 1.0 were explored in greater detail. Adverse events of special interest (AESI) were those for which a pre-specified hypothesis was proposed based on the safety profile of other drugs that lower LDL-C, or theoretical concerns related either to low LDL-C or to the administration of monoclonal antibodies. For each AESI, related AE terms were combined and analyzed as a prespecified group using the Cox model and various other statistical techniques.

Questions about the safety of low LDL-C concentrations have been raised. Therefore, we prespecified analyses in patients who achieved LDL-C less than 25 mg/dL.

The data were explored to identify any relationships between TEAEs and various factors such as age, sex, and anti-drug antibody (ADA) status

1.8.3.   Protection of Patient Safety

An external independent Data Monitoring Committee (DMC) monitored on an ongoing basis, the safety of patients enrolled in Phase 2/3 studies. In addition, a second DMC was set up for the OUTCOMES study. The Chairman of the Phase 2/3 DMC is also a member of DMC of the OUTCOMES study.

A designated member of the Phase 2/3 DMC was appointed to work in collaboration with an independent academic physician to monitor the safety of patients with low LDL-C. This independent academic physician has access to unblinded lipid data and is in charge of the review of all available data for patients including patients who achieved 2 consecutive LDL-C<25 mg/dL values. The DMC member, in consultation with the independent physician,

decides whether the site needs to be alerted that a given patient has experienced two consecutive LDL-C<25 mg/dL values. Once alerted, the Investigator closely reviews the results that relates to possible consequences of low LDL-C and requests additional laboratory evaluations or specialist consultation, as needed. In order to maintain the blind, alerts sent to sites also include sham alerts.

1.8.4. Extent of Exposure

Overall, 5234 patients were exposed to study treatment (alirocumab 75mg or 150 mg: 3340, placebo only: 1276, and ezetimibe plus placebo: 618) and included in the safety analyses. The global double-blind safety database includes 3451 patient-years of exposure to 75 mg Q2W or 150 mg Q2W alirocumab and 1827 patient years of exposure to double-blind control. The median duration of patient exposure to randomized treatment was approximately 65 weeks in the placebo-controlled pool and 25 weeks in the ezetimibe-controlled pool. There were 2408 patients treated with alirocumab for at least 52 weeks and 639 for at least 76 weeks.

1.8.5. Adverse Events in Clinical Trials

Overall Adverse Event Experience

The TEAE period is defined as the time from the first dose of double-blind randomized treatment up to 70 days after the day of last dose of double-blind injection to assess the possibility of residual effect of alirocumab throughout the maximum period in which alirocumab was predicted to be measurable in serum.

The percentages of patients experiencing any TEAE, any treatment emergent SAE, and any TEAE leading to permanent treatment discontinuation were similar in the alirocumab and comparator groups (Table 3). No clinically relevant differences between the treatment groups were observed for any individual system organ class (SOC) for treatment emergent SAEs or for any TEAEs that led to permanent treatment discontinuation.

Table 3: **Overview of Adverse Event Profile in Safety Population of Placebo-controlled and Ezetimibe-controlled Studies**

AE Type	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1276)		Alirocumab (N=2476)		Ezetimibe (N=618)		Alirocumab (N=864)	
Any TEAE	975	(76.4%)	1876	(75.8%)	421	(68.1%)	607	(70.3%)
Any treatment emergent SAE	182	(14.3%)	340	(13.7%)	69	(11.2%)	113	(13.1%)
Any TEAE leading to permanent treatment discontinuation	65	(5.1%)	131	(5.3%)	60	(9.7%)	76	(8.8%)
Death on study	10	(0.8%)	18	(0.7%)	7	(1.1%)	2	(0.2%)

Most Common Treatment Emergent Adverse Events (TEAEs)

Common TEAEs were screened using the Cox model to identify those whose 95% CI of hazard ratio excluded 1. Five TEAEs were identified as having a higher incidence in the alirocumab group than the placebo group. In contrast, 11 had a higher incidence in the placebo group than the alirocumab group (Table 20). Two of these TEAEs (injection site reactions and pruritus) occurred more frequently in the alirocumab group than in the control group in both the placebo- and ezetimibe-controlled pools (Table 4).

Table 4: **Number and Percent of Patients with TEAEs Consistently Greater in Alirocumab Group in the Various Pools**

TEAE	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Injection site reactions (HLT)				
n (%)	66 (5.2%)	180 (7.3%)	13 (2.1%)	26 (3.0%)
N events per 100 patient-years	4.7	6.7	2.8	3.6
Hazard ratio versus control (95% CI)	1.47 (1.11 to 1.95)		1.58 (0.80 to 3.09)	
Pruritus				
n (%)	5 (0.4%)	28 (1.1%)	3 (0.5%)	7 (0.8%)
N events per 100 patient-years	0.3	1.0	0.7	1.0
Hazard ratio versus control (95% CI)	2.84 (1.10 to 7.36)		1.68 (0.43 to 6.59)	

HLT: high level term

Deaths

In the Phase 3 studies, deaths were reported in 20 alirocumab patients (0.6%) and 17 control patients (0.9%). The primary causes of deaths were CV events (15 [0.5%] with alirocumab, 11 [0.6%] with control). See Section 9.6 for additional details on deaths in the studies. There were no deaths in Phase 1 or Phase 2 studies.

AEs of Special Interest (AESIs)

The approach to analysis of AESI included the Cox model (stratified on study) to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the alirocumab group compared to control in the placebo- or ezetimibe-controlled pools or in the global pool for certain AESIs. The following AESI were analyzed:

- Local injection site reactions: The incidence rate per 100 patient-years (PYs) in the global pool of Phase 2/3 studies was 6.0 with alirocumab versus 4.2 with control (HR: 1.50; 95% CI: 1.15 to 1.95). All but one event were mild or moderate in severity and no serious events were reported. Local injection site reactions led to permanent treatment discontinuation in 0.2% of alirocumab-treated patients and 0.3% of control-treated patients. In the Phase 3 studies, local injection site reactions were more common in alirocumab-treated patients with positive treatment-emergent ADA than those without (10.2% versus 5.9%). Injection site reactions in ADA positive patients were all mild with only one event leading to treatment discontinuation.

- General allergic events (excluding events at the injection site): These events could be generalized or localized but did not include events at the injection site as these latter events were considered injection site reactions. In the placebo-controlled pool, the incidence rates per 100 PYs were 7.9 and 7.2 in the alirocumab and placebo groups, respectively (HR: 1.10; 95% CI: 0.87 to 1.40). In the ezetimibe-controlled pool, the incidence rates per 100 PYs were 8.4 and 7.3 in the alirocumab and ezetimibe groups, respectively (HR: 1.31; 95% CI: 0.85 to 2.02). This difference was attributed to a higher incidence of pruritus AEs which were typically mild and transient with no serious cases reported. General allergic events occurred more frequently in the first 24 weeks of treatment in the alirocumab groups. Discontinuations due to rare allergic adverse events were reported more frequently in the alirocumab; evaluation of these

cases could not exclude a possible association between alirocumab treatment and reports of nummular eczema, hypersensitivity, and hypersensitivity vasculitis. All of these resolved without clinical sequelae after discontinuation of alirocumab and, in some cases, treatment with a short course of corticosteroids.

- Neurologic events (focusing on potential myelin sheath-related disorders): We looked at the effect of treatment on myelin-dependent adverse events. The central nervous system synthesizes all the cholesterol it needs and is therefore not dependent on LDL-C, and monoclonal antibodies are too large to pass the blood brain barrier. So, if there are effects, we would only expect them to be in the peripheral nervous system. There was no observed imbalance between treatment groups for any particular adverse event with regard to prespecified neurologic events. In the placebo-controlled pool, the incidence rates of neurologic events were 3.1 and 3.2 per 100 PY for patients in the alirocumab and placebo groups, respectively (HR: 0.98; 95% CI: 0.68 to 1.41). In the ezetimibe-controlled pool, the rates per 100 PY were 4.0 in the alirocumab group and 3.3 in the ezetimibe group (HR: 1.43; 95% CI: 0.76 to 2.69).

  Three standardized MedDRA queries (SMQs) were included in the AESI of neurologic events: demyelination, "Guillain-Barre" category, and peripheral neuropathy. The incidence of TEAEs in the latter 2 SMQs, representing peripheral neurologic events, was balanced between treatment groups. There was an imbalance in the demyelinating SMQ: 5 patients in the alirocumab groups compared to none in the controls. Looking at the demyelination category in more detail, we see individual events that have different pathologic mechanisms and that are not unexpected for this patient population. Two patients had trigeminal neuralgia, which is usually due to nerve compression and one had optic perineuritis, which, in this patient population, would typically be due to giant cell arteritis. A single case each of multiple sclerosis and transverse myelitis is consistent with the expected incidence rates for the patient population studied. Narratives are provided in Section 13.5. Thus, there does not appear to be a safety signal. However, these types of rare events will be further evaluated in the ongoing OUTCOMES study.

- Neurocognitive disorders: Because of the blood-brain barrier, the brain and central nervous system do not access lipoproteins produced peripherally (by the liver and intestine) but instead have the ability to produce cholesterol required for neuronal cell function. Nonetheless, neurocognitive events have been described in post-marketing use of statins. A mechanism for this, independent of LDL-C, has not been elucidated. Neurocognitive adverse events in the alirocumab program were analyzed using 2 different groupings of MedDRA terms. The first was a broad company MedDRA query (CMQ) that the Sponsor proposed and the second was a more focused set of terms that the FDA proposed. In the placebo- and ezetimibe-controlled pools, neurocognitive events were reported overall at a low incidence and were similar between the alirocumab and control groups using both FDA's and Sponsor's CMQ. In the placebo-controlled pool, neurocognitive events were reported in 0.8% and 0.7% of patients in the alirocumab and placebo groups, respectively (HR: 1.18; 95% CI: 0.54 to 2.58) using the Sponsor's CMQ and in 0.8% and 0.9% of patients in the alirocumab and placebo groups, respectively (HR: 0.96; 95% CI: 0.46 to 2.00)

using the FDA's query. In the ezetimibe-controlled pool, the HR was <1.0 in both the analyses. Moreover, there was no meaningful difference in in the incidence or type of events in alirocumab-treated patients who experienced 2 or more consecutive LDL-C values <25 mg/dL compared to those who did not. In the LONG TERM study, which was the largest of the four 78-week studies included in the placebo-controlled pool, neurocognitive events occurred at a higher rate in the alirocumab group compared to the placebo group using the Sponsor's CMQ, but not with the FDA's query. Overall, the majority of the analyses suggest that the incidence of neurocognitive events with alirocumab use is similar to control. However, there were only 29 patients with these events in the alirocumab groups combined. With an expected 60,000 patient-years of follow-up, the OUTCOMES study is expected to provide sufficient data for more robust analyses of these rare events. To this end, we have made neurocognitive events an AESI in this study and are enlisting a group of outside experts to advise us on the collection of these data, blinded to treatment and LDL-C level. The expert group will issue quarterly report for the DMC and provide analysis after the data are unblinded.

- Diabetes Mellitus: Increases in HbA_{1c} and fasting serum glucose levels have been reported with statins in recent CV outcomes trials. Given these reports, the potential relationship of alirocumab use to glycemic control was analyzed in the safety database. The approach used a variety of methods: analysis of diabetes-related TEAEs, overall changes in mean levels of HbA_{1c}, and shifts in glucose control status as determined by changes in levels of fasting glucose and HbA_{1c}. The data do not suggest a clinically meaningful effect of alirocumab on glycemic control (see Section 9.9.6).

- Hepatic disorders: Hepatic disorder TEAEs (including single elevations of ALT reported as a TEAE) were infrequent with incidence rates per 100 PYs of 2.2 and 1.6 in the alirocumab and placebo groups, respectively (HR: 1.36; 95% CI: 0.84 to 2.20). In the ezetimibe-controlled pool, the incidence rates were 2.2 in the alirocumab group and 3.1 in the ezetimibe group (HR: 0.69; 95% CI: 0.34 to 1.43). Most of the imbalance in the placebo-controlled pool were reports of the TEAE "ALT increased"; however, there was no corresponding imbalance in patients with increases in ALT >3x upper limit of normal (ULN) or >5x ULN. No cases of combined increase of ALT and bilirubin not due to clearly identifiable causes (Hy's law) were seen.

- Musculoskeletal related disorders: In the placebo-controlled pool, 15.1% of patients in the alirocumab group versus 15.4% of patients in the placebo group experienced a skeletal muscle-related TEAE. A skeletal muscle-related TEAE leading to permanent treatment discontinuation occurred in 0.4% of patients in the alirocumab group and 0.5% in the placebo group. One case of rhabdomyolysis in the alirocumab group was related to trauma; this case resolved with hydration. A second case (elevation of creatinine phosphokinase [CPK] 5x ULN) was initially reported as "rhabdomyolysis", but subsequently re-coded by the investigator as "myositis" after the BLA cut-off date. Clinically meaningful changes in CPK levels were not associated with alirocumab use.

The ALTERNATIVE study was designed to evaluate alirocumab as a therapy for patients with statin intolerance and was based on a history of statin-related musculoskeletal side effects to 2 or more statins with at least one administered at or below the lowest approved dose. In ALTERNATIVE, there were fewer patients with skeletal muscle-related TEAEs in the alirocumab group than the atorvastatin (HR: 0.61; 95% CI: 0.38 to 0.99) or ezetimibe (HR: 0.70; 95% CI: 0.47 to 1.06) groups. Fewer patients in the alirocumab group discontinued in the study for musculoskeletal AEs compared to the atorvastatin group (15.9% versus 22.2%).

- Cardiovascular events confirmed by adjudication: Cardiovascular events in the Phase 3 clinical program and all deaths were adjudicated by an independent cardiovascular Clinical Events Committee (CEC) (see Section 9.2.3). Several composite endpoints were pre-specified in the Phase 3 global pool. The composite Major Adverse Cardiac Events (MACE) endpoint included CHD death, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, and unstable angina requiring hospitalization (with definite evidence of progression of ischemic condition). The composite MACE endpoint is the primary efficacy endpoint in the ongoing OUTCOMES study as agreed to by FDA. An additional composite endpoint included MACE plus Congestive Heart Failure leading to hospitalization and Revascularization procedures due to ischemia.

  In the global pool, which compared alirocumab data with combined data from both the ezetimibe and placebo controls, 94 MACE events (58 [1.8%] patients in the alirocumab group and 36 [2.0%] patients in the control group) were confirmed with a hazard ratio (95% CI) of 0.82 (0.54 to 1.25). With regard to other pre-specified events confirmed by adjudication, coronary revascularization procedures was adjudicated at somewhat higher frequency in the alirocumab group than in the comparator group (2.5% of alirocumab-treated patients and 2.0% in the control group). Including these events in the composite, the hazard ratio (95% CI) was 1.07 (0.78 to 1.46). We will look at these further in the ongoing OUTCOMES study.

  The single largest study contributing to the analyses of adjudicated CV events was the LONG TERM study. In a post-hoc analysis of LONG TERM there was a lower rate of MACE in the alirocumab 150 mg Q2W group compared to placebo with a hazard ratio (95% CI) of 0.52 (0.31 to 0.90).

Adverse Events in Patients with LDL-C <25 mg/dL

There is scant information in the clinical literature on the safety of very low levels of LDL-C. The controlled studies for alirocumab were designed to evaluate the safety of alirocumab in patients who achieved low LDL-C values and the LONG TERM study was designed to ensure that there were an adequate number of patients who achieved LDL values below 25 mg/dL. Overall, in the global pool, 1371 patients treated with alirocumab (41.0%) had at least 1 value of LDL-C <25 mg/dL including 23.8% who had 2 or more consecutive LDL-C levels <25 mg/dL. Approximately 70% of patients with these low LDL-C values were in the LONG TERM study, in which patients in the alirocumab arm received 150 mg throughout the duration of the study.

The rates of TEAEs at the MedDRA SOC and PT levels among patients in the alirocumab group with 2 consecutive LDL-C values <25 mg/dL were compared to the rates in patients in the

alirocumab group who did not have these low LDL-C values. Interpretation was limited because of baseline differences in these post-randomization subgroups. Patients who developed low LDL-C were older, had higher BMI, were mostly male, more likely to have a history of MI or stroke, and had lower baseline LDL-C values than patients who did not develop low LDL-C. 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. To correct for these differences, a propensity analysis was performed in the global pool of Phase 3 studies, similar to the one done for the JUPITER study[22] where the risk of a patient developing a particular AE of interest is adjusted based on the differences in baseline factors. The result is a hazard ratio and 95% CI for the risk of developing the AE of interest in alirocumab-treated patients with 2 or more LDL-C values < 25 mg/dL compared to the alirocumab-treated patients who did not achieve these low LDL-C values. This approach identified no excess risk for developing neurological (HR: 0.49; 95% CI: 0.26 to 0.93), neurocognitive (HR: 0.38; 95% CI: 0.12 to 1.21) or diabetes-related (HR: 1.17; 95% CI: 0.74 to 1.83) events in alirocumab-treated patients with LDL-C <25 mg/dL compared to those who did not have these low values.

One case was sufficiently unusual to merit further discussion. A 47 year old man with baseline LDL-C value of 94 mg/dL received alirocumab 150 mg Q2W per protocol in the LONG TERM study. His LDL-C values were in the 15 to 30 mg/dL range until week 24 when he experienced a calculated LDL value of 1.5 on Day 168. He subsequently developed symptoms of gastroenteritis, followed by the Miller Fisher variant of Guillain-Barre syndrome on Day 190. Investigational product was discontinued. His symptoms quickly began to resolve after intravenous immunoglobulin treatment, and completely resolved over 7 months. As this onset and recovery is typical of Miller-Fisher syndrome, external experts concluded that the low LDL-C is unlikely to be a causative factor.

Dose and Exposure-Related Effects

Both the 75 mg and 150 mg dosing regimens were well tolerated. No dose-related signals were observed for the percentages of patients who reported TEAEs, serious TEAEs, individual TEAEs, or TEAEs leading to permanent treatment discontinuation with either dosing regimen.

No AEs were associated with long-term treatment with alirocumab.

1.9.   Overall Conclusions

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of death and disability in the Western world. The principle of treatment for patients with high cardiovascular risk is risk factor modification including reduction in LDL-C, which is a cornerstone of pharmacologic therapy. A wealth of epidemiologic, genetic, and clinical trial data demonstrate that reductions in LDL-C are directly related to reductions in CV risk. Accordingly, LDL-C lowering has been considered a well-validated treatment strategy for cardiovascular benefit and has been accepted for drug approval by the FDA and other regulators world-wide. Despite the availability and use of statins and ezetimibe for hypercholesterolemia, current treatment options do not always provide sufficient efficacy for patients to eliminate the excess cardiovascular risk attributable to their LDL-C level.

Alirocumab has been assessed in an extensive clinical program that includes 10 Phase 3 double-blind, randomized controlled trials with best standard of care therapies (potent statins at the maximally tolerated dose in the vast majority of the studies, with or without other LMTs) and as monotherapy or in combination with a non-statin LMT.

Overall, the alirocumab clinical program demonstrated that alirocumab is well-tolerated and provides substantial reductions in LDL-C for a population of patients whose LDL-C is not adequately controlled with existing therapies including heFH patients, high CV risk patients on maximally tolerated doses of statins, and patients who cannot tolerate statins.

Although an 18,000-patient cardiovascular outcomes study is ongoing to assess the potential CV benefit of alirocumab and to further study adverse events of interest and rare events, it is proposed that alirocumab be approved before the results of the outcome trial are available. LDL-C reduction has been accepted for drug approval by the FDA and other regulators world-wide. Public statements by FDA as recent as 2013 indicate that their position on LDL-C had not changed.[15] Approval at this time is based on the unmet needs of patients for additional LDL-C lowering, the demonstration of substantial LDL-C lowering by alirocumab, and an acceptable safety profile. As described in this briefing book, the product offers an innovative treatment option for a variety of patients such as heFH patients, patients with high CV risk who are not well controlled, including those receiving a maximally tolerated dose of statin, and patients who cannot tolerate statins.

2.   PROPOSED INDICATION AND DOSING

2.1.   Proposed Indication

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to diet and other non-pharmacologic measures has been inadequate.

Alirocumab (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 (TGs), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo A-1).

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

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

Limitations of Use

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

2.2.   Proposed Dosing

The usual starting dose for PRALUENT is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks.

The dose of PRALUENT can be individualized based on patient characteristics such as goal of therapy and response. Lipid levels can be assessed as early as 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dosage adjusted accordingly.

2.3.   Dosage Forms and Strengths

Alirocumab is supplied in a 1-mL single-use pre-filled pen (PFP) or pre-filled syringe (PFS). Each PFP or PFS is designed to deliver 75 mg or 150 mg of alirocumab.

3.   LDL-C AND CARDIOVASCULAR RISK

LDL-C plays a central role in the clinical treatment guidelines for atherosclerosis and cardiovascular disease (ASCVD) and coronary heart disease (CHD). A comprehensive body of research, including studies in human genetics, longitudinal observational studies and preclinical mechanistic studies, has demonstrated the impact of elevated LDL-C levels on the development and progression of atherosclerosis. Interventional studies, including long term, event driven randomized clinical outcomes trials have repeatedly demonstrated that lowering LDL-C reduces the risk of cardiovascular events supporting LDL-C reduction as a valid surrogate for CHD risk reduction.[10-13]

There are multiple lines of evidence to support this:

- Animal studies show that increases in LDL-C can initiate and progress atherosclerotic lesions and that lowering LDL-C decreases atherosclerotic burden. Early studies demonstrated that either heritable or dietary changes that resulted in elevated LDL-C in rabbits and other animal models could produce arterial lesions with the characteristics of human atherosclerotic lesions. More recently, the apoE-knockout mouse models have become a standard model for demonstrating the impact of elevated atherogenic lipids on atherosclerotic lesion development and progression and illustrating the impact of lipid-lowering compounds to reduce LDL-C and total cholesterol levels and slow the progression of this disease process in a predictable fashion.

- Numerous (human) epidemiological studies have established that elevations in LDL-C result in increased risk for major cardiovascular events. These studies have consistently shown a strong, continuous relationship between levels of cholesterol and risk for CVD. For example, in one of the largest studies, MRFIT examined over 350,000 subjects initially free of CHD and found a 3.4 fold higher risk in the subjects at the highest quintile of total cholesterol (>245 mg/dL) than those at the lowest quintile of total cholesterol (<182 mg/dL).[23]

- Studies of human genetics demonstrate that mutations that result in changes in LDL-C directly result in differences in cardiovascular risk in a number of different ways.

  - For example, mutations in the LDLR, PCSK9 or apoB can result in familial hypercholesterolemia with its resultant premature CVD. This is most evident by studies of patients with heterozygous (HeFH) or the more severe homozygous familial hypercholesterolemia (hoFH). Prior to the introduction of statins, examinations of the FH population in the UK demonstrated a 100-fold increased risk for CHD mortality in patients aged 20-39 years.[24] A recent examination of subjects with HoFH found that these greatly affected individuals, experience their first cardiovascular event at age 20,[25] an age at which most subjects are generally free of other cardiovascular risk factors, thus distinctly demonstrating the singular role of LDL-C in progressing atherosclerosis that precipitates CV events.

  - Complementing the data on human genetics of FH, Mendelian randomization studies have demonstrated that loss-of-function mutations in genes that result in

lower LDL-C levels (including PCSK9 and HMG CoA reductase) result in lower rates of CHD in adulthood as compared to non-affected individuals. [32] Specifically in regard to the PCSK9 mutations, subjects with loss-of-function mutations have demonstrated LDL-C levels that are 28% (mutation Y142X or C679X) and 10-14% (mutation R46L) lower than unaffected individuals and result in rates of CV disease that are 88% and 42% lower, respectively, than the control population.[26,27] The similarities between mutations in different genes affecting LDL-C levels and their impact on CV risk have led to the general rule that a lower lifetime exposure to LDL-C results in a lower risk of CV events, with every 1 mmol/L (38.6 mg/dL) decrease in LDL-C resulting in a 55% lower risk for CV events.[28]

These data demonstrate that multiple genetic mechanisms of LDL-C lowering reduce CV risk and speak to the relationship of LDL-C to CV risk regardless of the mechanism that impacts the cholesterol levels.

- Finally, numerous <u>clinical studies</u> have demonstrated that pharmacologically reducing LDL-C levels, mainly with statins, reduces the risk of CHD, demonstrating both a strong direct relationship between the amount of LDL-C lowering and the degree of CVD risk reduction as well as between achieved LDL-C levels and incidence of CVD events. Recent data from the IMPROVE-IT study extend the benefits of lowering LDL-C to a non-statin agent, further supporting the principle linking LDL-C reductions to reductions in CV risk. In this study, patients with recent acute coronary syndrome were treated with statin or statin plus ezetimibe. Ezetimibe was shown to provide an additional 6.4% relative reduction in risk for CV events when used with a statin compared to a statin alone.[14] A large patient-level meta-analysis of nearly 170,000 individuals from 26 statin CV outcomes trials demonstrated a relationship between the reduction in LDL-C and CV risk reduction – with every 1 mmol/L (38.6 mg/dL) reduction translating to a 22% reduction in major CV events[29] The data from IMPROVE-IT are generally consistent with this relationship and extend the benefit to a mean LDL-C levels as low as approximately 50 mg/dL. Post-hoc analyses from these outcome studies extend this benefit to somewhat lower LDL-C levels (approximately 40 mg/dL)..

The assumption of a benefit on CV risk by inhibiting PCSK9 is further supported by CV event data from individuals with PCSK9 mutations; gain-of-function mutations in the PCSK9 gene have been identified in patients with increased LDL-C levels and a clinical diagnosis of familial hypercholesterolemia.[30] In contrast and as mentioned above, individuals with loss-of-function mutations in PCSK9 have significantly decreased levels of LDL-C and lower CV risk than seen in the overall population.[27] A few individuals have been reported to carry PCSK9 loss-of-function mutations in 2 alleles and have profoundly low LDL-C levels, with HDL-C and triglycerides (TGs) levels in the normal range.[31] Furthermore, consistent with the human genetics findings, antibody-blockade of PCSK9 in animal models of atherosclerosis can profoundly decrease the atherosclerosis, alone and in combination with statins.

Thus, it is likely that antibody-based therapeutics that lower LDL-C by blocking PCSK9 and increasing the number of LDLR, would decrease CV risk in humans.

4. UNMET MEDICAL NEED AND RATIONALE FOR PRODUCT DEVELOPMENT

4.1. Unmet Medical Need

Atherosclerotic cardiovascular disease (ASCVD), especially coronary heart disease (CHD),[7-9] remains the leading cause of death and disability in the Western world.[2,3] Approximately one third of deaths are due to cardiovascular disease with half due to CHD specifically (2014 AHA report[2]). In the US, approximately 16 million people have CHD. Intervention is focused on reducing excess risk and modifying risk factors. The accumulation of LDL-C in arterial walls is a central aspect of the initiation and progression of atherosclerosis and reducing LDL-C is a foundational component of treatment for most patients.

Statins are the most potent available therapy for lowering LDL-C and can provide dose-dependent reductions of up to approximately 50% from baseline. In contrast, non-statin therapies including ezetimibe provide less efficacy, demonstrating approximately 15-20% reduction as monotherapy or in addition to statin therapy. Current guidelines in the US focus on the use of high intensity statins to achieve >50% reductions in LDL-C in individuals at high risk for ASCVD.

Despite availability and use of these drugs, many individuals remain at high risk for ASCVD due to elevated LDL-C, including patients with heterozygous familial hypercholesterolemia; previous CVD events; multiple risk factors, including diabetes; or patients who do not tolerate statin therapy. Therefore, a substantial need exists for new therapies able to lower LDL-C levels.

Heterozygous Familial Hypercholesterolemia

Heterozygous familial hypercholesterolemia (heFH) is a common genetic cause of increased LDL-C levels and associated cardiovascular risk due to mutations in the LDL receptor gene, Apo B gene, and gain-of-function mutations in the PCSK9 gene. Patients with heFH have untreated LDL-C levels often between 200 and 400 mg/dL; prevalence may be as high as 1:250 to 1:200.[7,32] Recent ACC/AHA guidelines recommend high intensity statin therapy for all adults with primary LDL-C of at least 190 mg/dL recognizing that "maximal statin therapy might not be adequate to lower LDL-C sufficiently to reduce ASCVD event risk in individuals with primary severe elevations of LDL-C" and "non-statin cholesterol-lowering therapies are often needed to lower LDL-C to acceptable levels in these individuals".[9] As noted above, non-statin therapies provide only modest LDL-C lowering in combination with statins. Highly effective treatment options capable of meaningful lowering of LDL-C on top of statins are needed for heFH patients.

High Risk Patients with Elevated LDL-C on Maximal Tolerated Statins

High intensity statins (lowering LDL-C by approximately $\geq 50\%$) are recommended for individuals with clinical ASCVD and thus at increased risk for recurrent events and for primary prevention in all patients with type 1 or type 2 diabetes and those with an increased 10-year risk of ASCVD.[9] While the ACC/AHA guidelines do not recommend a specific LDL-C target goal, a specific LDL-C value (> 70 mg/dL) is recommended as criteria for considering patients uncontrolled and for instituting high intensity statins in this high risk group. According to this

guideline, the aim of high intensity statin therapy is to reduce LDL-C by >50% from untreated baseline by further intensification of statins or by the addition of non-statin LMTs in patients not achieving an anticipated response to statins. In practice, over half of patients with ASCVD at high risk for events did not lower LDL-C to specific target goals (<70 mg/dL in this population) as recommended previously by National Cholesterol Education Program – Adult Treatment Panel III (NCEP ATP-III)[33] and which have been retained by the National Lipid Association.[16] Thus there is a need for additional LDL-C lowering options to reduce the excess cardiovascular risk attributable to uncontrolled LDL-C level in patients at high risk for ASCVD events.

High Risk Patients with Elevated LDL-C Intolerant of Statins

The ACC/AHA guidelines recommend the use of non-statin therapies for high risk patients who have a less-than-anticipated response to statins, who are only able to tolerate a less-than-recommended intensity of statins or who are completely statin intolerant.[9] It is estimated that 10 to 15% of patients treated with high-dose statins show some degree of intolerance with many of these patients discontinuing statins due to muscle pain or weakness.[34] The therapeutic options for these patients are limited and include restarting on a lower dose or using a less potent statin, or treating with non-statin agents. Often these options will not provide sufficient LDL-C lowering for patients experiencing intolerance to statins.[35]

4.2.   Alirocumab Mechanism of Action

Alirocumab is a fully human monoclonal antibody (mAb) (IgG1 isotype) that binds with high affinity and specificity to PCSK9, resulting in LDL-C lowering.

The LDLR is the major pathway through which cholesterol-rich LDL particles are cleared from circulation and hepatic LDL uptake is thus a major determinant of circulating LDL-C levels. PCSK9 is secreted from cells following synthesis and autocatalytic cleavage and binds to LDLR on the surface of hepatocytes. By inhibiting the binding of PCSK9 to the LDLR, alirocumab increases the number of LDLR available to clear LDL particles, thereby lowering LDL-C levels. When an internalized LDLR is bound to PCSK9, the LDLR is trafficked to the lysosome, promoting the degradation of the LDLR and preventing its recycling to the cell surface (Figure 3).

Figure 3:   PCSK9-mediated Degradation of LDLR
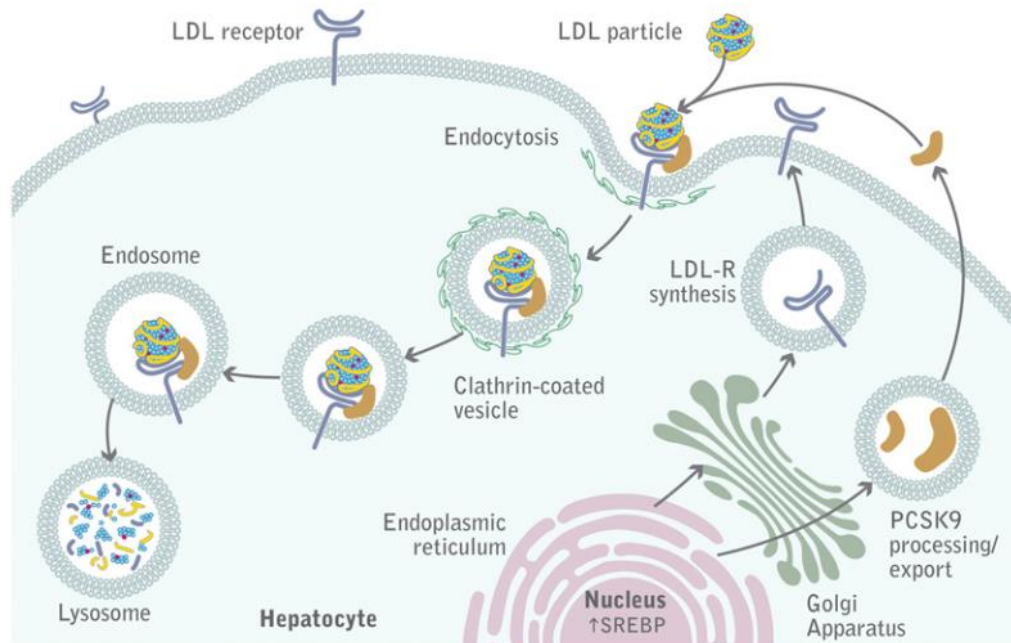
The mechanism by which alirocumab lowers LDL-C (i.e., via an increase in cell surface LDLR expression) is similar to that through which statins lower LDL-C. Statins also increase LDLR numbers on the surface of hepatocytes, but do so by inhibiting HMG CoA reductase. This results in an increase in the activity/nuclear translocation of sterol regulatory element-binding-protein-2 (SREBP-2), which increases transcription of the LDLR gene.[20] The increase in LDLR expression is the central mechanism by which statins lower LDL-C.

SREBP-2 also induces the expression of PCSK9, thus potentially limiting the ability of statins to increase LDLR and reduce LDL-C. Although blocking PCSK9 activity by alirocumab increases LDLR expression and thereby decreases circulating LDL-C whether or not statins are present, the effect in the presence of statins is greater given the ability of statins independently to increase LDLR expression.

Separate from these effects on LDLR and LDL-C, the statin-induced increase in PCSK9 production hastens the target-mediated clearance of alirocumab. Thus, although alirocumab efficacy is greater when coadministered with statins, statins potentially lessen the duration of maximal efficacy. Nonetheless, with the Q2W dosing proposed in the current application, no dosage adjustment is necessary when alirocumab is used with or without statins.

Statins and PCSK9 inhibitors thus ultimately reduce LDL-C in a similar manner, i.e., through an increase in LDLRs on the cell surface. Their similar mechanisms of action suggest that the CV benefit afforded by statins may well also manifest via the inhibition of PCSK9. This assumption is supported by CV event data from individuals with PCSK9 mutations and the Mendelian randomization studies discussed in Section 3.[28] Thus, it is likely that antibody-based therapeutics that lower LDL-C by blocking PCSK9 and increasing the number of LDLR will also decrease CV risk.

4.3. Non-clinical Pharmacology

The ability of alirocumab to lower LDL-C and other lipids was tested in a number of preclinical animal models. In mice expressing human PCSK9 and fed a high carbohydrate diet to generate dyslipidemia, alirocumab was effective in reducing diet-elevated LDL-C levels down to pre-diet baseline levels. In hamsters, which have a higher basal LDL-C level than mice, subcutaneous administration of alirocumab was equally effective in reducing LDL-C by approximately 60%. Administration of alirocumab in exploratory single dose PK/PD studies in non-human primates resulted in profound lowering of LDL-C. Animals subcutaneously administered REGN727 demonstrated approximately a 75% decrease in LDL cholesterol levels relative to baseline for up to 18 days following a single 5 mg/kg dose. Alirocumab was shown to be effective in all of these animal models in reducing elevated LDL-C in a dose-dependent fashion. Thus, alirocumab is a potent, fully human, monoclonal antibody that acts to inhibit PCSK9 function in both in vitro and in vivo preclinical settings.

The impact of hypercholesterolemia and the effect of alirocumab on slowing the progression of atherosclerosis was studied in the apoE*3Leiden.CETP mouse. This is a well-established model of hyperlipidemia and atherosclerosis, shares a number of characteristics with human dysbetalipoproteinemia, and is predictive of what is observed in humans with established lipid-lowering therapies.[36,37] In this study, alirocumab was administered at two dose levels, 3 or 10 mg/kg, alone or in combination with atorvastatin 3.6 mg/kg/day for 18 weeks. Treatment with alirocumab alone in this animal model resulted in reduction of total cholesterol of -37% and -46% at the 2 dose levels with further reductions observed in combination with atorvastatin (-48% and -58% at the 3 mg/kg and 10 mg/kg dose levels of alirocumab, respectively). Alirocumab alone dose-dependently decreased atherosclerotic lesion size by -71% and -88% at the 3 mg/kg and 10 mg/kg dose levels, respectively. This effect was enhanced by the combination with atorvastatin where reductions in atherosclerotic lesion area was reduced by -89% and -98% at the two doses of alirocumab.

5.   SAFETY PHARMACOLOGY AND TOXICOLOGY RESULTS

Summary

- Nonclinical toxicology studies with alirocumab showed no signals on general toxicology parameters, reproductive tissues or on embryofetal growth and development.
- Safety pharmacology studies indicate that treatment with alirocumab would not increase susceptibility to HCV infection

5.1.   Toxicology Results

Alirocumab was evaluated in a comprehensive biosafety testing program consistent with international guidelines, the claimed indication, the intended route of administration and the duration of treatment proposed in humans. Overall, there were no toxicologically significant effects in animal toxicology studies of alirocumab alone or in combination with atorvastatin. The only consistent effect was a sustained reduction in LDL-C, which was considered non-adverse and related to the pharmacologic mechanism of action. No adverse effects of alirocumab were observed on surrogate markers of male or female reproductive function or on reproductive organs during any animal toxicology study. No adverse effects on fetal or postnatal growth and development were observed during an embryofetal development study in rats or a pre- or post-natal development study in monkeys. Based on animal data, alirocumab is not predicted to increase the risk of developmental abnormalities in humans.

Optic nerve atrophy/degeneration was observed in the 26-week rat study, secondary to traumatic injury to the eye due to the retro-orbital blood collection procedure used in the study and the large number of retro-orbital bleeds required per study protocol. Chorioretinal lesions were observed during ophthalmological examinations in the 26-week monkey study at a similar incidence in treated and control animals. Although both of these eye findings were considered to be unrelated to the administration of alirocumab, the Sponsor included ophthalmologic assessment as an AESI in the Phase 3 program (see Section 9.9.7).

5.2.   Safety Pharmacology

Safety pharmacology endpoints (e.g., cardiovascular, respiratory, and central nervous system evaluations) were integrated into the toxicology studies conducted in rats and cynomolgus monkeys. Additionally, a series of in vitro and in vivo experiments were conducted to evaluate the relationship between PCSK9 and CD81, a major component of the Hepatitis C virus (HCV) entry complex. HCV entry into hepatocytes involves the interaction of the virion with numerous host cell proteins, including the tetraspanin CD81.[38] In 2009, it was reported that over-expression of a form of PCSK9 engineered to be non-secreted and cell membrane-bound could decrease surface expression of CD81 in vitro.[39] However, while LDLR levels are reduced in the presence of increasing levels of PCSK9, there is no correlation between the presence and amount of secreted, soluble PCSK9 and total or surface CD81 levels. Similarly, antibody blockade of PCSK9 using alirocumab had no impact on CD81 levels, while LDLR levels were restored in the presence of alirocumab. Addition of soluble PCSK9 or treatment with alirocumab had no effect

on the ability of HCV pseudoparticles to enter hepatocytes, on HCV genome replication kinetics or on the full HCV replication cycle. The data demonstrate that alirocumab has no effect on CD81 levels and that soluble PCSK9 and alirocumab do not alter any stage of the HCV replication cycle. Treatment with alirocumab is not expected to be associated with increased susceptibility to HCV infection. Hepatitis C virus status was monitored in the Phase 3 clinical program.

6. CLINICAL PHARMACOLOGY

Summary

- The pharmacokinetics of alirocumab is described by both linear and target-mediated kinetics.
- Clinical pharmacology data demonstrate that alirocumab treatment results in a large decrease in LDL-C through binding and inhibition of PCSK9. A dose-dependent reduction in LDL-C is observed until alirocumab concentrations are sufficient to maximally bind all available PCSK9. Upon saturation of PCSK9 binding, LDL-C reductions were generally between 55-70%.
- Statins and to a lesser extent, other LMTs, cause an increase in both LDLR and PCSK9 expression. This results in an increased clearance of alirocumab through the target-mediated pathway leading to a shorter duration of maximal LDL-C reduction. This impact of statin co-therapy is mitigated by the up-titration dosing scheme and the 150 mg Q2W dosing regimen used in Phase 3 studies.
- Studies using alirocumab in combination with statins (or other LMTs) show greater LDL-C reduction than with alirocumab monotherapy.
- Population pharmacokinetic (POP PK) and pharmacodynamics (PD) analysis did not identify any specific patient population characteristic that required a change in dosing recommendation beyond that accommodated by the up-titration scheme.

6.1. Clinical Pharmacology

A total of 19 studies provide clinical pharmacology data (ten Phase 1, five Phase 2, and four Phase 3 studies).

6.1.1. Pharmacokinetics

After subcutaneous (SC) administration of 50 mg to 300 mg alirocumab, median times to maximum serum concentrations (t_{max}) were 3-7 days. The pharmacokinetics and exposures to alirocumab after single SC administration of 75 mg into the abdomen, upper arm, or thigh were similar. The absolute bioavailability of alirocumab after SC administration was about 85% as determined by population pharmacokinetics analysis. Steady state was achieved after 2 to 3 doses with an accumulation ratio of about 2-fold without regard to dose level. Across Phase 3 studies, a slightly greater than dose proportional increase was observed at steady-state, with a 2.1- to 2.7-fold increase in total alirocumab concentrations for a 2-fold increase in dose (75 mg Q2W vs. 150 mg Q2W).

Following intravenous (IV) administration, the volume of distribution was about 0.04 to 0.05 L/kg indicating that alirocumab is distributed primarily in the circulatory system.

The pharmacokinetics of alirocumab is characterized as non-linear with target-mediated elimination. At lower systemic concentrations of alirocumab, the target-mediated pathway is predominant resulting in concentration-dependent and non-linear kinetics. With increasing systemic concentration of alirocumab sufficient to bind the available PCSK9, the target-mediated

pathway becomes saturated and the elimination of alirocumab is predominantly by non-saturable proteolytic catabolism resulting in linear kinetics with continuing increases in dose and systemic concentrations of alirocumab.

Based on POP PK, at subcutaneous doses of 75 mg Q2W or 150 mg Q2W monotherapy, the median apparent half-life of alirocumab at steady state was 17 to 20 days over the dosing interval. When alirocumab is administered in combination with statins (or other LMTs), which are known to increase the production of PCSK9, an enhanced target-mediated elimination phase is observed, resulting in a more rapid clearance, compared to alirocumab administered as monotherapy. When co-administered with a statin, the median apparent half-life of alirocumab at steady-state is approximately 12 days over the dosing interval.

6.1.1.1.   Population Pharmacokinetic Analysis

A POP PK model was developed which included clinical data from 14 studies (Phase 1 to Phase 3). All populations, doses, and background medications (i.e. alirocumab used as add-on to maximally tolerated statins only, statin plus other LMTs, monotherapy or as an add-on to non-statin LMTs alone) assessed in this clinical program where included in this model. The base model used to characterize the PK of alirocumab was a 2-compartment Michaelis-Menten model with first order absorption, and parallel linear (non-saturable) and nonlinear (saturable) elimination pathways. This base model was further used to develop a covariate model to investigate the influence of demographic factors, free and total PCSK9 levels, and effects of concomitantly used LMTs on the PK of alirocumab.

As expected for monoclonal antibodies, race, sex, and mild or moderate hepatic or renal impairment did not impact the PK of alirocumab. A few intrinsic factors were identified to have a small influence on alirocumab PK such as age, body weight, and free PCSK9. However, these effects resulted in less than a 1.6 fold variation in PK, none of these changes were clinically meaningful, none resulted in a recommended dose modification and all were accommodated by the up-titration dosing scheme.

Because patients with severe hepatic or renal impairment were excluded from the studies, there are no data on alirocumab exposure in such patients.

6.1.1.2.   Pharmacodynamics

Clinical pharmacodynamics studies demonstrated that alirocumab treatment results in a large and rapid decrease in LDL-C through binding and inhibition of PCSK9 (Figure 4). A dose-dependent reduction in LDL-C was observed until alirocumab concentrations are sufficient to bind all available PCSK9.

Figure 4: **Mean Concentration-Time Profile of Alirocumab, Free PCSK9 and Percent Change in LDL-C Following a Single Dose of Alirocumab 150 mg**
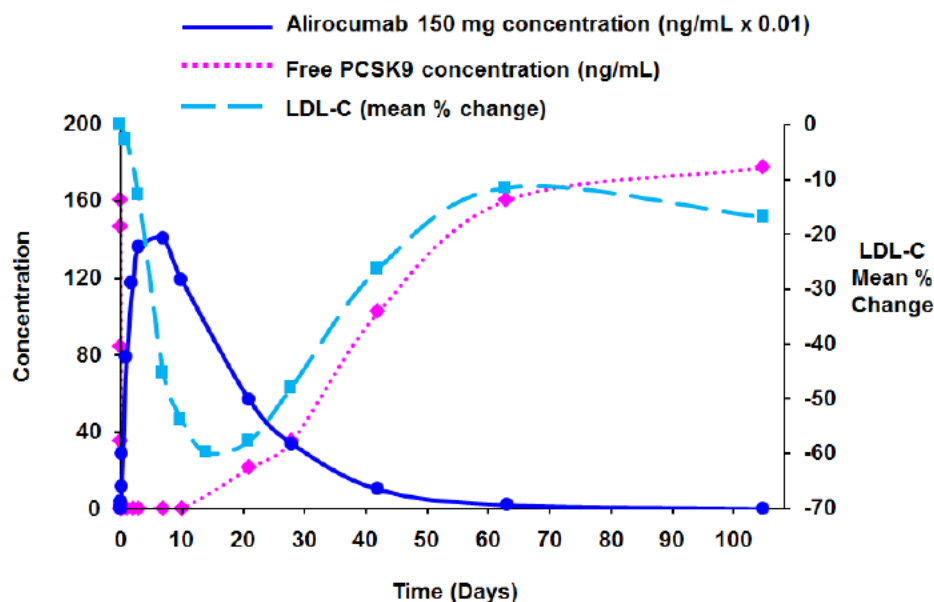
A pharmacodynamic interaction was observed when alirocumab was used with a variety of background LMTs. Specifically, studies which examined 150 mg alirocumab administered every 4 weeks showed that patients on a background of statins, ezetimibe or fenofibrate had higher baseline concentrations of both free and total PCSK9 than those on monotherapy (Table 5). However, patients administered alirocumab combined with a background lipid lowering agent exhibited slightly greater LDL-C reduction than those on monotherapy. It is believed that the additional LDL-C lowering observed when alirocumab is added on top of statins is related to the statin-mediated increase in LDLR expression and the ability of alirocumab to inhibit the statin-mediated additional PCSK9 production. Among the background lipid lowering therapies, the greatest enhancement of LDL-C lowering was observed with statins and more modest effects were observed with ezetimibe or fenofibrate.

Table 5: **Impact of Background Lipid-Lowering Therapies on the Pharmacodynamics of Alirocumab**

	Comparison of 150 mg Alirocumab Dosed Over a 4-Week Interval				
Background LMT	Free PCSK9 Level (ng/ml)	Alirocumab $t_{1/2}$ (day)	Week-2 LDL-C reduction	Week-4 LDL-C reduction	Peak to Trough Fluctuation
None	119	8.8	37 – 45%	39 %	-2 – 6 %
Ezetimibe	142	6.7	51 %	42 %	14 %
Fenofibrate	217	7.1	48 %	31 %	17 %
Statins	302	6.1	58 %	21%	37 %

Studies PKD12910 and R727-CL-1001.

Across the Phase 3 program, a difference in LDL-C lowering (LS means) between males and females (Section 8.2.1) was observed in 5 of the 10 studies, with an approximate 8 percentage-point greater LDL-C-lowering in males relative to females. However, relative to the total LDL-C lowering effect, this difference was small with a large overlap in response between males and females. The physiologic basis for this difference in LDL-C efficacy is presently not known

Men and women had similar levels of baseline free PCSK9 and similar reductions in free PCSK9 levels with alirocumab treatment in the four phase 3 trials where these parameters were measured (Figure 5). In contrast to the attenuated LDL-C lowering in females compared to males, a slightly higher alirocumab exposure was observed for females (POP PK), thus indicating that these small differences in LDL-C response are not explained by differences in exposure between males and females. It is important to point out that even with this small quantitative difference between men and women, there is still significant LDL-C reduction in both sexes.

Figure 5:   Comparison of Baseline Free PCSK9[a] and Absolute Change from Baseline to Week 12 in free PCSK9 Concentrations[b] by Sex
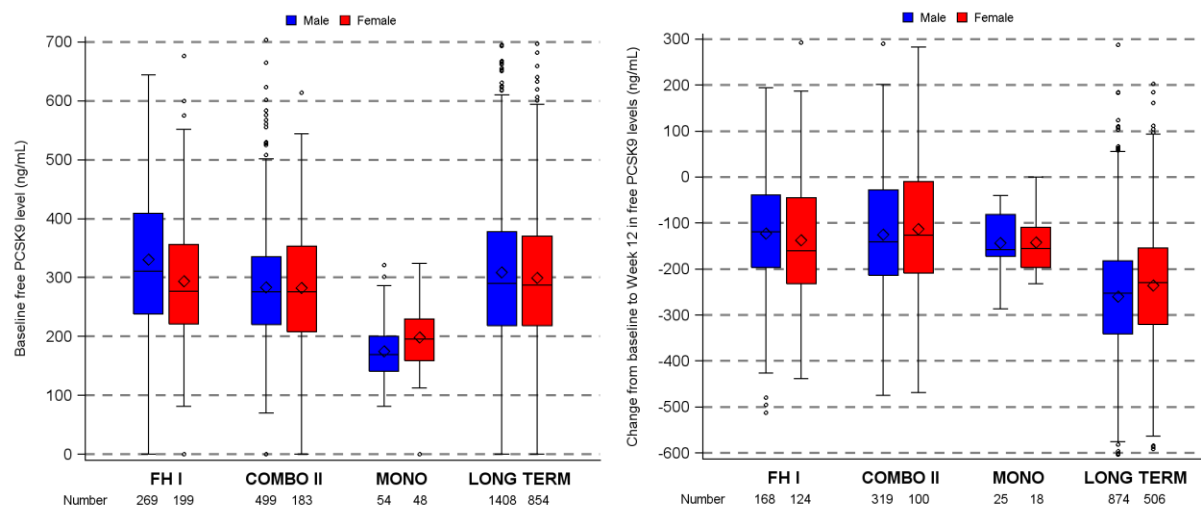
[a] Randomized population
[b] PK population – patients randomized to alirocumab in 4 Phase 3 studies

6.1.1.3.   Rationale for Dose Selection

The clinical pharmacology rationale for Phase 3 dose selection was based on a strong correlation between decreased free PCSK9, increased total PCSK9 and reduction in LDL-C. The 150 mg Q2W dose was selected because it provided maximum and consistent efficacy with little added LDL-C reduction observed at the higher doses studied in Phase 2 (Figure 6), and a safety profile comparable with the lower doses tested. In addition, doses higher than 150 mg Q2W did not result in meaningfully lower total PCSK9 indicating near target saturation. Together, these data indicate that there is little added LDL-C lowering benefit to be gained from doses higher than 150 mg Q2W.

However, 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 second lower alirocumab dose was explored. The 50 mg and 100 mg doses studied in Phase 2, shown in Figure 7, either did not provide the desired magnitude of efficacy or were not substantially different from the 150 mg dose, respectively. The 75 mg Q2W dose was selected from the Phase 2 dose-response model to provide an approximately 50% reduction in LDL-C from baseline.

Figure 6:   LDL-C Lowering by Dose Level in Phase 2 Dose Range Finding Studies

Figure 7:   LDL-C LS Means ± SE Percent Change from Baseline in Patients Dosed with Alirocumab Q2W in Study DFI11565
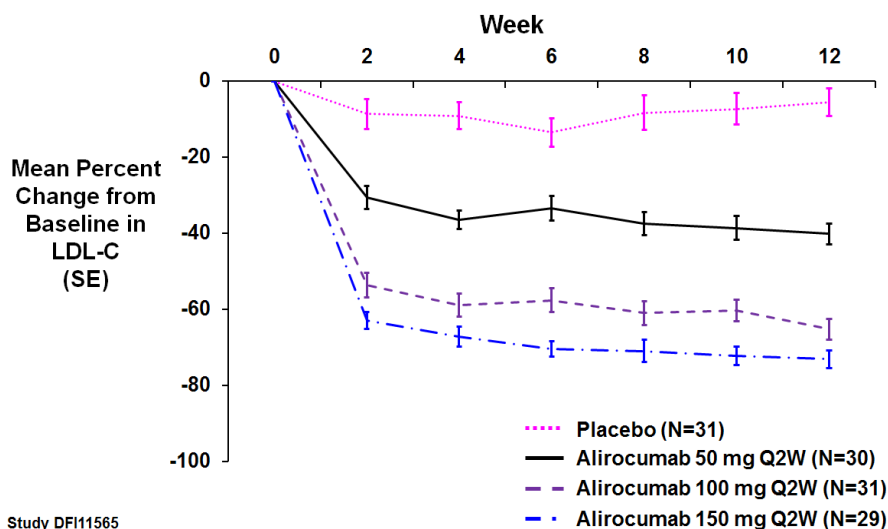
In the Phase 3 studies, the 75 mg Q2W dose was sufficient to achieve an approximate 50% reduction in LDL-C in the majority of patients (see Table 10 and Table 11). Some patients using 75 mg Q2W and the maximally tolerated dose of statin as background therapy required a dose up-titration. These patients achieved an additional mean reduction in LDL-C of 14%. This confirms the ability of the 150 mg dose to further reduce LDL-C when the response to 75 mg has been inadequate to achieve the therapeutic goal. A modest additional mean reduction of 3% based on the pooled mean of effect was observed after up-titration to 150 mg in studies where patients were not using statins as background therapy, with the majority of the effect seen in approximately 25% of patients who achieved at least an additional 10% LDL-C lowering. This modest increase in efficacy when doubling the dose (and thus when doubling alirocumab exposure) suggests that for most of the patients not receiving statins as background therapy, the saturation of the effect is reached with the dose of 75 mg Q2W. By contrast, in patients with background statin therapy, the greater production in PCSK9 due to treatment with statins may require more patients to be started on or up-titrated to the 150 mg dose.

6.1.2.   Anti-Drug Antibody Assessment

As with all therapeutic proteins, alirocumab has the potential to induce anti-drug antibodies (ADAs) when administered to humans. Therefore, serum samples for immunogenicity assessment were collected in all studies. The ADA response was generally assessed at baseline, during the treatment, and after the last alirocumab administration.

In Phase 3 studies, a treatment-emergent ADA response was defined as either no ADA positive response at baseline and 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 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.

Across all Phase 3 studies, 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 of these treatment-emergent ADA responses (63%) in the alirocumab group were classified as transient responses. The median time to the onset of treatment-emergent ADA response was 12 weeks (first post-baseline ADA assessment in most studies) in the alirocumab group. The incidence of treatment-emergent ADA response was similar according to up-titration status.

Most of the ADA positive samples exhibited low titers ($\leq$240). A few patients (21/3033) had an ADA response with maximum titers above 240 (and up to 3840). ADA responses in all patients were either negative or exhibited lower titers at subsequent visits indicating that there were no persistent ADA responses.

ADA status was not identified as a significant covariate impacting alirocumab population parameters. In general, ADA status had no clinically relevant impact on PK or PD. Analysis of safety data in patients with a positive ADA status did not find any clinically meaningful difference, compared to patients defined with a negative ADA status, with the exception of an increased rate of injection site reactions.

Samples from Phase 3 studies that were positive in the ADA assay were also examined for neutralizing activity. Only a few patients (1.2%) exhibited neutralizing antibodies (Nab), all of them in the alirocumab group. Most of these patients had only one positive neutralizing sample, indicating most patients only exhibited a transient neutralizing response. When looking at the durability of this response, only 10 patients (0.3%) had 2 or more NAb positive samples. The data in these patients do not suggest a consistent correlation between NAb and LDL-C lowering efficacy or safety.

7.   STUDY DESIGN OF PHASE 3 PROGRAM

Summary

- The clinical program was designed to assess the efficacy and safety of alirocumab in patients with primary heFH and non-FH, including patients with mixed dyslipidemia, and diabetic patients as:
    - add-on to statins, with or without other LMTs,
    - as monotherapy, or
    - as add-on to non-statin LMT in patients who are not on statin therapy, including patients with statin intolerance.
- All 10 Phase 3 studies were at least 6 months in duration and 5 studies (LONG TERM, HIGH FH, FH I, FH II, and COMBO II) were at least 18 months in duration.
- 5296 patients were randomized in the 10 Phase 3 studies with double-blind treatment durations of 24 weeks to 24 months.
    - In the 5 placebo-controlled trials (N=3499), patients received a maximally tolerated dose of statin and additional LMTs were allowed.
    - In the 5 ezetimibe-controlled trials (N=1797), patients received either background therapy of a statin at maximally tolerated dose without other LMT, a potent statin at less than maximal dose, or no statin. A comparison to statin intensification was included in 2 of the studies.
- Eight studies (N=2848) used an up-titration scheme (initiation with 75 mg Q2W and potential up-titration to 150 mg Q2W). The other two studies (N=2448) used continuous 150 mg Q2W dosing.
- The primary endpoint was the percent change in calculated LDL-C at 24 weeks with the primary analysis based on an intention-to-treat (ITT) approach.
- Ranked key secondary endpoints explored the effects of alirocumab on other aspects of LDL-C efficacy as well as efficacy in other lipid parameters such as Apo B, Lp(a), and HDL-C.

7.1.   Introduction

The ODYSSEY clinical program was designed to assess the efficacy of alirocumab as add-on to statins, with or without other LMTs, in patients with and without primary hypercholesterolemia including patients with mixed dyslipidemia and diabetic patients, or either as monotherapy or as add-on to their existing non-statin LMT, among patients not on statin therapy, including patients with statin intolerance.

The Phase 3 program evaluated two doses to flexibly meet patient's needs based on their baseline LDL-C and their target LDL-C. Data from outcomes studies with other drugs that lower LDL-C indicate that there is a benefit to lowering mean LDL-C values to <50 mg/dL. Post-hoc analyses from these outcome studies extend this benefit to somewhat lower LDL-C levels (approximately 40 mg/dL). However, the benefit/risk for considerably lower values of LDL-C

(eg., <25 mg/dL) is unknown. It was intended that by providing two doses of alirocumab, health care providers could more precisely target patients' individual goals.

The patients included in this program were primarily from three core patient populations that, based on guidelines at the time of study initiation, had significant unmet medical need due to their inability to achieve their LDL-C goal on maximally tolerated doses of existing therapies (mainly statins with or without other LMTs). There were: (1) heFH patients, (2) non-FH patients including patients with mixed dyslipidemia and diabetic patients at high/very high CV risk, and (3) patients who are intolerant to statins due to muscle-related adverse effects.

The integrated efficacy database includes the ten Phase 3 clinical studies that have either been completed (COMBO I, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO) or for which the primary double-blind treatment period (first-step analysis) has been completed (FH I, FH II, HIGH FH, COMBO II, and LONG TERM). The Phase 3 program was comprised of 5296 patients with heFH and non-FH, including patients with mixed dyslipidemia (Table 1, Figure 8).

Figure 8:   Overview of Phase 3 Studies by Patient Population

*   For COMBO II, other LMTs not allowed at study entry
** Moderate dosing of atorvastatin or rosuvastatin at study entry

7.2.   Study Designs and Methods

7.2.1.   Study Duration

All Phase 3 studies had a minimum double-blind treatment period of 24 weeks allowing for steady state PK to be fully achieved in all patients, including those receiving up-titration at 12 weeks. In 6 of the 10 studies (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM), the study blind was maintained for a duration of 12 to 24 months to provide additional data on durability of efficacy and long-term safety/tolerability.

7.2.2.   Study Treatment Dose and Regimen

Two Q2W doses, 75 mg and 150 mg, were used in the Phase 3 studies. Eight studies used an up-titration scheme (initiation of alirocumab with 75 mg Q2W and potential up-titration to 150 mg Q2W). Up-titration was done in a blinded manner 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 (Figure 9). Of the 3188 patients randomized to alirocumab, approximately half (N=1563) participated in the 8 studies using the 75/150 mg up-titration scheme. The other 2 studies, LONG TERM and HIGH FH, which randomized 1625 patients to alirocumab, used the continuous 150 mg Q2W dosing regimen (Figure 10).

Figure 9:   **Diagram of Phase 3 Study Designs with Potential for Up-titration**
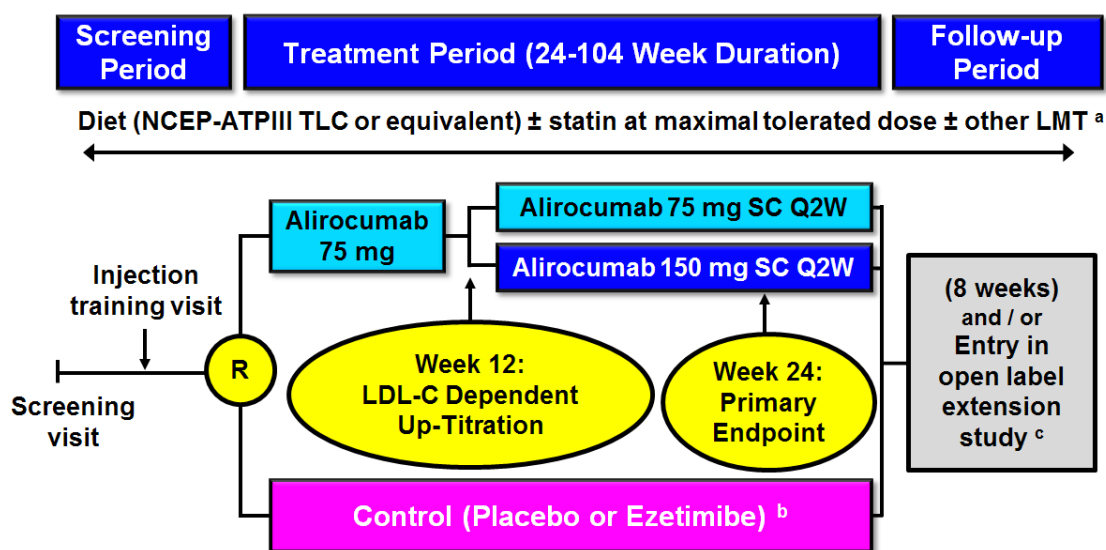
a   Depending on study design
b   For OPTIONS I, OPTIONS II, and ALTERNATIVE studies, an additional treatment arm utilized statins.
c   No follow-up period for patients entering in open-label extension study.

Figure 10:   Diagram of Phase 3 Study Designs with Continuous 150 mg Q2W Dosing
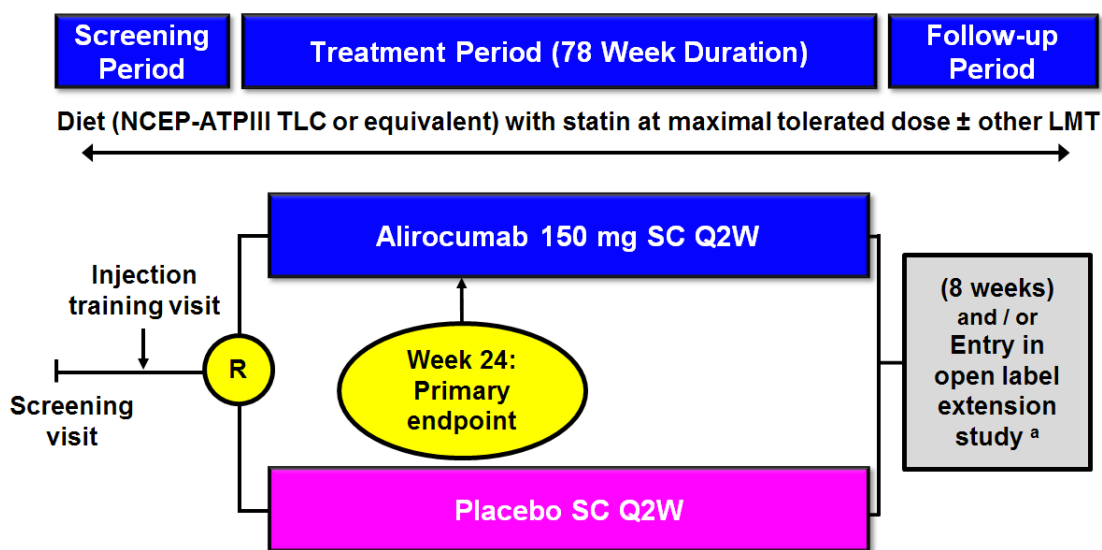
ᵃ   No follow-up period for patients entering in open-label extension study.

7.2.3.   Study Populations

The vast majority of studies, including all the studies in statin-treated patients, enrolled only patients at high and very high CV risk (97.0%). The definitions of CV risk were based on US and EU guidelines in effect at the time of clinical development plan finalization.[7,17,21] ESC/EAS 2011 guidelines [7] and 2012 update [17] were used to delineate very high and high CV risk.

Three studies (FH I, FH II, and HIGH FH) exclusively enrolled heFH patients (N=795). Patients with heFH were included in several other studies including a stratum of LONG TERM in which they represented approximately 18% (N=415) of the overall population. The definition of heFH was based on either genotyping or 2 widely accepted definitions based on patient clinical characteristics and phenotype for patients not genotyped: the Simon Broome criteria or the World Health Organization (WHO)/Dutch Lipid Network criteria for clinical diagnosis of heFH. [24,40]

The majority of patients (64.1%) had a history of CHD, 38.2% had mixed dyslipidemia (baseline TG ≥150 mg/dL) and 30.8% reported a history of type 2 diabetes mellitus. Demographics and medical characteristics of patients from the individual studies are provided in Table 6 for the placebo-controlled studies and in Table 7 for the ezetimibe-controlled studies. Baseline lipid values are presented in Section 13.2. The demographics of patients reflect the global nature of these studies. Approximately 35% of patients were from the US. Baseline demographics of US patients are provided in Section 13.3 and more closely reflect the US population.

Approximately 80% of the patients enrolled in the studies with alirocumab as an add-on to statin (N=4219) were receiving a maximally tolerated daily dose of potent statins at randomization and 59% of them (N=2504) were on atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg. Only patients on the three most effective statins (atorvastatin, rosuvastatin, or simvastatin) were included in the program. Two studies were performed in patients not receiving

statins: ALTERNATIVE was a study in patients with a documented history of statin intolerance and MONO was a monotherapy study in patients at moderate CV risk.

In ALTERNATIVE, statin intolerance was defined with a strict definition:

> inability to tolerate at least 2 statins, with at least one at or below the lowest daily dose, due to skeletal muscle-related symptoms that began or increased during statin therapy and stopped when statin therapy was discontinued.

This study included a 4-week single-blind, placebo-run-in period prior to treatment. Patients on placebo for statins reporting musculoskeletal symptoms during the run-in period were excluded. The study design included a re-challenge arm with a moderate dose of atorvastatin (20 mg). The latter was included to try to further validate the diagnosis of statin intolerance in a blinded manner with the caveats that re-challenge was limited to only this single statin and dose and that doing so restricted the study to patients willing to accept such a re-challenge and to patients without history of severe reactions to statins. Patients in ALTERNATIVE were predominantly at high/very high CV risk.

Table 6: Demographics and Patient Characteristics of Phase 3 Placebo-controlled Studies

Characteristic	FH I (N=486)	FH II (N=249)	HIGH FH (N=107)	COMBO I (N=316)	LONG TERM (N=2341)
Age (years), mean ± SD	51.9 ± 12.7	53.2 ± 12.8	50.6 ± 13.3	63.0 ± 9.3	60.5 ± 10.4
Age group					
<45	142 (29.2%)	59 (23.7%)	31 (29.0%)	13 (4.1%)	157 (6.7%)
≥45 to <65	263 (54.1%)	139 (55.8%)	62 (57.9%)	172 (54.4%)	1317 (56.3%)
≥65 to <75	72 (14.8%)	43 (17.3%)	13 (12.1%)	99 (31.3%)	678 (29.0%)
≥75	9 (1.9%)	8 (3.2%)	1 (0.9%)	32 (10.1%)	189 (8.1%)
Female, n (%)	212 (43.6%)	118 (47.4%)	50 (46.7%)	108 (34.2%)	884 (37.8%)
Race, n (%)					
White	444 (91.4%)	244 (98.0%)	94 (87.9%)	258 (81.6%)	2171 (92.7%)
Black or African American	5 (1.0%)	2 (0.8%)	2 (1.9%)	51 (16.1%)	77 (3.3%)
Asian	6 (1.2%)	3 (1.2%)	6 (5.6%)	3 (0.9%)	18 (0.8%)
Other	31 (6.4%)	0 (0.0%)	5 (4.7%)	4 (1.3%)	75 (3.2%)
Hispanic or Latino ethnicity, n (%)	24 (5.0%)	1 (0.4%)	6 (5.6%)	34 (10.8%)	121 (5.2%)
Weight (kg), mean ± SD	84.6 ± 16.9	84.6 ± 16.3	82.8 ± 15.7	94.5 ± 21.2	86.9 ± 18.4
BMI (kg/m^2), mean ± SD	29.3 ± 4.9	28.3 ± 4.7	28.9 ± 4.9	32.4 ± 6.6	30.3 ± 5.6
Region, n (%)					
North America	141 (29.0%)	0	33 (30.8%)	316 (100%)	548 (23.4%)
Western Europe	157 (32.3%)	174 (69.9%)	11 (10.3%)	0	1056 (45.1%)
Eastern Europe	68 (14.0%)	75 (30.1%)	29 (27.1%)	0	432 (18.5%)
Rest of World	120 (24.7%)	0	34 (31.8%)	0	305 (13.0%)
Hypertensive, n (%)	210 (43.2%)	81 (32.5%)	61 (57.0%)	280 (88.6%)	1762 (75.3%)
Type 2 diabetic, n (%)	56 (11.5%)	10 (4.0%)	15 (14.0%)	136 (43.0%)	809 (34.6%)
Current smoker, n (%)	69 (14.2%)	49 (19.7%)	21 (19.6%)	60 (19.0%)	484 (20.7%)
heFH, n (%)	486 (100%)	249 (100%)	107 (100%)	0	415 (17.7%)
CV risk level, n (%)					
Very high	249 (51.2%)	96 (38.6%)	61 (57.0%)	316 (100%)	2141 (91.5%)
High	237 (48.8%)	153 (61.4%)	46 (43.0%)	0	200 (8.5%)
Moderate	0	0	0	0	0

Table 7: Demographics and Patient Characteristics of Phase 3 Ezetimibe-controlled Studies

Characteristic	COMBO II (N=720)	OPTIONS I (N=355)	OPTIONS II (N=305)	ALTERNATIVE (N=314)	MONO (N=103)
Age (years), mean ± SD	61.6 ± 9.3	62.9 ± 10.2	60.9 ± 10.4	63.4 ± 9.5	60.2 ± 5.0
Age group					
<45	24 (3.3%)	18 (5.1%)	15 (4.9%)	9 (2.9%)	0
≥45 to <65	410 (56.9%)	174 (49.0%)	173 (56.7%)	161 (51.3%)	84 (81.6%)
≥65 to <75	229 (31.8%)	125 (35.2%)	93 (30.5%)	100 (31.8%)	19 (18.4%)
≥75	57 (7.9%)	38 (10.7%)	24 (7.9%)	44 (14.0%)	0
Female, n (%)	190 (26.4%)	124 (34.9%)	118 (38.7%)	142 (45.2%)	48 (46.6%)
Race, n (%)					
White	610 (84.7%)	306 (86.2%)	256 (83.9%)	295 (93.9%)	93 (90.3%)
Black or African American	28 (3.9%)	38 (10.7%)	27 (8.9%)	12 (3.8%)	10 (9.7%)
Asian	53 (7.4%)	6 (1.7%)	11 (3.6%)	4 (1.3%)	0
Other	29 (4.0%)	5 (1.4%)	11 (3.6%)	3 (1.0%)	0
Hispanic or Latino ethnicity, n (%)	20 (2.8%)	67 (18.9%)	41 (13.4%)	6 (1.9%)	1 (1.0%)
Weight (kg), mean ± SD	88.5 ± 18.1	89.6 ± 22.2	89.2 ± 20.4	83.6 ± 19.0	85.5 ± 17.6
BMI (kg/m^2), mean ± SD	30.1 ± 5.3	31.0 ± 6.4	31.3 ± 6.6	29.1 ± 5.8	29.3 ± 6.4
Region, n (%)					
North America	234 (32.5%)	264 (74.4%)	201 (65.9%)	231 (73.6%)	49 (47.6%)
Western Europe	109 (15.1%)	59 (16.6%)	71 (23.3%)	50 (15.9%)	54 (52.4%)
Eastern Europe	220 (30.6%)	0	0	0	0
Rest of World	157 (21.8%)	32 (9.0%)	33 (10.8%)	33 (10.5%)	0
Hypertensive, n (%)	580 (80.6%)	278 (78.3%)	221 (72.5%)	197 (62.7%)	32 (31.1%)
Type 2 diabetic, n (%)	221 (30.7%)	177 (49.9%)	126 (41.3%)	75 (23.9%)	4 (3.9%)
Current smoker, n (%)	155 (21.5%)	66 (18.6%)	56 (18.4%)	21 (6.7%)	11 (10.7%)
heFH, n (%)	0	32 (9.0%)	41 (13.4%)	47 (15.0%)	0
CV risk level, n (%)					
Very high	720 (100%)	214 (60.3%)	192 (63.0%)	170 (54.1%)	0
High	0	141 (39.7%)	113 (37.0%)	89 (28.3%)	0
Moderate	0	0	0	43 (13.7%)	103 (100%)

7.2.4. Choice of Control Group

All Phase 3 studies were double-blind, placebo- or active-controlled, parallel-group superiority studies. The investigational medical product (IMP), alirocumab or placebo for alirocumab, was self-administered SC Q2W. Placebo for alirocumab contained the same excipients as in the active product at the same concentrations and delivered using the same delivery device – prefilled syringe or prefilled pen.

Placebo-controlled Studies

The 5 placebo-controlled studies (FH I, FH II, HIGH FH, COMBO I, and LONG TERM) were single-dummy design; all patients received either alirocumab or placebo injection in addition to a background therapy of statin at the MTD. Additionally, patients in these studies could concomitantly receive almost any other LMT, if previously received.

Ezetimibe-controlled Studies

The five ezetimibe-controlled studies were double-dummy design; all patients received either alirocumab or placebo injection (as above) and received ezetimibe 10 mg per os (PO) once daily (QD) or matching oral placebo.

- In the COMBO II study, alirocumab was compared to ezetimibe in patients who were receiving background therapy of statin at the MTD without any other LMT. This comparison in patients already receiving high-intensity statin therapy, provides an assessment of efficacy and safety of alirocumab versus a non-statin LMT.

- The OPTIONS studies evaluated the addition of alirocumab to less-than-maximal doses of atorvastatin (OPTIONS I) or rosuvastatin (OPTIONS II) compared to several other options:

  – the addition of ezetimibe to less-than-maximal doses of statin,

  – doubling the statin dose, or

  – switching to a more potent statin (OPTIONS I only).

  These studies provide additional supportive information regarding the efficacy of alirocumab as it might be used in patients who are only able to tolerate a less-than-maximal dose of a statin, in comparison with other options.

- The MONO and ALTERNATIVE studies compared alirocumab to ezetimibe in patients not taking background statin therapy. The MONO study evaluated the efficacy of alirocumab used as monotherapy in patients at moderate CV risk with an LDL-C between 100 and 190 mg/dL. The ALTERNATIVE study enrolled statin intolerant patients and also included a statin re-challenge arm utilizing atorvastatin 20 mg (2:2:1 randomization for alirocumab, ezetimibe, or atorvastatin, respectively) to validate the definition of statin intolerance used for patients' eligibility.

7.2.5. Approach to Efficacy Analysis in Phase 3 Studies

Primary: Intention to Treat (ITT) Approach

In all Phase 3 studies the primary analyses of efficacy endpoints were conducted using an ITT approach, including all lipid data, regardless of whether the patient was receiving therapy or not. Based on the requirements of the MMRM model used, all patients with an available baseline calculated LDL-C value and at least 1 calculated LDL-C value prior to or up to the Week 24 visit were included in the ITT approach.

Note: The primary endpoint was based on calculated LDL-C. Measured LDL-C was a secondary endpoint in certain studies.

Secondary: On-Treatment Approach

The on-treatment approach included all patients that took at least one dose or part of a dose of the double-blind randomized treatment during the efficacy treatment period but, unlike the ITT approach, only considered lipid data during the efficacy treatment period. The efficacy treatment period was defined as:

- For placebo-controlled studies: The time period from the first double-blind injection received (alirocumab or placebo) up to the day of last injection +21 days

- For active-controlled studies: The time period from the first double-blind capsule or injection, whichever came first, up to the day of last injection +21 days or the day of last capsule intake +3 days, whichever came first

This on-treatment approach assessed the benefit of treatment among patients adherent to treatment up to the considered time point.

Sensitivity Analyses for Non-Random Missingness

Additional sensitivity analyses were conducted to account for possible non-random missingness in the data, including a pattern mixture model.

7.2.6. Study Endpoints

7.2.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint of all 10 Phase 3 studies was the percent change in calculated LDL-C at Week 24.

7.2.6.2. Secondary Efficacy Endpoints

All Phase 3 studies had secondary efficacy endpoints which included LDL-C at other time points, the proportion of patients reaching pre-specified LDL-C targets, and other lipid parameters in order to more fully characterize the efficacy profile of alirocumab. In addition, measured LDL-C was assessed as a secondary endpoint in some studies. The list of secondary endpoints and ordering for hierarchical testing is shown in Section 13.1.

7.2.7.   Statistical Methods and Treatment of Missing Data

Primary analyses of efficacy endpoints were conducted using an ITT approach. The mixed effect MMRM was used for primary efficacy analyses. Mixed models included categorical covariates for (study-dependent) randomization strata, time point, treatment-by time point interaction, and strata-by-time point interaction, as well as continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. LS means were estimated from the model for each treatment group, and differences between treatment groups were obtained using appropriate contrasts.

The MMRM approach relies on the "missing-at-random" (MAR) assumptions. Since the true mechanism of missing data cannot be tested a sensitivity analysis was conducted on the primary endpoint to evaluate the impact of missing data assuming data were "missing-not-at-random" (MNAR). This sensitivity analysis was based on a pattern mixture model (PMM) based on the 2 following assumptions:

- Missing calculated LDL-C values during the on-treatment period were considered "missing at random".

- Patients who stopped taking their study treatment no longer benefited from it in the future, and thus tended to have calculated LDL-C values returning to baseline.

A hierarchical testing procedure was pre-specified to test the primary and the key secondary endpoints while controlling for multiplicity. Statistical significance of the primary efficacy endpoint at the 0.05 significance level was required before drawing conclusions about key secondary endpoints. Conclusions about successive key secondary endpoints required statistical significance at the 0.05 alpha level of the preceding endpoints, which ensured a control of the type-I error rate at the 0.05 level. In the OPTIONS studies, alpha was split amongst the different comparators.

7.2.8.   Subgroup Analyses

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup factor, time point-by-subgroup factor and treatment-by time point-by subgroup factor interaction terms and a subgroup factor term were added in the primary MMRM model. The significance level of the treatment-by subgroup factor interaction term at Week 24 was also provided for each factor for descriptive purpose. The full list of all pre-specified subgroup analyses for the primary endpoints is provided in Section 13.1.

8.   PHASE 3 EFFICACY

Summary

- All studies met the primary efficacy endpoint demonstrating superior mean percent reduction from baseline in LDL-C at Week 24 by the addition of alirocumab to baseline therapy as compared to the addition of placebo or ezetimibe. LS mean percent changes in LDL-C from baseline to <u>Week 24</u> were
  - In the placebo-controlled studies:
    - -48.6% with 75 mg with potential up-titration to 150 mg Q2W
    - -60.4% with 150 mg Q2W continuous dosing
  - In the ezetimibe-controlled studies:
    - -45.6 to -48.9% with 75 mg with potential up-titration to 150 mg Q2W
- At <u>Week 12</u>, the LS mean percent changes in LDL-C from baseline were:
  - -44.5 to -49.2% with 75 mg Q2W prior to potential up-titration to 150 mg Q2W
  - -62.6% with 150 mg Q2W continuous dosing
- The lipid-lowering effect of alirocumab was observed within 15 days after the first dose reaching maximum effect at approximately 4 weeks and was sustained throughout the treatment period.
- Most patients achieved their LDL-C goal on 75 mg dosing (73.7%) and did not require up-titration. Up-titration was associated with an additional 14.2% mean reduction in patients on a background statin and an additional 3.1% mean reduction in patients not on a background statin.
- Distinct efficacy between 75 mg and 150 mg Q2W doses allows for starting dose selection based on individual patient characteristics, particularly baseline LDL-C and the goal of therapy, and dose adjustment based on treatment response.
- Patients treated with alirocumab were considerably more likely to achieve their LDL-C targets than placebo (on top of statins in most studies) or active control (ezetimibe) in all studies.
  - In placebo-controlled studies, 59.8 to 75.0% (75/150 mg) and 32.4 to 79.3% (150 mg) of alirocumab patients achieved LDL-C <70 mg/dL at Week 24 compared to 0.8 to 9.0% of placebo patients.
  - In ezetimibe-controlled studies, 32.5 to 78.6% (75/150 mg) of alirocumab patients achieved LDL-C <70 mg/dL compared to 0.8 to 52.2% for ezetimibe.
- Reductions in LDL-C were sustained through 52 weeks. More than 80% of the Phase 3 population enrolled in studies with a minimum 52-week double-blind period.
- In general, treatment with alirocumab also resulted in significantly greater reductions in Total-C, non-HDL-C, Apo B, and Lp(a) as compared to placebo or ezetimibe, whether or not patients were concomitantly being treated with a statin.
- Alirocumab reduced TGs and increased HDL-C and Apo A-1 as compared to placebo.

8.1. Disposition of Subjects In Efficacy Analyses

High percentages of patients completed the studies up to the first-step analysis time point (Week 24). Rates of missing data at Weeks 12 and 24 for the placebo- and ezetimibe-controlled studies are provided in Table 8 and Table 9, respectively. Complete 24 week data were available for 91.0% of Phase 3 study participants. 24-week completion rates ranged from 88.6% in OPTIONS II to 95.1% in FH II. Reasons for treatment discontinuation are shown in Table 52.

Table 8: **Rates of Missing Data for Phase 3 Placebo-controlled Studies**

Calculated LDL-C availability	FH I (N=485)	FH II (N=247)	HIGH FH (N=106)	COMBO I (N=311)	LONG TERM (N=2310)
Week 12					
Value available	456 (94.0%)	228 (92.3%)	101 (95.3%)	292 (93.9%)	2182 (94.5%)
On-treatment value	454 (93.6%)	227 (91.9%)	101 (95.3%)	285 (91.6%)	2152 (93.2%)
Post-treatment value	2 (0.4%)	1 (0.4%)	0	7 (2.3%)	29 (1.3%)
Missing data	29 (6.0%)	19 (7.7%)	5 (4.7%)	19 (6.1%)	128 (5.5%)
Week 24					
Value available	439 (90.5%)	235 (95.1%)	96 (90.6%)	286 (92.0%)	2094 (90.6%)
On-treatment value	431 (88.9%)	232 (93.9%)	95 (89.6%)	273 (87.8%)	2035 (88.1%)
Post-treatment value	8 (1.6%)	3 (1.2%)	1 (0.9%)	13 (4.2%)	57 (2.5%)
Missing data	46 (9.5%)	12 (4.9%)	10 (9.4%)	25 (8.0%)	216 (9.4%)

Table 9: **Rates of Missing Data for Phase 3 Ezetimibe-controlled Studies**

Calculated LDL-C availability	COMBO II (N=707)	OPTIONS I (N=345)	OPTIONS II (N=298)	ALTERNATIVE (N=310)	MONO (N=103)
Week 12					
Value available	675 (95.5%)	320 (92.8%)	279 (93.6%)	297 (95.8%)	96 (93.2%)
On-treatment value	662 (93.6%)	312 (90.4%)	272 (91.3%)	257 (82.9%)	91 (88.3%)
Post-treatment value	13 (1.8%)	8 (2.3%)	7 (2.3%)	40 (12.9%)	5 (4.9%)
Missing data	32 (4.5%)	25 (7.2%)	19 (6.4%)	13 (4.2%)	7 (6.8%)
Week 24					
Value available	649 (91.8%)	314 (91.0%)	264 (88.6%)	281 (90.6%)	95 (92.2%)
On-treatment value	630 (89.1%)	285 (82.6%)	246 (82.6%)	220 (71.0%)	88 (85.4%)
Post-treatment value	19 (2.7%)	29 (8.4%)	18 (6.0%)	61 (19.7%)	7 (6.8%)
Missing data	58 (8.2%)	31 (9.0%)	34 (11.4%)	29 (9.4%)	8 (7.8%)

8.2. Primary Efficacy Endpoint

8.2.1. Patients Insufficiently Controlled on Statins with or without Other LMT Using an Up-Titration Scheme (75 mg/150 mg Q2W)

In the six studies using the 75 mg/150 mg up-titration scheme on top of background statins (COMBO I, COMBO II, OPTIONS I, OPTIONS II, FH I, and FH II), patients were titrated at Week 12 in a blinded manner based on their LDL-C levels at Week 8. Results from these studies demonstrated a clinically relevant reduction in LDL-C from baseline to Week 24. In the alirocumab arms the mean change in LDL-C at Week 24 ranged from -42.7% (OPTIONS II)

to -50.6% (COMBO II) in ITT analyses (Figure 11). The large majority of patients in the alirocumab groups remained on the 75 mg dose (range, 57% in FH I to 86% in OPTIONS I).

Figure 11:   Percent Change from Baseline in Calculated LDL-C at Week 24 in Phase 3 Studies

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)		N Patients	
	Control	Alirocumab	Alirocumab - Control	P-value	Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	0.8 (1.0)	-61.0 (0.7)		<0.0001	780	1530
HIGH FH	-6.6 (4.9)	-45.7 (3.5)		<0.0001	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-2.3 (2.7)	-48.2 (1.9)		<0.0001	106	205
FH I	9.1 (2.2)	-48.8 (1.6)		<0.0001	163	322
FH II	2.8 (2.8)	-48.7 (1.9)		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-20.7 (1.9)	-50.6 (1.4)		<0.0001	240	467
OPTIONS I	-21.4 (3.3)	-48.5 (3.2)		<0.0001	99	101
OPTIONS II	-11.6 (4.4)	-42.7 (4.3)		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-14.6 (2.2)	-45.0 (2.2)		<0.0001	122	126
MONO	-15.6 (3.1)	-47.2 (3.0)		<0.0001	51	52

-80 -60 -40 -20   0   20   40   60   80

← Favors alirocumab   Favors control →

All treatment differences between alirocumab and the comparators (placebo or ezetimibe) were highly statistically significant in the trials except for two treatment comparisons in OPTIONS II (Figure 12). The smaller sample sizes (~50 per arm) in the OPTIONS studies were associated with more variability than had been predicted in the assumptions used to calculate study power. However, data from the alirocumab group in the OPTIONS studies were consistent with the other Phase 3 studies. There is no indication in the rest of the program that the effect of alirocumab varies by background statin or dose.

Figure 12: **Percent Change from Baseline in Calculated LDL-C at Week 24 in All Treatment Comparisons in OPTIONS I and OPTIONS II**

Study	Statin at baseline	Control arm	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	P-value	N Patients	
			Control	Alirocumab	Alirocumab - Control		Control	Alir.
OPTIONS I								
	Atorva 20	Atorva 20 + Eze 10	-20.5 (4.7)	-44.1 (4.5)		0.0004	53	55
		Atorva 40	-5.0 (4.6)	-44.1 (4.5)		<0.0001	53	55
	Atorva 40	Atorva 40 + Eze 10	-22.6 (4.3)	-54.0 (4.3)		<0.0001	46	46
		Atorva 80	-4.8 (4.2)	-54.0 (4.3)		<0.0001	47	46
		Rosuva 40	-21.4 (4.2)	-54.0 (4.3)		<0.0001	45	46
OPTIONS II								
	Rosuva 10	Rosuva 10 + Eze 10	-14.4 (4.4)	-50.6 (4.2)		<0.0001	47	48
		Rosuva 20	-16.3 (4.1)	-50.6 (4.2)		<0.0001	48	48
	Rosuva 20	Rosuva 20 + Eze 10	-11.0 (7.2)	-36.3 (7.1)		0.0136	50	53
		Rosuva 40	-15.9 (7.1)	-36.3 (7.1)		0.0453	52	53

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← Favors alirocumab   Favors control →

Note: Confidence intervals are adjusted for multiplicity (99% CI for OPTIONS I and 98.75% CI for OPTIONS II).

8.2.2. Patients Insufficiently Controlled on Statins with or without Other LMT Using 150 mg Q2W Continuous Dosing

Two studies used 150 mg Q2W exclusively in patients insufficiently controlled on statins with or without another LMT: LONG TERM, which included patients with and without heFH; and HIGH FH, which exclusively included patients with heFH. LS mean percent changes in LDL-C from baseline in patients treated with alirocumab 150 mg Q2W were -61.0% in LONG TERM and -45.7% in HIGH FH compared to +0.8% and -6.6% for placebo, respectively (Figure 11).

It was noted that the 150 mg dose produced more profound lipid lowering in the large LONG TERM study than in the small HIGH FH study; we presumed this might reflect chance due to the small sample size in HIGH FH. To pursue this, we examined the effects on the subset of heFH patients in the LONG TERM study, corresponding to those in the small HIGH FH study. In this subset of LONG TERM patients, alirocumab resulted in a -56.3% reduction in LDL-C compared to a 7.0% increase in the control patients. Thus, heFH patients appear to respond as well to alirocumab as other patients with elevated baseline LDL-C.

8.2.3. Non-Statin-Treated Patients with Alirocumab as Monotherapy or Add-On to Non-Statin LMT Using an Up-Titration Scheme (75 mg/150 mg Q2W)

Two ezetimibe-controlled studies, MONO and ALTERNATIVE, assessed the efficacy of alirocumab 75/150 mg Q2W in non-statin-treated patients. All patients in the MONO study were on diet alone without any background LMT. In the ALTERNATIVE study of statin-intolerant patients, 43.3% received LMTs other than statin or ezetimibe as background therapy. Among

patients who received at least 1 study dose after Week 12, 49.5% of patients in ALTERNATIVE and 30.4% of patients in MONO up-titrated to the 150 mg dose.

The mean reductions in LDL-C from baseline at Week 24 with alirocumab were -45.0% in the ALTERNATIVE study and -47.2% in the MONO study. The treatment differences for alirocumab versus ezetimibe at Week 24 were -30.4% in ALTERNATIVE and -31.6% in MONO, which were both highly statistically significant (Figure 11).

8.2.4. On-Treatment Population Results and Sensitivity Analysis for Missing Data

Primary endpoint results in the ITT and on-treatment populations using MMRM analysis as well as the PMM sensitivity analysis, which assumed data were MNAR, are shown in Figure 13. (For details on statistical methods, see Section 7.2.7.)

The mean percent LDL-C reductions at Week 24 in the on-treatment population were modestly higher than ITT results (approximately 1 to 5 percentage points across studies). These differences between the on-treatment and ITT analyses do not change the statistical significance or clinical interpretation with regard to the primary endpoint for any of the treatment comparisons.

The PMM analyses, which assumed that patients off treatment with alirocumab did not receive an LDL-C-lowering benefit, were typically 2 to 5 percentage points lower than the MMRM analyses of the ITT population; however, the statistical conclusions about the superiority of alirocumab over placebo or active control were not affected. Since the amount of missing data was low and the superiority claims were not affected, these analyses suggest that the primary endpoint results are robust for different assumptions underlying missing data.

Figure 13: **Percent Change from Baseline in Calculated LDL-C at Week 24: Comparison of MMRM ITT, On-treatment, and PMM Analyses**

Comparison Study	Analysis	% change from baseline LS means (SE) Control	% change from baseline LS means (SE) Alirocumab	Difference in % change from baseline LS mean difference (95% CI) Alirocumab - Control
Alirocumab 150 vs Placebo				
LONG TERM	MMRM ITT	0.8 (1.0)	-61.0 (0.7)	
	MMRM On-treatment	0.7 (1.0)	-62.8 (0.7)	
	PMM	0.7 (1.1)	-57.8 (0.8)	
HIGH FH	MMRM ITT	-6.6 (4.9)	-45.7 (3.5)	
	MMRM On-treatment	-6.6 (5.0)	-45.5 (3.5)	
	PMM	-6.9 (5.0)	-43.3 (3.6)	
Alirocumab 75/150 vs Placebo				
COMBO I	MMRM ITT	-2.3 (2.7)	-48.2 (1.9)	
	MMRM On-treatment	-0.8 (2.6)	-50.7 (1.9)	
	PMM	-1.5 (3.0)	-44.2 (2.1)	
FH I	MMRM ITT	9.1 (2.2)	-48.8 (1.6)	
	MMRM On-treatment	8.8 (2.2)	-49.3 (1.6)	
	PMM	9.0 (2.3)	-47.2 (1.7)	
FH II	MMRM ITT	2.8 (2.8)	-48.7 (1.9)	
	MMRM On-treatment	2.7 (2.7)	-49.4 (1.9)	
	PMM	2.8 (2.9)	-47.3 (2.1)	
Alirocumab 75/150 vs Ezetimibe				
COMBO II	MMRM ITT	-20.7 (1.9)	-50.6 (1.4)	
	MMRM On-treatment	-21.8 (1.8)	-52.4 (1.3)	
	PMM	-20.1 (2.0)	-47.8 (1.4)	
ALTERNATIVE	MMRM ITT	-14.6 (2.2)	-45.0 (2.2)	
	MMRM On-treatment	-17.1 (2.0)	-52.2 (2.0)	
	PMM	-13.2 (2.4)	-44.3 (2.3)	
MONO	MMRM ITT	-15.6 (3.1)	-47.2 (3.0)	
	MMRM On-treatment	-17.2 (2.0)	-54.1 (2.0)	
	PMM	-14.3 (3.2)	-45.1 (3.2)	

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Favors alirocumab   Favors control

8.2.5. Subgroup Analyses

Given the large number of subgroups pre-specified to evaluate consistency of efficacy, only notable findings are highlighted in the section below.

8.2.5.1. Baseline Characteristics

In the ten Phase 3 studies, baseline demographic factors were balanced and included sex, age, body mass index (BMI), race, ethnicity, prior history of myocardial infarction or ischemic stroke, mixed dyslipidemia status, diabetes mellitus, moderate chronic kidney disease, free and total PCSK9 levels, baseline levels of LDL-C, Lp(a), HDL-C, and fasting TGs, and heFH status.

No consistent interaction across studies was observed in the analysis of LDL-C change by region or by race or ethnicity. Reductions in LDL-C were in line with expectation in the studies where patients from a given region, race, or ethnicity were well represented.

However, a difference in LDL-C reduction by sex was observed in 5 out of the 10 Phase 3 studies with females showing a trend for less LDL-C reduction (Figure 14). Overall, in a pooled analysis of the efficacy at week 12, the mean reductions in LDL-C from baseline with the 75 mg Q2W dose was -50.1% for men and -41.8% for women. For the 150 mg dose at week 12, the mean reductions in LDL-C from baseline were -67.0% and -55.8% for men and women, respectively. Despite these conflicting observations in the data, the effect of both 75/150 mg and 150 mg Q2W regimens was clinically meaningful in both sexes. For details of the sex differences in LDL-C reduction, see Section 6.1.1.2.

Figure 14:   Percent Change from Baseline in Calculated LDL-C at Week 24: Subgroup Analysis According to Sex (ITT analysis)

Comparison Study	Subgroup	N	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	Interaction P-value
			Control	Alirocumab	Alirocumab - Control	
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	Male	1438	-0.7 (1.3)	-65.5 (0.9)		0.0014
	Female	872	3.2 (1.6)	-53.4 (1.2)		
HIGH FH	Male	56	-2.1 (6.2)	-52.2 (5.1)		0.0591
	Female	50	-13.9 (8.0)	-39.7 (4.8)		
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	Male	205	-4.2 (3.2)	-50.5 (2.4)		0.9126
	Female	106	2.6 (5.0)	-44.4 (3.2)		
FH I	Male	273	9.9 (2.9)	-52.8 (2.1)		0.0510
	Female	212	8.1 (3.4)	-43.8 (2.4)		
FH II	Male	130	2.1 (3.8)	-51.4 (2.7)		0.5301
	Female	117	3.6 (4.1)	-45.6 (2.8)		
Alirocumab 75/150 vs Ezetimibe (with statins)						
COMBO II	Male	524	-21.1 (2.2)	-52.1 (1.6)		0.3583
	Female	183	-19.7 (3.6)	-45.8 (2.8)		
OPTIONS I	Male	128	-26.4 (3.9)	-58.9 (3.9)		0.1533
	Female	72	-11.9 (5.4)	-31.1 (5.1)		
OPTIONS II	Male	112	-8.0 (5.8)	-49.1 (5.7)		0.0668
	Female	86	-16.4 (6.6)	-34.5 (6.6)		
Alirocumab 75/150 vs Ezetimibe (without statins)						
ALTERNATIVE	Male	135	-15.5 (3.1)	-48.4 (3.0)		0.3816
	Female	113	-13.4 (3.4)	-40.7 (3.3)		
MONO	Male	55	-12.8 (4.1)	-52.2 (4.1)		0.0495
	Female	48	-18.8 (4.5)	-41.2 (4.4)		

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←Favors alirocumab   Favors control→

8.2.5.2. Drug-Drug

Statins and other LMTs increase the production of PCSK9 by hepatocytes, and alirocumab is partially eliminated through PCSK9 mediated clearance. Therefore, subgroup analyses were performed on LDL-C change by background LMT at randomization. With Q2W dosing, no consistent interaction across studies was detected for statin therapy, combination therapy, or by intensity of statin treatment.

Subgroup analyses according to the 4 dose levels at randomization of each of the statins allowed as background therapy in the studies (atorvastatin, rosuvastatin, and simvastatin) showed, in general, very consistent reductions in LDL-C with alirocumab regardless of the statin dose. In particular, the difference observed in the OPTIONS II study with rosuvastatin was not seen in other, larger studies.

8.2.6. Maintenance of Effect

Six out of the 10 Phase 3 studies, representing approximately 80% of the global Phase 3 population (N=4219), had a duration of at least 52 weeks. The effect of alirocumab on LDL-C level seen at Week 4 was well maintained over time in all these studies.

Figure 15 shows the percent change in LDL-C from baseline over time up to Week 52 using 150 mg Q2W dosing in the pooled LONG TERM and HIGH FH studies. Figure 16 shows the percent change in LDL-C over time using the 75/150 mg Q2W dosing in the pooled FH I, FH II, and COMBO I studies. An LDL-C reduction compared to baseline in the alirocumab group was observed from the first post-dose measurement at Week 4 and was maintained at all time points up to Week 52.

Figure 15: **LS Mean (95% CI) Calculated LDL-C Percent Change from Baseline over Time in ITT Population with 150 mg Q2W Dosing in Pooled LONG TERM and HIGH FH Studies**
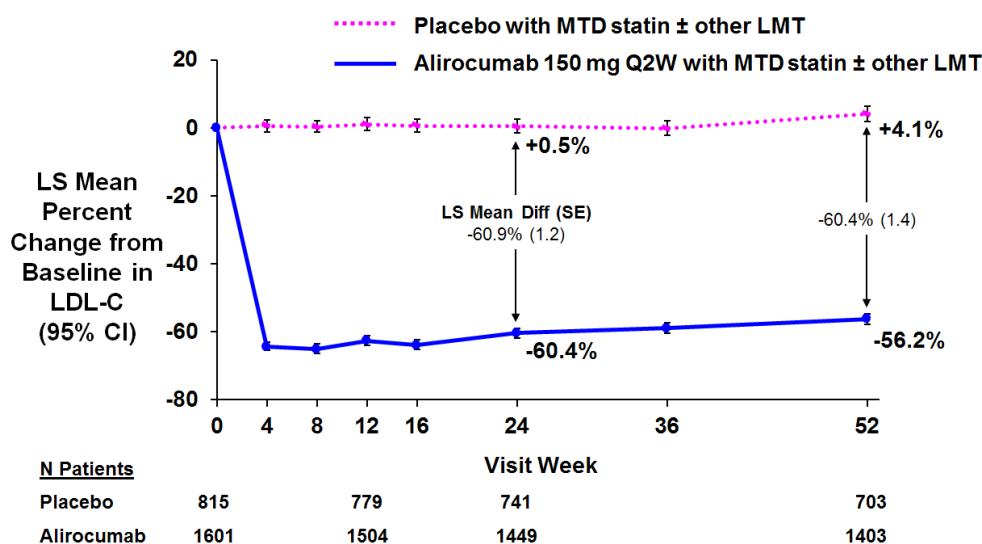
Pooled ITT analysis from LONG TERM and HIGH FH studies.

Figure 16: **LS Mean (95% CI) Calculated LDL-C Percent Change from Baseline Over Time in ITT Population with 75/150 mg Q2W Dosing in Pooled FH I, FH II, and COMBO I Studies**
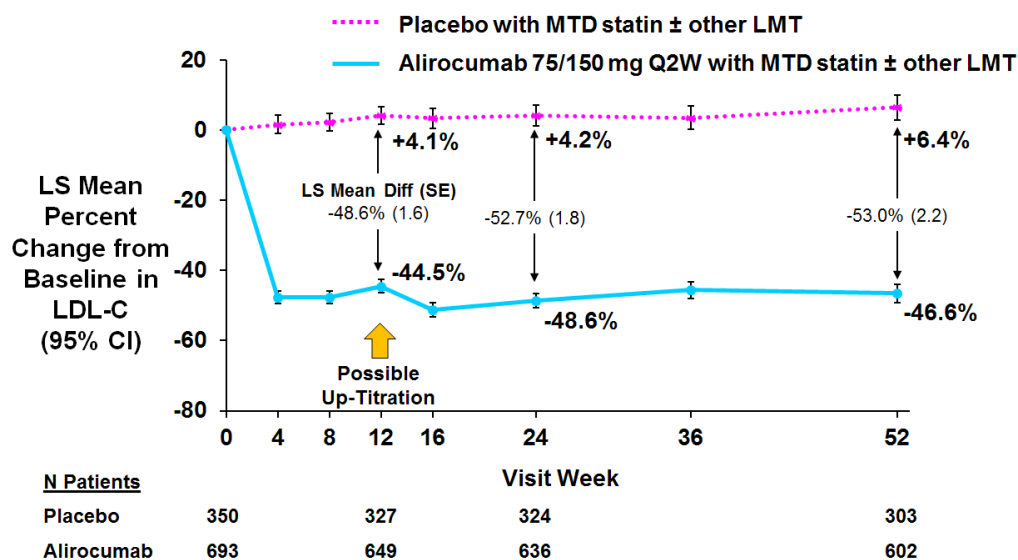
Pooled ITT analysis from FH I, FH II, and COMBO I studies.

8.3. Key Secondary Endpoints

Most key secondary endpoints were significant across the studies. The only exception is the OPTIONS II study, for which key secondary endpoints could not be considered statistically significant because 2 of the 4 treatment comparisons for the primary efficacy endpoint were not met. However, the observed improvements in parameters were similar to the other studies.

8.3.1. Efficacy at Week 12 and Efficacy of Up-Titration

Analysis of the LS mean reductions at Week 12 prior to potential up-titration allows for a comparison of the efficacy of the two doses. Across the pooled Phase 3 placebo-controlled studies, the LS mean percent change in LDL-C from baseline to Week 12 was -44.5% with 75 mg Q2W and -62.6% with 150 mg Q2W. Since the majority of patients were maintained on the 75 mg Q2W regimen, mean reductions in LDL-C at Week 12 were similar to those observed at Week 24, regardless of background LMT; see Table 10.

Table 10:   **LS Mean Percent Change from Baseline in LDL-C at Week 12 (before up-titration) and Week 24 in Pooled Analyses of Phase 3 Placebo-controlled Studies in Patients on Background Statin**

Dose	Alirocumab (Additive Effect Beyond Statin)	Placebo (Additive Effect Beyond Statin)
Week 12 (secondary endpoint, before up-titration)		
75 mg[a]	-44.5 %	4.1 %
150 mg[b]	-62.6 %	1.1 %
Week 24 (primary endpoint)		
75/150 mg (up-titration studies) [a,c]	-48.6 %	4.2 %
150 mg[b]	-60.4 %	0.5 %

[a] Based on pooled analyses of up-titration studies (COMBO I, FH I, and FH II). N=693 in the alirocumab group, N=350 in the placebo group.
[b] Based on pooled analyses of studies using the 150 mg Q2W dose (LONG TERM and HIGH FH). N=1601 in the alirocumab group, N=815 in the placebo group.
[c] Dose was up-titrated to 150 mg Q2W in 228 (34.5%) patients treated beyond 12 weeks.

Across the pooled 5 Phase 3 ezetimibe-controlled studies, the LS mean percent change in LDL-C from baseline to Week 12 was -49.2% and -47.4% 75 mg Q2W (alirocumab with and without background statin, respectively); see Table 11.

Table 11:   **LS Mean Percent Change from Baseline in LDL-C with Alirocumab at Week 12 (before up-titration) and Week 24 in Pooled Analyses of Five Phase 3 Ezetimibe-controlled Studies**

Dose	Without Background Statin[a]		With Background Statin[b]	
	Alirocumab (N=178)	Ezetimibe (N=173)	Alirocumab (Additive Effect Beyond Statin) (N=669)	Ezetimibe (Additive Effect Beyond Statin) (N=436)
Week 12 (secondary endpoint, before up-titration)				
75 mg	-47.4 %	-16.7 %	-49.2 %	-22.3 %
Week 24 (primary endpoint)				
75/150 mg (up-titration studies)[c]	-45.6 %	-14.8 %	-48.9 %	-19.3 %

[a] Based on pooled analysis of MONO and ALTERNATIVE studies
[b] Based on pooled analysis of COMBO II, OPTIONS I, and OPTIONS II studies
[c] Dose was up-titrated in 43.9% of patients without background statins and treated beyond Week 12, and in 17.7% of patients treated with background statins beyond Week 12.

In studies in which patients received alirocumab on top of statins, up-titration was associated with an additional 14.2% mean reduction at Week 24. In studies in which patients did not receive a background statin, an additional 3.1% mean reduction was observed, with the majority of the effect seen in approximately 25% of patients who achieved at least an additional 10% LDL-C lowering. The FH I and ALTERNATIVE studies provide examples of the impact of titrating alirocumab with and without background statin (see Figure 17 and Table 18 , respectively).

Figure 17: **LS Mean Percent Change (95% CI) in LDL-C over Time for Patients on Statins by Alirocumab Up-titration Status (FH I)**
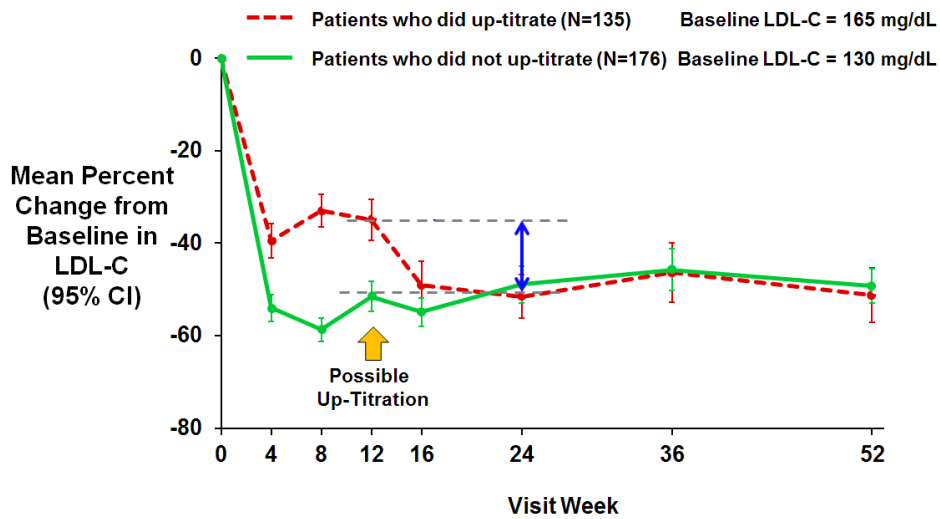
Observed data from ITT population. 95% CIs are presented as descriptive due to post-randomization stratification.

Figure 18: **LS Mean Percent Change (95% CI) in LDL-C over Time for Patients not on Statins by Alirocumab Up-titration Status (ALTERNATIVE)**
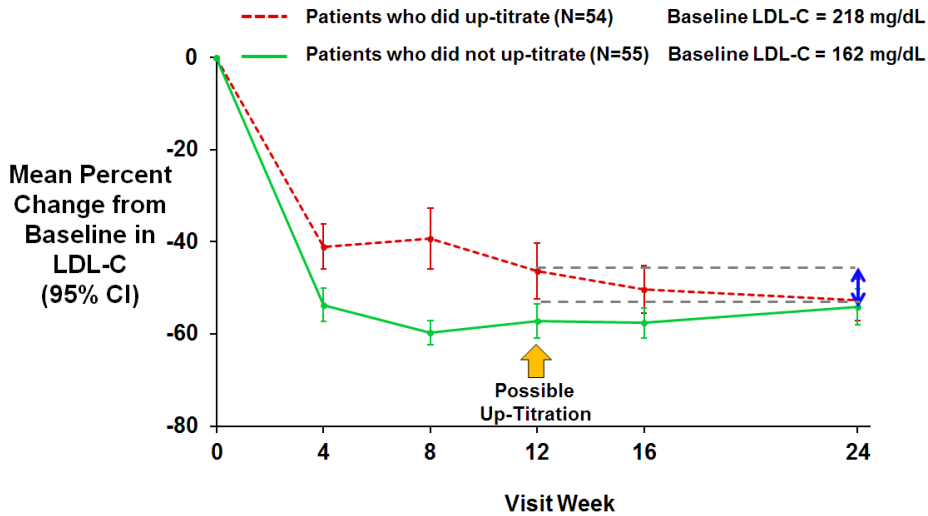
Observed data from ITT population. 95% CIs are presented as descriptive due to post-randomization stratification.

8.3.2. LDL-C Treatment Goals

Even in the studies with the highest mean baseline LDL-C (ALTERNATIVE and HIGH FH), approximately one third of patients were able to achieve an LDL-C level of <70 mg/dL at Week 24 from a mean baseline over 190 mg/dL. This proportion varied from 59.4% to 79.3% in the other studies (Figure 19). The range of the percent of patients on alirocumab who achieved a ≥50% reduction in LDL-C at Week 24 was from 54.6% in COMBO I to 75.7% in LONG TERM (Figure 20).

Figure 19: **Proportion of Patients Reaching Calculated LDL-C <70 mg/dL at Week 24 (ITT analysis)**

Comparison Study	% of patients reaching target		Odds Ratio (95% CI) Alirocumab vs. Control	P-value	N Patients	
	Control	Alirocumab			Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	8.0%	79.3%		<0.0001	780	1530
HIGH FH	2.9%	32.4%		0.0082	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	9.0%	75.0%		<0.0001	106	205
FH I	0.8%	59.8%		<0.0001	163	322
FH II	1.2%	68.2%		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	45.6%	77.0%		<0.0001	240	467
OPTIONS I	52.2%	78.6%		<0.0001	99	101
OPTIONS II	42.5%	68.6%		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	0.8%	32.5%		<0.0001	122	126
MONO	2.4%	59.4%		<0.0001	51	52

0.1 1 10 100 1000

← Favors control   Favors alirocumab →

Figure 20: **Proportion of Patients Achieving a ≥ 50% Reduction in Calculated LDL-C at Week 24 (ITT analysis)**

Comparison Study	% of patients reaching target		Odds Ratio (95% CI) Alirocumab vs. Control	P-value	N Patients	
	Control	Alirocumab			Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	1.9%	75.7%		<0.0001	780	1530
HIGH FH	8.7%	55.3%		<0.0001	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	3.3%	54.6%		<0.0001	106	205
FH I	0.0%	56.8%		<0.0001	163	322
FH II	0.0%	60.2%		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	8.9%	62.2%		<0.0001	240	467
OPTIONS I	9.1%	64.4%		<0.0001	99	101
OPTIONS II	9.7%	56.2%		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	2.5%	57.9%		<0.0001	122	126
MONO	0.0%	61.5%		<0.0001	51	52

0.1 1 10 100 1000

← Favors control   Favors alirocumab →

8.3.3. Non-HDL-C, Apo B, and Total Cholesterol

Non-HDL-C, Apo B and Total-C capture a broader spectrum of atherogenic lipoproteins than LDL-C. Non-HDL-C and Apo B are recognized treatment targets in recent therapeutic guidelines.[7] The change over time of these parameters mirrored those observed for LDL-C. LS mean difference versus control in percent change from baseline in Apo B to Week 24 ranged from -30.3 to -54.0% in the placebo-controlled studies and from -21.4% to -25.8% in the active-controlled studies (Figure 21). LS mean difference versus control in percent change from baseline in non-HDL-C ranged from -35.8 to -52.4% and from -22.9 to -25.6% in the placebo- and ezetimibe-controlled studies, respectively (Figure 22). LS mean difference versus control in percent change from baseline Total-C ranged from -25.0 to -38.7% and -14.6 to -20.8% in the placebo- and ezetimibe-controlled studies, respectively (Figure 23).

Figure 21: Percent Change in Apo B from Baseline to Week 24 (ITT analysis)

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	P-value	N Patients	
	Control	Alirocumab	Alirocumab - Control		Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	1.2 (1.0)	-52.8 (0.7)		<0.0001	780	1530
HIGH FH	-8.7 (3.8)	-39.0 (2.7)		<0.0001	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-0.9 (2.3)	-36.7 (1.6)		<0.0001	106	205
FH I	4.7 (1.6)	-41.1 (1.2)		<0.0001	163	322
FH II	-3.5 (2.0)	-42.8 (1.4)		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-18.3 (1.5)	-40.7 (1.1)		<0.0001	240	467
OPTIONS I	-12.0 (2.5)	-37.3 (2.5)		<0.0001	99	101
OPTIONS II	-10.8 (2.7)	-32.2 (2.7)		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-11.2 (1.7)	-36.3 (1.7)		<0.0001	122	126
MONO	-11.0 (2.4)	-36.7 (2.3)		<0.0001	51	52

-60 -40 -20 0 20 40 60

Favors alirocumab   Favors control

Figure 22: Percent Change in Non-HDL-C from Baseline to Week 24 (ITT analysis)

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI) Alirocumab - Control	P-value	N Patients	
	Control	Alirocumab			Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	0.7 (0.9)	-51.6 (0.6)		<0.0001	780	1530
HIGH FH	-6.2 (4.3)	-41.9 (3.1)		<0.0001	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-1.6 (2.5)	-39.1 (1.8)		<0.0001	106	205
FH I	9.6 (2.0)	-42.8 (1.4)		<0.0001	163	322
FH II	3.1 (2.5)	-42.6 (1.8)		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-19.2 (1.7)	-42.1 (1.2)		<0.0001	240	467
OPTIONS I	-17.6 (2.8)	-41.7 (2.7)		<0.0001	99	101
OPTIONS II	-12.0 (3.3)	-36.7 (3.2)		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-14.6 (1.7)	-40.2 (1.7)		<0.0001	122	126
MONO	-15.1 (2.9)	-40.6 (2.8)		<0.0001	51	52

-60 -40 -20 0 20 40 60

← Favors alirocumab   Favors control →

Figure 23: Percent Change in Total-C from Baseline to Week 24 (ITT analysis)

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI) Alirocumab - Control	P-value	N Patients	
	Control	Alirocumab			Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	-0.3 (0.7)	-37.8 (0.5)		<0.0001	780	1530
HIGH FH	-4.8 (3.6)	-33.2 (2.6)		<0.0001	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-2.9 (1.8)	-27.9 (1.3)		<0.0001	106	205
FH I	7.3 (1.5)	-31.4 (1.1)		<0.0001	163	322
FH II	2.1 (1.9)	-30.6 (1.4)		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-14.6 (1.2)	-29.3 (0.9)		<0.0001	240	467
OPTIONS I	-12.8 (2.0)	-30.0 (2.0)		<0.0001	99	101
OPTIONS II	-9.9 (2.3)	-24.5 (2.3)		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-10.9 (1.4)	-31.8 (1.4)		<0.0001	122	126
MONO	-10.9 (2.2)	-29.6 (2.1)		<0.0001	51	52

-50 -40 -30 -20 -10 0 10 20 30 40 50

← Favors alirocumab   Favors control →

8.3.4. Lipoprotein (a)

A consistent effect on Lp(a) was seen with alirocumab, with a statistically significant reduction ranging from -20.5 to -30.3% in the placebo-controlled studies versus -3.7 to -10.0% in the placebo group at Week 24 (Figure 24). In the ezetimibe-controlled studies, a similar decrease was seen with alirocumab, ranging from -16.7 to -27.8% compared to -5.1 to -12.3% for ezetimibe. A statistically significant difference was generally observed for alirocumab in comparison to ezetimibe, with the exception of the MONO study in which the ezetimibe effect was largest (-12.3%) and the difference between groups was not significant.

Figure 24: **Percent Change in Lp(a) from Baseline to Week 24 (ITT analysis)**

Comparison Study	% change from baseline Robust mean (SE)		Difference in % change from baseline Robust mean difference (95% CI) Alirocumab – Control	P-value	N Patients	
	Control	Alirocumab			Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	-3.7 (1.0)	-29.3 (0.7)		<0.0001	780	1530
HIGH FH	-8.7 (5.0)	-23.5 (3.7)		0.0164	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-5.9 (2.8)	-20.5 (2.0)		<0.0001	106	205
FH I	-7.5 (2.0)	-25.2 (1.4)		<0.0001	163	322
FH II	-10.0 (2.5)	-30.3 (1.8)		<0.0001	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-6.1 (2.0)	-27.8 (1.4)		<0.0001	240	467
OPTIONS I	-5.5 (2.9)	-25.9 (2.9)		<0.0001	99	101
OPTIONS II	-5.1 (3.2)	-25.2 (3.2)		<0.0001	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-7.3 (2.5)	-25.9 (2.4)		<0.0001	122	126
MONO	-12.3 (3.8)	-16.7 (3.7)		0.4013	51	52

-60 -40 -20 0 20 40 60

← Favors alirocumab   Favors control →

8.3.5. Fasting Triglycerides

Reductions in fasting TGs were observed across all of the Phase 3 studies with alirocumab. These ranged from -6.0 to -15.6% in the placebo-controlled studies and from -9.3 to -15.3% in the ezetimibe-controlled studies at Week 24 (Figure 25). Changes in fasting TGs were heterogeneous in the placebo groups, ranging from +6.3 to -5.4%, whereas ezetimibe decreased TGs by -3.6 to -12.8%. Accordingly, differences between alirocumab treatment and placebo were statistically significant in 3 of the 5 placebo-controlled studies while the comparisons to ezetimibe were not significant. Larger decreases in fasting TGs were observed in patients with mixed dyslipidemia, who represented 38.2% of the overall Phase 3 population, with decreases of -14.4 to -32.0% with alirocumab compared to -8.3 to -27.4% with placebo and -11.7 to -29.1% with ezetimibe.

Figure 25:   Percent Change in Fasting TGs from Baseline to Week 24 (ITT analysis)

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	P-value	N Patients	
	Control	Alirocumab	Alirocumab - Control		Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	1.8 (1.2)	-15.6 (0.8)		<0.0001	780	1530
HIGH FH	-1.9 (4.8)	-10.5 (3.3)		0.1386	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-5.4 (3.2)	-6.0 (2.3)		0.8699	106	205
FH I	6.3 (2.2)	-9.6 (1.6)		<0.0001	163	322
FH II	0.5 (2.8)	-10.4 (2.0)		0.0012	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-12.8 (2.0)	-13.0 (1.5)		0.9117	240	467
OPTIONS I	-8.1 (2.7)	-15.3 (2.7)		0.0568	99	101
OPTIONS II	-9.9 (3.2)	-10.1 (3.1)		0.9632	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	-3.6 (2.8)	-9.3 (2.7)		0.1426	122	126
MONO	-10.8 (4.3)	-11.9 (4.2)		0.8433	51	52

-40   -20   0   20   40

Favors alirocumab   Favors control

8.3.6.   HDL-C

Modest increases in HDL-C were typically observed with alirocumab, regardless of the dose and the background therapy, ranging from +3.5 to +8.8% compared to a heterogeneity of responses with placebo (ranging from -3.8 to +3.9%) and increases ranging from +0.5 to +6.8% with ezetimibe (Figure 26).

8.3.7.   Apolipoprotein A-1

Improvements in apolipoprotein A-1 (Apo A-1) were generally correlated with changes in HDL-C in the alirocumab and comparator groups, but did not reach statistical significance in most studies. For alirocumab, changes ranged from +2.8 to +7.0% across the Phase 3 studies (Figure 27).

Figure 26:   Percent Change in HDL-C from Baseline to Week 24 (ITT analysis)

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	P-value	N Patients	
	Control	Alirocumab	Alirocumab - Control		Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	-0.6 (0.5)	4.0 (0.4)		<0.0001	780	1530
HIGH FH	3.9 (2.7)	7.5 (1.9)		0.2745	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-3.8 (1.5)	3.5 (1.1)		0.0001	106	205
FH I	0.8 (1.2)	8.8 (0.9)		<0.0001	163	322
FH II	-0.8 (1.6)	6.0 (1.2)		0.0009	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	0.5 (1.1)	8.6 (0.8)		<0.0001	240	467
OPTIONS I	1.0 (1.7)	6.2 (1.7)		0.0306	99	101
OPTIONS II	0.8 (1.7)	8.1 (1.7)		0.0026	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	6.8 (1.7)	7.7 (1.7)		0.6997	122	126
MONO	1.6 (1.9)	6.0 (1.9)		0.1116	51	52

-20 -15 -10 -5   0   5   10   15   20

← Favors control   Favors alirocumab →

Figure 27:   Percent Change in Apo A-1 from Baseline to Week 24 (ITT analysis)

Comparison Study	% change from baseline LS means (SE)		Difference in % change from baseline LS mean difference (95% CI)	P-value	N Patients	
	Control	Alirocumab	Alirocumab - Control		Control	Alir.
Alirocumab 150 vs Placebo (with statins)						
LONG TERM	1.2 (0.6)	4.0 (0.4)		<0.0001	780	1530
HIGH FH	2.0 (2.1)	5.6 (1.5)		0.1715	35	71
Alirocumab 75/150 vs Placebo (with statins)						
COMBO I	-2.5 (1.2)	3.3 (0.9)		0.0002	106	205
FH I	0.3 (1.0)	5.0 (0.7)		0.0002	163	322
FH II	-1.6 (1.3)	2.8 (0.9)		0.0062	81	166
Alirocumab 75/150 vs Ezetimibe 10 (with statins)						
COMBO II	-1.3 (0.8)	5.0 (0.6)		<0.0001	240	467
OPTIONS I	-0.2 (1.2)	7.0 (1.2)		<0.0001	99	101
OPTIONS II	1.9 (1.4)	6.6 (1.4)		0.0142	97	101
Alirocumab 75/150 vs Ezetimibe 10 (without statin)						
ALTERNATIVE	2.9 (1.2)	4.8 (1.2)		0.2768	122	126
MONO	-0.6 (1.6)	4.7 (1.6)		0.0196	51	52

-20 -15 -10 -5   0   5   10   15   20

← Favors control   Favors alirocumab →

8.3.8. High Sensitivity C-Reactive Protein

In addition to lipid parameters, high-sensitivity C-reactive protein (hs-CRP) was measured as a biomarker of inflammation in the Phase 3 studies given the data that supports hs-CRP as a risk marker for CHD that is decreased by statins. Among the phase 3 clinical studies, there was no evidence for a change in hs-CRP with alirocumab compared to either placebo or ezetimibe. However, there were no entry criteria for hs-CRP and many patients were on a background of statins at entry. Since reductions in hs-CRP with statins are dependent on baseline elevations, an examination within the subset of patients that had baseline hs-CRP levels > 2 mg/L at baseline was also conducted. Among these patients, modest reductions were seen with alirocumab but they were not appreciably different than the changes observed with placebo. These data need to be considered along with the strong evidence in favor of LDL-C lowering as a surrogate for CV risk reduction and the genetic data that support various PCSK9 mutations as conferring a reduced risk for CV disease. Taken together, they raise questions with regard to the importance of hs-CRP reduction as an independent mechanism whereby statins reduce CV risk.

8.4. Efficacy Discussion and Conclusions

The alirocumab clinical development program included 10 Phase 3 studies with more than 5200 patients. Treatment with alirocumab was effective in reducing LDL-C either as an add-on to statins or in patients not on statins, with or without additional LMTs.

When pooling Phase 3 studies by comparator and the presence/absence of background statin therapy, the LS mean reductions in LDL-C from baseline to Week 24 were -45.6% to -48.9% with 75/150 mg Q2W dosing and -60.4% with 150 mg Q2W. Alirocumab demonstrated superiority of treatment over placebo when used as an add-on to a maximally tolerated statin dose in the 5 placebo-controlled trials. Alirocumab also demonstrated superiority in ezetimibe-controlled studies when administered as an add-on to a statin or to non-statin LMTs or as monotherapy including in patients with a history of statin intolerance. Analysis at week 12 allows for an examination of the 75 mg dose efficacy prior to titration. LS mean LDL-C reductions were -44.5% to -49.2% with the 75 mg dose compared to -62.6% with the 150 mg dose at week 12. Maximum efficacy was observed as early as 4 weeks after the initial dose, and efficacy was well maintained through at least 52 weeks in the six 52-week to 2-year studies.

LDL-C reductions observed with 75 mg and 150 mg Q2W doses allow for initial dose selection to be individualized, taking into account baseline LDL-C levels and CV risk status, and the goal of therapy. The usual starting dose is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks. Lipid levels can be assessed as early as 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dosage adjusted accordingly. This treatment scheme is in line with more individualized LDL-C targets as recommended by the most recent US guidelines. .

Similar LDL-C lowering efficacy was observed in heFH and non-FH patients, patients with mixed dyslipidemia and diabetic patients. Some differences by sex were observed, however clinically meaningful efficacy was achieved in both males and females. With the Q2W regimen, a consistent effect was seen regardless of the background therapy, including potent statins,

despite their impact on PCSK9 levels and, consequently, on alirocumab target-mediated clearance. Therefore, no dose adjustment is needed in any of the sub-populations.

While reductions in LDL-C represent the primary goal of treatment in guidelines and the primary efficacy parameter in the alirocumab program, alirocumab typically had beneficial effects on other lipid parameters. A consistent decrease in Lp(a) was observed. In statin-treated patients, the effect of alirocumab on TGs was significantly greater than placebo in most studies and was similar to improvements observed with ezetimibe.

9.   INTEGRATED PHASE 2 AND PHASE 3 SAFETY

Summary

- The safety profile of alirocumab in the Phase 3 program supports a positive benefit-risk assessment.

- No dose-related signals in safety were identified.

- A total of 5234 patients with hypercholesterolemia from the Phase 2 and Phase 3 studies were included in the double-blind safety pool. Ultimately, 3340 patients were treated with alirocumab for an overall exposure of 3451 patient-years. Nearly all patients in the Phase 3 studies were at high or very high CV risk, approximately 65% had a history of CHD and 30% reported a history of diabetes mellitus.

- The rates of TEAEs, treatment-emergent SAEs, and TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups.

- Among the common TEAEs, injection site reactions (HLT) (7.3% vs 5.2%) and pruritus (1.1% vs 0.4%) were identified as more common in patients taking alirocumab than control in multiple analyses.

- Discontinuations due to rare allergic adverse events such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were reported. The adverse events all resolved after discontinuation of therapy and, in some cases, a short course of topical or systemic corticosteroids.

- The rates of neurologic events, neurocognitive events, hepatic disorders, and clinically-meaningful changes in glycemic control were generally similar to placebo and ezetimibe in the pooled data.

- Studies were designed to have sufficient numbers of patients with low LDL-C values to support subgroup analyses. No specific safety signal was identified with 2 consecutive LDL-C values <25 mg/dL (n=795) or <15 mg/dL (n=288).

- No musculoskeletal safety concerns were identified. In the ALTERNATIVE study, fewer statin-intolerant patients taking alirocumab had skeletal muscle-related TEAEs than atorvastatin (HR: 0.61; 95% CI: 0.38 to 0.99) or ezetimibe (HR: 0.70; 95% CI: 0.47 to 1.06).

- All-cause mortality was 0.6% in the alirocumab group and 0.9% in the control group. The primary cause of death (as per adjudication) in the majority of these patients was CV events. There were no deaths in Phase 1 or 2 studies.

- In a pre-specified analysis of MACE in the global pool of Phase 3 studies, the hazard ratio was 0.82 (95% CI: 0.54 to 1.25). For a broader endpoint that included CHF and revascularizations that also had been prespecified, the hazard ratio was 1.07 (95% CI: 0.78 to 1.46). In a post-hoc analysis of MACE in the largest study (LONG TERM), the hazard ratio was 0.52 (95% CI 0.31 to 0.90). A large ongoing study (OUTCOMES) is powered to investigate the potential benefit of alirocumab on CV mortality and morbidity.

9.1.   Sources of Clinical Data

All patients randomized to alirocumab 75 mg or 150 mg, placebo, or ezetimibe in the four Phase 2 studies and ten Phase 3 studies are included in the integrated safety analysis. The numbers of patients included in the integrated safety analysis by study and intervention with the planned study durations are summarized in Table 12. Statin-only treatment arms in the ALTERNATIVE and OPTIONS studies were not pooled with the other controls and were examined separately.

The four completed Phase 2 studies include 3 dose-finding studies (DFI11565, CL-1003, and DFI12361) and one exploratory study (DFI 11566). Other Phase 2 studies were not pooled for assessment due to either their unique patient population (e.g., patients with PCSK9 or ApoB mutations) or their open-label design. All Phase 2 studies were of 12 weeks duration except for DFI11566 (8 weeks).

Table 12:   Number of Patients in Phase 2/3 Studies included in Integrated Safety Analyses

Phase	Study	Duration (Weeks)	N in Safety Population		
			Alirocumab	Placebo	Ezetimibe
Phase 2					
Placebo-controlled	CL-1003	12	16[a]	15	
	DFI11565	12	31[a]	31	
	DFI11566	8	61	31	
	DFI12361	12	50[b]	25	
Total			158	102	
Phase 3					
Placebo-controlled	FH I	78	322	163	
	FH II	78	167	81	
	HIGH FH	78	72	35	
	COMBO I	52	207	107	
	LONG TERM	78	1550	788	
Total			2318	1174	
Ezetimibe-controlled	COMBO II	104	479		241
	OPTIONS I	24	104		101
	OPTIONS II	24	103		101
	ALTERNATIVE	24	126		124
	MONO	24	52		51
Total			864		618
Grand Total			3340	1276	618

[a] Number of patients included in the alirocumab 150 mg Q2W group only.

[b] Number of patients included in the alirocumab 75 mg and 150 mg Q2W groups.

The ten Phase 3 studies included in the efficacy analyses are also included in the safety assessment. At the time of BLA submission, five of the studies were completed (COMBO I, MONO, OPTIONS I, OPTIONS II, double-blind treatment period of ALTERNATIVE) and the others are ongoing, but had completed the first-step analysis. For these ongoing studies, the cut-off date for safety data was the date when the last patient completed the Week 52 visit, except for LONG TERM, which had a cut-off date when approximately 600 patients had

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completed the 18-month double-blind treatment period. The safety database thus includes longer-term data from patients who enrolled early and who had exceeded the exposures mandated for the last patient(s) at the cut-off date (Table 14). The LONG TERM and FH I studies have since completed and the final data were provided to FDA in the 4-month safety update report. As agreed to with FDA, this briefing book will mostly present the data in the initial BLA; any exceptions will be noted.

9.1.1.   Safety Monitoring Procedures

An external independent Data Monitoring Committee (DMC) monitored the safety of patients enrolled in the Phase 2/3 studies on an ongoing basis. This DMC was set-up at the beginning of the Phase 2 program and monitored all studies dedicated to the LDL-C lowering indication. This DMC reviewed data at the study level as well as analyses pooled by the placebo-controlled studies and ezetimibe-controlled studies.

In addition, a second DMC was set up for the OUTCOMES study as this very large trial had a specific design and enrolled a different population. The Chairman of the Phase 2/3 DMC is also a member of the OUTCOMES study DMC, so any safety signal that might emerge could be shared and thoroughly considered by both DMCs during their periodic meetings.

The Phase 2/3 DMC is also an external and independent committee involved in the specific monitoring implemented for assessing the safety of LDL-C <25 mg/dL in studies with a treatment duration of at least 6 months. A designated DMC member was appointed to work in collaboration with an independent academic physician with access to unblinded lipid data to lead the review of all data for patients who achieved two consecutive LDL-C values <25 mg/dL. These two individuals are responsible for deciding whether or not a site needs to be notified that a given patient has experienced two consecutive LDL-C values <25 mg/dL. The site alert directs the Investigator to closely review results from the specific monitoring outlined in the protocol that focuses on potential consequences of low LDL-C, and to request additional evaluation or specialist consultation, as needed. In order to maintain the blind sites were also sent sham alerts about patients randomized to control.

Both DMCs continue to analyze the aggregate data for patients achieving an LDL-C <25 mg/dL during their periodic reviews and are to recommend adjustments to the monitoring plan, if needed.

9.1.2.   Safety Populations

Data from the Phase 2/3 studies are presented in the following categories:

- Pool of placebo-controlled Phase 2/3 studies (alirocumab versus placebo, each in addition to statin therapy)

- Pool of ezetimibe-controlled Phase 3 studies (including studies with and without concomitant statin therapy)

- Global pools of placebo- and ezetimibe-controlled Phase 2/3 studies, which were used to evaluate selected safety topics: injection site reactions, deaths, ADAs, and AEs in patients with 2 consecutive LDL-C <25 mg/dL. A global pool of placebo- and ezetimibe-controlled Phase 3 studies was used to evaluate adjudicated CV events.

Similarly, anti-drug antibodies were assessed separately in the global pool of Phase 3 studies.

The alirocumab 75 mg Q2W and 150 mg Q2W dosing regimens were aggregated. The initial rationale for aggregating across doses was suggested by the completed Phase 2 studies showing no dose-related safety signals and was confirmed by the absence of dose-related trends in the Phase 3 studies.

9.2. Methods for Safety Assessments

9.2.1. Safety Observation Period and AE Classification

The safety observation period started from the date that informed consent was signed and was divided into the following periods:

- Pre-treatment period: the time from the signed informed consent up to the first dose of the double-blind randomized treatment

- TEAE period: the time from the first dose of the double-blind randomized treatment up to 70 days after the last dose of the double-blind injection (to allow alirocumab serum concentrations to decline well below levels that could be measured)

- Post-treatment period: the time starting the day after the end of the TEAE period (71 days after the day of last dose of double-blind injection)

AEs were classified according to the respective observation period during which they developed or worsened or became serious.

9.2.2. Adverse Events and Laboratory Safety of Interest with Prespecified Monitoring/Adverse Events of Special Interest

Adverse events with prespecified monitoring (AEPMs) in the Phase 2 program and AESIs in the Phase 3 program were defined as AEs, serious or non-serious, that needed to be monitored, documented, and managed in a prespecified manner described in the individual study protocols. They were chosen based on the alirocumab mode of action, theoretical risks raised from literature and/or potential risks based on any findings in preclinical studies or in statin labeling. AEPMs/AESIs discussed in this briefing book include the following events:

- Local injection site reactions
- General allergic events
- Neurologic events
- Ophthalmologic events

- Neurocognitive events
- Musculoskeletal events
- ALT increase/hepatic events

In addition, new onset or worsening diabetes mellitus was evaluated.

9.2.3. Cardiovascular Events

In the Phase 3 program, the following suspected CV events and all deaths that occurred from randomization were to be sent to the Clinical Events Committee (CEC):

- Myocardial infarction (MI)

- Cerebrovascular events (including stroke, transient ischemic attack, intracranial bleeding, ischemia or bleeding of spine or retina)

- Unstable angina requiring an emergency room visit or requiring/prolonging hospitalization (with definite evidence of progression of ischemic condition)

- Congestive heart failure (CHF) requiring an emergency room visit or requiring/prolonging hospitalization

- All coronary revascularization procedures

- All deaths

In addition to specific AE case report forms CEC physicians could review coronary revascularization events and/or cardiac biomarkers to identify additional events of MI and unstable angina requiring hospitalization that may have not already been identified by the Investigators as potential CV events.

All adjudication was performed by the Duke Clinical Research Institute. The events were adjudicated to the following event categories:

- CHD death

- Nonfatal MI

- Fatal and nonfatal ischemic stroke

- Unstable angina requiring hospitalization (with definite evidence of progression of ischemic condition)

- Congestive heart failure requiring hospitalization

- Ischemia-driven coronary revascularization procedure

CV events that were confirmed by adjudication were analyzed using a time-to-first event analysis of the major adverse CV events (MACE): CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization. This MACE definition is the same designated as the primary efficacy composite endpoint in the OUTCOMES study. A broader composite of MACE plus CHF and revascularization (referred to as Treatment-Emergent CV Events Confirmed by Adjudication) was also analyzed.

9.2.4. Analysis of TEAEs

The analysis of all TEAEs was split into different tiers for signal detection and analysis of AEs:

- AESI: TEAEs with a scientific and/or regulatory basis for which a detailed analytical approach was prospectively defined.

- Common adverse events were adverse events for which there were no pre-specified hypotheses. We screened each of these adverse events separately using the Cox model and explored in greater detail those whose 95% CI of the hazard ratio excluded one.

9.2.5.   Sensitivity Analyses to Support Pooling the Doses in the Safety Pools

Alirocumab 75 mg Q2W was the starting dose in 8 of the 10 Phase 3 studies. Based on the results of LDL-C levels at Week 8, the dose could be up-titrated at Week 12 to 150 mg Q2W in a blinded manner. Alirocumab 150 mg Q2W continuous dosing was used in the other two Phase 3 studies. Of the 3188 patients randomized to alirocumab, approximately half (N=1563) participated in the 8 studies using the 75/150 mg up-titration scheme. The other 2 studies, LONG TERM and HIGH FH, with 1625 patients randomized to alirocumab, used the continuous 150 mg Q2W dosing regimen.

To identify any dose-related trends, patients who up-titrated to alirocumab 150 mg were compared to patients who remained on 75 mg. This approach showed no notable differences in adverse events between doses. However, this analysis compared post-randomization subgroups.

Therefore, the up-titration studies were compared to the studies that used 150 mg for the entire treatment period. This comparison was a reasonable way to compare the doses because more than 70% of patients in the up-titration studies only received the 75 mg dose of alirocumab. Again, no notable differences were identified.

These data support the evaluation of safety based on pooling of both doses of alirocumab.

9.3.   Patient Disposition and Extent of Exposure

9.3.1.   Disposition of Patients

In total, 5234 patients were exposed to a study treatment (alirocumab: 3340, placebo: 1276, and ezetimibe: 618) and included in the safety analyses. Table 13 shows the disposition of patients in the placebo-controlled and ezetimibe-controlled pools. The rates and reasons for not completing the study treatment periods were similar between the alirocumab and comparator groups. Of note, discontinuations for "other reasons" were not related to safety. Additionally, the rates of discontinuation for AEs were similar for alirocumab and control groups.

Table 13:   Patient Disposition for Randomized Patients in Safety Pools of Placebo-controlled and Ezetimibe-controlled Studies

	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1277)		Alirocumab (N=2482)		Ezetimibe (N=620)		Alirocumab (N=864)	
Randomized and 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%)
Completed study treatment period	349	(27.3%)	664	(26.8%)	284	(45.8%)	303	(35.1%)
Treatment ongoing	713	(55.8%)	1377	(55.5%)	206	(33.2%)	406	(47.0%)
Did not complete the study treatment period (as per CRF)	214	(16.8%)	435	(17.5%)	128	(20.6%)	155	(17.9%)
Reason for not completing the study treatment period								
Adverse event	66	(5.2%)	136	(5.5%)	60	(9.7%)	76	(8.8%)
Poor compliance to protocol	50	(3.9%)	79	(3.2%)	14	(2.3%)	18	(2.1%)
Other reasons[a]	97	(7.6%)	220	(8.9%)	54	(8.7%)	61	(7.1%)
Missing	1	(<0.1%)	0		0		0	

[a] Includes patients who completed the planned treatment duration but who otherwise did not fulfill the strict CRF criteria for study treatment period completion.

9.3.2.   Extent of Exposure

The safety analysis includes 3340 patients treated with alirocumab and 1894 patients treated with either placebo or ezetimibe in the double-blind Phase 2/3 studies.

In the placebo-controlled pool, approximately 80% of the patients were exposed for at least 52 weeks. The mean duration of exposure was similar in both treatment groups of approximately 58 weeks.

In the ezetimibe-controlled pool, the mean duration of exposure for alirocumab was 42 weeks and 36 weeks for ezetimibe. Approximately 47% of the patients in the alirocumab group and 40% in the ezetimibe group were exposed for at least 52 weeks.

Table 14: **Exposure to Randomized Treatment in Safety Population of Placebo-controlled and Ezetimibe-controlled Studies**

	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Cumulative injection exposure (patient-years)	1407.6	2758.5	419.4	692.2
Duration of injection exposure (weeks)				
Mean (SD)	57.6 (22.4)	58.3 (21.9)	35.5 (22.0)	41.9 (23.1)
Median	65.1	65.1	24.0	27.3
Min: Max	2.0 : 84.9	2.0 : 84.0	2.0 : 94.1	2.0 : 93.4
Duration of IMP injection exposure by category				
≥1 day to <4 weeks	13 (1.0%)	24 (1.0%)	15 (2.4%)	21 (2.4%)
≥4 weeks to <16 weeks	160 (12.5%)	270 (10.9%)	62 (10.0%)	60 (6.9%)
≥16 weeks to <52 weeks	92 (7.2%)	177 (7.1%)	331 (53.6%)	371 (42.9%)
≥52 weeks to <76 weeks	721 (56.5%)	1424 (57.5%)	179 (29.0%)	345 (39.9%)
≥76 weeks	289 (22.7%)	575 (23.3%)	30 (4.9%)	64 (7.4%)

Note: Duration of IMP injection exposure in weeks is defined as: (last IMP injection date + 14 days – first IMP injection date)/7, regardless of intermittent discontinuations.

9.4. Demographics and Medical Characteristics of Study Population

9.4.1. Demography

Details of the demographics and patient characteristics in the placebo-controlled and ezetimibe-controlled pools are shown in Table 15.

In the placebo-controlled pool, most of the randomized patients were white (89.0 to 90.1%), the proportion of Black patients ranged from 4.1 to 4.5%, approximately 6.3% of patients were of Hispanic or Latino ethnicity, and nearly 3% were Asian. Most patients were men (60%), the mean age was 59 years, and approximately 6% of patients were aged 75 years or more.

In the ezetimibe-controlled pool, most patients were white (86.2 to 88.3%), the proportion of Black patients ranged from 5.8 to 6.0%, 5.8 to 6.7% were of Hispanic or Latino ethnicity, and 4.4 to 4.7% were Asian. The mean age was 62 years and approximately 9% were aged 75 years or older. Approximately 65% of the patients were male.

The above data reflect the global nature of the Phase 3 program. The demographics of patients at US sites more closely match the US demographics of the patients intended for alirocumab treatment.

Table 15: **Demographics and Patient Characteristics at Baseline in Pools 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)
Age (years), mean ± SD	58.5 ± 11.3	58.6 ± 11.6	62.1 ± 9.5	61.9 ± 9.4
Age group (years), n (%)				
<45	145 (11.4%)	290 (11.7%)	21 (3.4%)	28 (3.2%)
≥45 to <65	733 (57.4%)	1381 (55.8%)	354 (57.3%)	483 (55.9%)
≥65 to <75	322 (25.2%)	642 (25.9%)	185 (29.9%)	275 (31.8%)
≥75	76 (6.0%)	163 (6.6%)	58 (9.4%)	78 (9.0%)
Sex, n (%)				
Male	763 (59.8%)	1482 (59.9%)	387 (62.6%)	581 (67.2%)
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 or African American	57 (4.5%)	101 (4.1%)	37 (6.0%)	50 (5.8%)
Asian	37 (2.9%)	75 (3.0%)	27 (4.4%)	41 (4.7%)
Other	46 (3.6%)	68 (2.7%)	8 (1.3%)	28 (3.2%)
Hispanic or Latino ethnicity, n (%)	77 (6.2%)	153 (6.3%)	41 (6.7%)	50 (5.8%)
Weight (kg), mean ± SD	86.8 ± 18.0	86.0 ± 18.8	87.0 ± 18.7	88.2 ± 19.8
BMI (kg/m^2), n (%)				
<25	200 (15.7%)	438 (17.7%)	111 (18.0%)	152 (17.6%)
≥25 to <30	515 (40.5%)	979 (39.6%)	226 (36.6%)	336 (38.9%)
≥30	558 (43.8%)	1054 (42.7%)	281 (45.5%)	376 (43.5%)
Region, n (%)				
North America	426 (33.4%)	795 (32.1%)	331 (53.6%)	419 (48.5%)
Western Europe	467 (36.6%)	929 (37.5%)	131 (21.2%)	156 (18.1%)
Eastern Europe	200 (15.7%)	403 (16.3%)	73 (11.8%)	147 (17.0%)
Rest of World	183 (14.3%)	349 (14.1%)	83 (13.4%)	142 (16.4%)

9.4.2. Medical History

Patients' CV history and CV risk factors are provided only for Phase 3 studies since patients were only specifically questioned about CHD and CHD risk equivalents in Phase 3 studies.

All patients in the Phase 3 placebo-controlled study pool and the majority of patients in the ezetimibe-controlled group were at high or very high CV risk based on derivations from guidelines in effect at the time the studies were initiated (NCEP-ATP III [21], ESC/EAS 2011[7], and ESC/other European societies 2012 [17]). The majority of patients in both pools had a history of CHD, other CV history, and/or a cluster of risk factors that classified them in the very high CV risk category (Table 16).

Table 16: **Overview of Cardiovascular History and Other CV Risk Factors in Pools of Phase 3 Placebo- controlled Studies and Ezetimibe-controlled Studies**

	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1174)	Alirocumab (N=2318)	Ezetimibe (N=618)	Alirocumab (N=864)
Any CV 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 MI	421 (35.9%)	757 (32.7%)	206 (33.3%)	352 (40.7%)
Silent MI	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[a]	322 (27.4%)	616 (26.6%)	203 (32.8%)	305 (35.3%)
Coronary heart disease risk equivalents	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%)
Moderate chronic kidney disease	138 (11.8%)	284 (12.3%)	50 (8.1%)	82 (9.5%)
Known history of diabetes mellitus (type 1 or 2) and additional risk factors	207 (17.6%)	387 (16.7%)	57 (9.2%)	84 (9.7%)
Other medical history of special interest				
Hypertension	820 (69.8%)	1570 (67.7%)	438 (70.9%)	641 (74.2%)
Type 1 diabetes	11 (0.9%)	13 (0.6%)	1 (0.2%)	3 (0.3%)
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%)
Categorization of CV risk per protocol				
Very high CV risk	975 (83.0%)	1883 (81.2%)	431 (69.7%)	674 (78.0%)
High CV risk	199 (17.0%)	435 (18.8%)	120 (19.4%)	114 (13/2%)
Moderate CV risk	0	0	65 (10.5%)	71 (8.2%)

[a] Diagnosed by invasive or non-invasive testing.

9.4.3. Disease Characteristics at Baseline

In the placebo-controlled pool, patients' disease characteristics at baseline were well-balanced and approximately one third of patients had heFH. In the ezetimibe-controlled pool, disease characteristics were also well-balanced at baseline with non-FH accounting for over 90% of patients. The mean time from hypercholesterolemia diagnosis was approximately ten years in both pools (Table 17).

Table 17: Disease Characteristics in Pools of Placebo-controlled and Ezetimibe-controlled Studies

	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1189)	Alirocumab (N=2334)	Ezetimibe (N=618)	Alirocumab (N=864)
Type of hypercholesterolemia				
Heterozygous familial hypercholesterolemia (heFH)	433 (36.4%)	853 (36.5%)	43 (7.0%)	40 (4.6%)
Non-familial hypercholesterolemia (non-FH)	756 (63.6%)	1481 (63.5%)	575 (93.0%)	824 (95.4%)
Time from hypercholesterolemia diagnosis (years)				
Mean ± SD	10.4 ± 9.0	10.3 ± 9.0	10.3 ± 9.1	10.0 ± 8.1
Median	8.0	8.3	8.3	8.3

9.4.4. Other Relevant Baseline Characteristics

In the placebo- and ezetimibe-controlled pools, the median HbA_{1c} was 5.8% in each of the pooled treatment arms, and approximately 20% of patients had baseline HbA_{1c} values $\geq 6.5\%$. Approximately 30% of the Phase 3 population was diabetic at study entry.

In this population mostly treated with statins, high-sensitivity C-reactive protein (hs-CRP) levels were generally low. In the placebo- and ezetimibe-controlled pools, median hs-CRP values were approximately 0.16 mg/dL and 0.17 mg/dL, respectively.

In both the placebo-and ezetimibe-controlled pools, the baseline estimated glomerular filtration rates (eGFR) were categorized as being mildly decreased (≥ 60 and <90 mL/min/1.73m^2). Between 14.7% and 17.5% of the pooled arms had a moderate decrease in GFR (≥ 30 to <60 mL/min/1.73m^2). The distribution of baseline eGFR was balanced across the treatment groups.

9.4.5. Relevant Concomitant Medications

Most patients were receiving maximum tolerated doses of statins. Approximately 54% of patients in the placebo-controlled pool and 46% of patients in the ezetimibe-controlled pool were taking "high-intensity statins", defined as atorvastatin 40 to 80 mg and rosuvastatin 20 to 40 mg. In the placebo-controlled pool, approximately one quarter of patients were taking ezetimibe, and a third were taking any LMT other than nutraceuticals.

In the ezetimibe-controlled pool, background LMTs reflected the inclusion criteria of the studies comprising the pool, with 2 studies conducted among patients who did not receive statins (MONO and ALTERNATIVE) and other studies using less than maximal doses of statins (OPTIONS studies).

In both pools, 87% to 90% of patients received concomitant CV medications. Antithrombotic agents were taken by more than 70% of patients with acetylsalicylic acid being the most frequently reported individual concomitant medication taken by 59.7 % of patients.

9.5. Common Adverse Events

9.5.1. Overall Summaries of Adverse Events

In the placebo-controlled pool, the percentages of patients who experienced at least one TEAE, at least one treatment-emergent SAE, and any TEAE leading to permanent treatment discontinuation were similar between the alirocumab and placebo groups (Table 18). On-study deaths were reported in 0.7% of patients in the alirocumab group and 0.8% patients in the placebo group.

In the ezetimibe-controlled pool, the percentages of patients receiving alirocumab and placebo with at least one TEAE, treatment-emergent SAE, or TEAE leading to treatment discontinuation were similar. On-study deaths were reported in 0.2% of patients in the alirocumab group and 1.1% of patients in the ezetimibe group.

Table 18: **Overview of Treatment Emergent Adverse Events in Pools of Placebo-controlled and Ezetimibe-controlled Studies**

AE Type	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1276)		Alirocumab (N=2476)		Ezetimibe (N=618)		Alirocumab (N=864)	
Any TEAE	975	(76.4%)	1876	(75.8%)	421	(68.1%)	607	(70.3%)
Any treatment emergent SAE	182	(14.3%)	340	(13.7%)	69	(11.2%)	113	(13.1%)
Any TEAE leading to permanent treatment discontinuation	65	(5.1%)	131	(5.3%)	60	(9.7%)	76	(8.8%)
Death on study	10	(0.8%)	18	(0.7%)	7	(1.1%)	2	(0.2%)

9.5.2. Common Adverse Events in the Placebo-Controlled Pool

TEAEs that were reported by at least 5% of patients in any group were as follows (listed in decreasing order in the alirocumab group): nasopharyngitis (11.3% in the alirocumab group versus 11.1% with the placebo group), injection site reaction (HLT) (7.3% versus 5.2%), upper respiratory tract infection (6.1% versus 7.0%), influenza (5.7% versus 4.6%), headache (4.8% versus 5.2%), and arthralgia (4.0% versus 5.5%) (Table 19).

Table 19: **Number (%) of Patients with TEAE(s) that Occurred ≥ 5% in Any Treatment Group**

Adverse Events	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1276)		Alirocumab (N=2476)		Ezetimibe (N=618)		Alirocumab (N=864)	
Injection site reactions (HLT)	66	(5.2%)	180	(7.3%)	13	(2.1%)	26	(3.0%)
Nasopharyngitis	141	(11.1%)	279	(11.3%)	35	(5.7%)	47	(5.4%)
Upper respiratory tract infection	89	(7.0%)	152	(6.1%)	37	(6.0%)	51	(5.9%)
Influenza	59	(4.6%)	141	(5.7%)	14	(2.3%)	32	(3.7%)
Headache	66	(5.2%)	119	(4.8%)	21	(3.4%)	34	(3.9%)
Myalgia	44	(3.4%)	104	(4.2%)	47	(7.6%)	58	(6.7%)
Arthralgia	70	(5.5%)	98	(4.0%)	25	(4.0%)	36	(4.2%)

HLT: high-level MedDRA term

9.5.3. Common Adverse Events in the Ezetimibe-Controlled Pool

TEAEs that were reported in ≥5% of patients in any group were as follows (listed in decreasing order in the alirocumab group): myalgia (6.7% in the alirocumab group versus 7.6% in the ezetimibe group), upper respiratory tract infection (5.9% versus 6.0%), and nasopharyngitis (5.4% versus 5.7%) (Table 19).

9.5.4. Analysis of Common Adverse Events

Analysis of common TEAEs revealed that the lower bound of the 95% CI for the HR versus placebo was greater than 1.0 for injection site reactions (HLT), pruritus (PT), upper respiratory tract signs and symptoms (HLT), appetite disorders (HLT), and oropharyngeal pain (PT) (Table 20). The majority of injection site reactions (HLT) were reported as injection site reactions (PT) in both treatment groups. For upper respiratory tract signs and symptoms (HLT), oropharyngeal pain (PT) was the most frequent PT reported. For appetite disorders, both decreased and increased appetite were reported, with decreased appetite being twice more frequently reported than increase appetite. Of note, there was no imbalance for AEs consistent with weight loss or malnutrition.

In contrast, the following common TEAEs were more frequently reported in the placebo group than the alirocumab group with an upper bound of the 95% CI for the HR versus placebo less than 1.0: musculoskeletal and connective tissue and pain discomfort (HLT), arthralgia (PT), pain in extremity (PT), neck pain (PT), asthenia (PT), musculoskeletal chest pain (PT), bladder and urethral symptoms (HLT), migraine headaches (HLT), respiratory tract disorders NEC (HLT), and non-site-specific gastrointestinal hemorrhages (HLT) (Table 20).

A similar analysis for the ezetimibe-controlled pool found that the lower bound of the 95% CI for the HR versus ezetimibe was greater than 1.0 for bronchospasm and obstruction (HLT). The difference was mostly due to the term "chronic obstructive pulmonary disease (COPD)", which was reported in 1.2% of patients in the alirocumab group and no patients in the ezetimibe group. In contrast, the incidence of COPD in the placebo-controlled pool was 0.9% with alirocumab and 1.5% with placebo.

Overall, only 2 TEAEs, injection site reactions and pruritus occurred more frequently in the alirocumab group than in the control group in both the placebo-controlled and ezetimibe-controlled pools and were therefore judged as potentially related to alirocumab therapy.

Table 20:   Summary Analysis of TEAEs whose 95% CI of HR Excludes 1.0 in the Placebo-controlled Pool

Adverse Events, n (%)	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
TEAEs occurring at a higher incidence in the alirocumab group				
Injection site reactions (HLT)	66 (5.2%)	180 (7.3%)	13 (2.1%)	26 (3.0%)
Upper respiratory tract signs and symptoms (HLT)	12 (0.9%)	50 (2.0%)	4 (0.6%)	8 (0.9%)
Oropharyngeal pain	6 (0.5%)	30 (1.2%)	4 (0.6%)	5 (0.6%)
Pruritus	5 (0.4%)	28 (1.1%)	3 (0.5%)	7 (0.8%)
Appetite disorders (HLT)	1 (0.1%)	22 (0.9%)	0	0
TEAEs occurring at a higher incidence in the placebo group				
Musculoskeletal and connective tissue pain and discomfort (HLT)	150 (11.8%)	236 (9.5%)	45 (7.3%)	58 (6.7%)
Arthralgia	70 (5.5%)	98 (4.0%)	25 (4.0%)	36 (4.2%)
Pain in extremity	53 (4.2%)	65 (2.6%)	11 (1.8%)	16 (1.9%)
Neck pain	19 (1.5%)	16 (0.6%)	5 (0.8%)	3 (0.3%)
Musculoskeletal chest pain	17 (1.3%)	13 (0.5%)	0	0
Asthenia	15 (1.2%)	14 (0.6%)	6 (1.0%)	8 (0.9%)
Bladder and urethral symptoms (HLT)	15 (1.2%)	12 (0.5%)	5 (0.8%)	2 (0.2%)
Migraine headaches (HLT)	12 (0.9%)	9 (0.4%)	0	0
Non-site specific gastrointestinal hemorrhages (HLT)	9 (0.7%)	3 (0.1%)	0	0
Diverticula (HLT)	7 (0.5%)	4 (0.2%)	2 (0.3%)	4 (0.5%)
Respiratory tract disorders NEC (HLT)	7 (0.5%)	4 (0.2%)	0	0

HLT: high-level MedDRA term

9.6.   Deaths

In the global pool of Phase 2/3 studies, 20 (0.6%) and 17 (0.9%) on-study deaths were reported in the alirocumab and the control groups, respectively. All deaths occurred in the Phase 3 studies. The primary adjudicated cause of death was CV events (Table 21). The current data are insufficient to draw a conclusion on the effect of alirocumab on the incidence of death. A large scale study (OUTCOMES), which is ongoing, is powered to investigate the potential benefits of alirocumab on CV mortality and morbidity.

Table 21: **Summary of Death Adjudication Results in Global Safety Pool of Phase 3 Studies**

Cause of death	Control (N=1792)		Alirocumab (N=3182)	
Death on study	17	(0.9%)	20	(0.6%)
CHD death	9	(0.5%)	12	(0.4%)
Any cardiovascular death	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%)

Note: one death reported as extensive traumatic intracranial hemorrhage in the alirocumab group was included in the total number of deaths but had not been adjudicated at the cut-off date.

9.7. Treatment Emergent Serious Adverse Events

The overall incidence of treatment-emergent SAEs was similar in the alirocumab and placebo groups: 340 (13.7%) versus 182 (14.3%), respectively (Table 22). No relevant difference between the treatment groups was observed for any individual SOC. The overall incidence of treatment-emergent SAEs was similar in the alirocumab and ezetimibe groups: 113 (13.1%) versus 69 (11.2%), respectively (Table 22).

Table 22: **Summary of Treatment Emergent SAEs in Placebo-controlled and Ezetimibe-controlled Pools by SOC**

Treatment Emergent SAEs by System Organ Class	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1276)		Alirocumab (N=2476)		Ezetimibe (N=618)		Alirocumab (N=864)	
Any treatment emergent SAE	**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 tissue 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%)
Respiratory, thoracic and mediastinal disorders	15	(1.2%)	23	(0.9%)	3	(0.5%)	5	(0.6%)
Gastrointestinal disorders	18	(1.4%)	22	(0.9%)	4	(0.6%)	13	(1.5%)
General disorders and administrative site conditions	15	(1.2%)	19	(0.8%)	8	(1.3%)	5	(0.6%)
Vascular disorders	11	(0.9%)	16	(0.6%)	4	(0.6%)	4	(0.5%)
Renal and urinary disorders	8	(0.6%)	15	(0.6%)	3	(0.5%)	2	(0.2%)
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%)

Note: Only SOCs that recorded a treatment-emergent SAE rate of 0.5% or higher in any arm is shown.

9.8. Adverse Events Leading to Permanent Treatment Discontinuation

In the placebo-controlled pool, the overall incidence of TEAEs leading to treatment discontinuation was similar in the alirocumab (131 [5.3%]) and placebo (65 [5.1%]) groups (Table 23); these occurred at a similar rate over time (Figure 28). In the alirocumab group, the most frequently reported TEAEs that led to treatment discontinuation were injection site reaction, nausea, myalgia, fatigue, and ALT increased.

In the ezetimibe-controlled pool, the overall incidence of TEAEs leading to treatment discontinuation was similar in the alirocumab (76 [8.8%]) and ezetimibe (60 [9.7%]) groups with a comparable rate over time (Figure 29). In the alirocumab group, the most frequently reported TEAEs that led to treatment discontinuation were myalgia, headache, and injection site reaction. The relatively high rate of skeletal muscle-related TEAEs is primarily driven by the ALTERNATIVE study which included a patient population solely with documented statin intolerance.

Table 23: **Number (%) of Patients with TEAE(s) Leading to Permanent Treatment Discontinuation in Placebo-controlled and Ezetimibe-controlled Pools**

Preferred Term	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1276)		Alirocumab (N=2476)		Ezetimibe (N=618)		Alirocumab (N=864)	
Any TEAE leading to discontinuation	65	(5.1%)	131	(5.3%)	60	(9.7%)	76	(8.8%)
Nausea	2	(0.2%)	5	(0.2%)	2	(0.3%)	2	(0.2%)
Injection site reaction	4	(0.3%)	5	(0.2%)	1	(0.2%)	3	(0.3%)
Myalgia	1	(<0.1%)	4	(0.2%)	23	(3.7%)	21	(2.4%)
Fatigue	4	(0.3%)	4	(0.2%)	1	(0.2%)	2	(0.2%)
ALT increased	1	(<0.1%)	4	(0.2%)	1	(0.2%)	2	(0.2%)
Anemia	0		3	(0.1%)	0		0	
Vertigo	1	(<0.1%)	3	(0.1%)	1	(0.2%)	0	
Diarrhea	2	(0.2%)	3	(0.1%)	1	(0.2%)	1	(0.1%)
Pruritus	0		3	(0.1%)	0		0	
Hypersensitivity	1	(<0.1%)	2	(<0.1%)	0		2	(0.2%)
Arthralgia	1	(<0.1%)	2	(<0.1%)	4	(0.6%)	2	(0.2%)
Pain in extremity	1	(<0.1%)	2	(<0.1%)	2	(0.3%)	2	(0.2%)
Dizziness	3	(0.2%)	1	(<0.1%)	1	(0.2%)	2	(0.2%)
Headache	2	(0.2%)	1	(<0.1%)	3	(0.5%)	3	(0.3%)
Vision blurred	0		1	(<0.1%)	0		2	(0.2%)
Myocardial infarction	2	(0.2%)	1	(<0.1%)	0		0	
Abdominal discomfort	0		1	(<0.1%)	2	(0.3%)	1	(0.1%)
Abdominal pain	2	(0.2%)	1	(<0.1%)	1	(0.2%)	0	
Back pain	3	(0.2%)	1	(<0.1%)	2	(0.3%)	2	(0.2%)
Transaminases increased	0		1	(<0.1%)	0		2	(0.2%)
Dementia	2	(0.2%)	0		0		0	
Atrial fibrillation	2	(0.2%)	0		0		2	(0.2%)
Muscular weakness	1	(<0.1%)	0		3	(0.5%)	1	(0.1%)
Musculoskeletal pain	0		0		0		2	(0.2%)
Renal cyst	1	(<0.1%)	0		0		2	(0.2%)
Chest discomfort	0		0		0		2	(0.2%)
Blood cortisol decreased	2	(0.2%)	0		0		0	
Blood creatine phosphokinase increased	2	(0.2%)	0		0		1	(0.1%)

Note: TEAEs occurring in at least 3 patients or at least 2 patients at a rate of 0.2% in any treatment arm are shown.

Figure 28: **Study-adjusted Kaplan-Meier Cumulative Incidence Curve for Time to Premature Treatment Discontinuation due to AE in Pool of Placebo-controlled Studies**
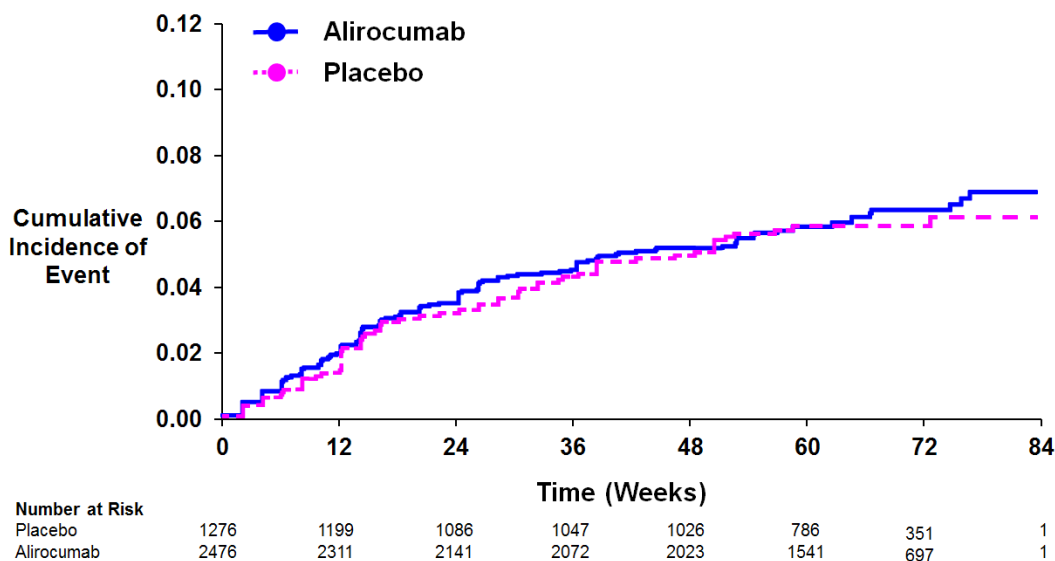
Figure 29: **Study Adjusted Kaplan-Meier Cumulative Incidence Curve for Time to Premature Treatment Discontinuation due to AE in Pool of Ezetimibe-controlled Studies**
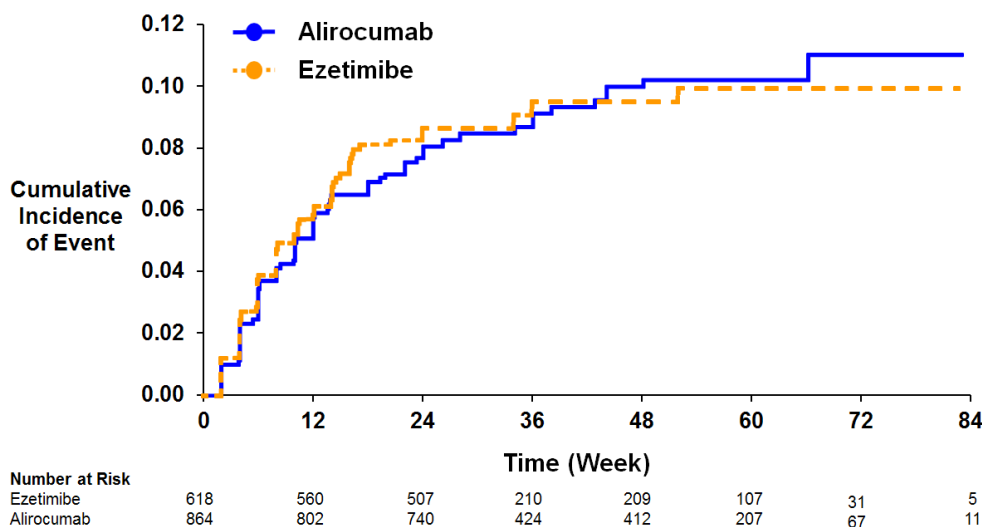
9.9. Adverse Events of Special Interest (AESI)

9.9.1. Local Injection Site Reactions

In the global pool of placebo- and ezetimibe-controlled studies, the percentages of patients who reported local injection site reactions were 6.1% and 4.1% in the alirocumab and pooled control groups, respectively (Table 24).

Table 24:   Summary of Local Injection Site Reaction AEs

	Global Pool	
Local injection site reactions	**Control (N=1894)**	**Alirocumab (N=3340)**
Any event, n (%)	78 (4.1%)	205 (6.1%)
Events per 100 person-years	4.2	6.0
Hazard ratio (95% CI)	1.50 (1.15 to 1.95)	
SAEs, n (%)	0 (0.0%)	0 (0.0%)
Leading to discontinuation, n (%)	6 (0.3%)	8 (0.2%)

The majority of local injection site reactions were mild and transient; only a single patient in the alirocumab treatment group reported a severe local injection site reaction, which resolved without treatment or any action taken. No serious local injection site reactions were reported in any treatment group. Symptoms associated with local injection site reactions, included erythema/redness (2.9%), swelling (2.3%), pain (1.9%), and hematoma (0.3%).

Most injection site reactions occurred before Week 24 in both groups. The cumulative probability of an injection site reaction by Week 24 was 5.2% in the alirocumab group and 3.4% in the control group.

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% of patients compared to 5.9% in patients without treatment-emergent ADA (N=2886). Injection site reactions in ADA positive patients were all mild with only one event leading to treatment discontinuation. No other risk factors were identified for the occurrence of local injection site reactions.

9.9.2.   Allergic Adverse Events

Overall, potential general allergic events were reported at slightly higher rates in the alirocumab group versus control in each of the placebo-controlled and ezetimibe-controlled pools (Table 25). This small difference was attributed to a higher incidence of pruritus in the alirocumab groups. There were no consistent differences between groups in other allergic TEAEs.

Table 25: **Number (%) of Patients with General Allergic TEAE(s) by PT in Placebo-controlled and Ezetimibe-controlled Pools**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any general allergic TEAE				
n (%)	99 (7.8%)	213 (8.6%)	33 (5.3%)	59 (6.8%)
N events per 100 patient-years	7.2	7.9	7.3	8.4
Hazard ratio versus control (95% CI)	1.10 (0.87 to 1.40)		1.31 (0.85 to 2.02)	
SAEs, n (%)	5 (0.4%)	9 (0.4%)	2 (0.3%)	1 (0.1%)
Leading to discontinuation, n (%)	3 (0.2%)	16 (0.6%)	2 (0.3%)	7 (0.8%)
General allergic TEAE, n (%)				
Hypersensitivity (SMQ)	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%)
Rhinitis allergic	7 (0.5%)	7 (0.3%)	4 (0.6%)	4 (0.5%)

Note: only events occurring in at least 0.5% of patients in any group are shown.

Table 26: **Number (%) of Patients with General Allergic TEAE(s) Leading to Permanent Treatment Discontinuation in Placebo- and Ezetimibe-controlled Pools**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any allergic TEAE	2 (0.2%)	14 (0.6%)	2 (0.3%)	7 (0.8%)
Anaphylaxis	1	0	0	0
Angioedema	0	1	0	0
Conjunctivitis	0	2	0	0
Contact dermatitis	0	0	0	1
Flushing	0	1	0	1
Hypersensitivity	1	2	0	2
Hypersensitivity vasculitis[a]	0	0	0	1
Interstitial lung disease	0	1	0	0
Nummular eczema	0	1	0	0
Pruritus	0	3	0	0
Rash	0	3	1	1
Sneezing	0	0	0	1
Urticaria	0	0	1	0

[a] 1 patient in Phase 2 at 300 mg alirocumab dose discontinued study drug due to hypersensitivity vasculitis

In patients treated with alirocumab, potential general allergic events based on the Company MedDRA query were infrequently serious or the reason for permanent treatment discontinuation. General allergic events occurred at a similar incidence rate in patients with and without treatment-emergent ADA. Among the 147 patients in Phase 3 studies with positive

treatment-emergent ADA in the alirocumab group, general allergic events occurred in 8.8% of patients compared to 8.2% in patients without treatment-emergent ADA.

Discontinuations due to rare allergic adverse events, such as hypersensitivity, nummular eczema, and hypersensitivity vasculitis were noted (Table 26). All events resolved without clinical sequelae after discontinuation of alirocumab and, in some cases, treatment with a short course of corticosteroids. With respect to the other terms, the patient with angioedema had a history of recurrent angioedema, the patient with interstitial lung disease had rheumatoid arthritis, and contact dermatitis was attributed to an external cause.

9.9.2.1.   Placebo-Controlled Pool

Among the 213 patients who reported a general allergic TEAE in the alirocumab group, 61.5% and 34.7% reported mild or moderate events, respectively, compared to 66.7% and 28.3% mild or moderate in the placebo group.

Serious general allergic TEAEs were reported by 0.4% of patients in both treatment groups. No fatal case was reported. A total of 0.6% and 0.2% of patients in the alirocumab and placebo groups, respectively, discontinued due to a general allergic TEAE. Among the serious TEAEs reported in patients treated with alirocumab, cases of eczema nummular and hypersensitivity led to permanent treatment discontinuation.

Pruritus was the only TEAE reported with a notably higher rate in the alirocumab group compared to placebo (HR: 2.84 [95% CI: 1.10 to 7.36]). These reports could have been of generalized or localized pruritus but not at the injection site. Of the 28 patients in the alirocumab group who reported pruritus, 11 were reported to be of not allergic etiology, and none of the reports was serious. First onset of pruritus was more frequently reported in the first 24 weeks of treatment with alirocumab compared to placebo. It was the main reason for permanent treatment discontinuation in 3 patients. In most other patients, the event had recovered by the cut-off date of the first-step analysis. Most patients who reported pruritus had negative ADA.

9.9.2.2.   Ezetimibe-Controlled Pool

Consistent with the placebo-controlled pool, general allergic TEAEs were generally mild or moderate in intensity. Severe general allergic TEAEs were reported in 2 patients in the ezetimibe group and in no patients with alirocumab.

Serious general allergic TEAEs were rare events, reported in a single patient in the alirocumab group (hypersensitivity) and in 2 patients in the ezetimibe group (hypersensitivity and urticaria). General allergic TEAEs leading to permanent treatment discontinuation were reported more frequently in the alirocumab group (0.8%) compared to the ezetimibe group (0.3%).

9.9.3.   Neurologic Events

The effect of treatment on myelin-dependent adverse events was assessed in the global safety pool. The central nervous system synthesizes all the cholesterol it needs and is therefore not dependent on LDL-C and monoclonal antibodies are too large to pass the blood brain barrier. Therefore, if there are effects, we would only expect them to be in the peripheral nervous system. There was no observed imbalance between treatment groups for any particular PT with regard to prespecified neurologic events. In the placebo-controlled pool, the incidence rates of neurologic

events were 3.1 and 3.2 per 100 PY for patients in the alirocumab and placebo groups, respectively (HR: 0.98; 95% CI: 0.68 to 1.41). In the ezetimibe-controlled pool, the rates per 100 PY were 4.0 in the alirocumab group and 3.3 in the ezetimibe group (HR: 1.43; 95% CI: 0.76 to 2.69) (Table 27).

Table 27: **Number (%) of Patients with Neurological TEAE(s) in the Pools of Placebo-controlled and Ezetimibe-controlled Patients**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any neurologic TEAE				
n (%)	45 (3.5%)	86 (3.5%)	15 (2.4%)	29 (3.4%)
N events per 100 patient-years	3.2	3.1	3.3	4.0
Hazard ratio versus control (95% CI)	0.98 (0.68 to 1.41)		1.43 (0.76 to 2.69)	
SAEs, n (%)	1 (<0.1%)	5 (0.2%)	1 (0.2%)	2 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	5 (0.2%)	3 (0.5%)	4 (0.5%)
Demyelination (SMQ), n (%)	0	4 (0.2%)	0	1 (0.1%)
Guillain-Barre syndrome (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%)
Balance disorder	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	0
Gait disturbance	2 (0.2%)	1 (<0.1%)	1 (0.2%)	0
Hypoesthesia oral	2 (0.2%)	1 (<0.1%)	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%)
Neuropathy peripheral	5 (0.4%)	2 (<0.1%)	2 (0.3%)	3 (0.3%)
Neuralgia	2 (0.2%)	3 (0.1%)	1 (0.2%)	1 (0.1%)
Burning sensation	2 (0.2%)	4 (0.2%)	0	1 (0.1%)
Gait disturbance	2 (0.2%)	1 (<0.1%)	1 (0.2%)	0

Note: only events occurring in at least 0.2% of patients in any group are shown.

Among the 3 MedDRA queries, the 2 peripheral nervous system categories had similar incidences of AEs in the alirocumab and control group. The "demyelination" category had the fewest events, but was the only MedDRA query with an imbalance between alirocumab and control (Table 28).

Table 28: **Number (%) of Patients with Demyelination TEAE(s) in the Pools of Placebo-controlled and Ezetimibe-controlled Patients**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Demyelination (SMQ), n (%)	0	4 (0.2%)	0	1 (0.1%)
Trigeminal neuralgia	0	2 (<0.2%)	0	0
Demyelination	0	1 (<0.1%)	0	0
Optic neuritis (perineuritis)	0	1 (<0.1%)	0	0
Myelitis transverse	0	0	0	1 (0.1%)

Looking at the demyelination category in more detail, we see individual events that have different pathologic mechanisms and that are not unexpected for this patient population. Two patients had trigeminal neuralgia, which is usually due to nerve compression. One had optic perineuritis, which, in this patient population, would typically be due to giant cell arteritis. And a single case each of multiple sclerosis and transverse myelitis is consistent with the expected incidence rates for the patient population studied.

So there does not appear to be a safety signal. Nonetheless, we will continue to evaluate these types of rare events in our ongoing cardiovascular outcomes trial. Narratives for these two these cases are provided in Section 13.5.

9.9.3.1. Placebo-Controlled Pool

The only TEAE reported with a higher incidence in the alirocumab group was paresthesia (1.0% with alirocumab versus 0.7% with placebo). All cases of paresthesia were of mild or moderate intensity and none were considered serious or led to premature discontinuation. Other TEAEs suggestive of neuropathy were not reported at a higher incidence in the alirocumab group and several, including decreased vibratory sense and neuropathy peripheral, occurred at a higher incidence in the placebo group. The percentage of patients who experienced neurologic events that led to permanent treatment discontinuation was 0.2% in both groups.

9.9.3.2. Ezetimibe-Controlled Pool

Paresthesia was reported with a higher incidence in the alirocumab than the ezetimibe group (6 [0.7%] in the alirocumab group versus 2 [0.3%] in the ezetimibe group) whereas muscular weakness was higher in the ezetimibe group (3 [0.3%] in the alirocumab group versus 5 [0.8%] in the ezetimibe group). The number of patients who experienced serious neurologic events was low and similar in both the alirocumab and the ezetimibe groups. The percentage of patients who experienced neurologic events that led to permanent treatment discontinuation was 0.5% in both groups.

9.9.4. Neurocognitive Events

Neurocognitive events were AEs of interest because they have been described with post-marketing use of statins. The brain synthesizes all the cholesterol it needs and is therefore not dependent on serum LDL-C. Thus, this effect of statins may be through some unique mechanism, such as the inhibition of brain HMG Co-A reductase.

In the placebo-controlled pool, almost all patients took concomitant statins in addition to alirocumab or placebo. In the ezetimibe-controlled pool, approximately 75-80% of all patients received a concomitant statin.

Neurocognitive events of interest were analyzed in 2 ways. The first used a Company MedDRA Query (CMQ)-based on the 5 following high-level group terms (HLGTs): deliria including confusion, cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders. The second used a more focused set of terms proposed by the FDA and based on a systematic review of neurocognitive events with statins[41].

In the placebo- and ezetimibe-controlled pools, neurocognitive events were reported overall at a low incidence and were similar between the alirocumab and control groups using both FDA's and Sponsor's CMQ (Table 29 and Table 30). Moreover, there was no meaningful difference in in the incidence or type of events in alirocumab-treated patients who experienced 2 or more consecutive LDL-C values <25 mg/dL compared to those who did not. Importantly, the placebo-controlled pool includes four 78-week studies and one 52-week study. In the LONG TERM study, which was the largest of the four 78-week studies included in the placebo-controlled pool, neurocognitive events occurred at a higher rate in the alirocumab group compared to the placebo group using the Sponsor's CMQ (as reported in Robinson 2015[42]) but not with the FDA's query. Importantly, no patient treated with alirocumab in the Phase 2/3 program discontinued due to a neurocognitive event (Table 31).

Overall, the data suggest that the incidence of neurocognitive events with alirocumab use is similar to control, but with only 29 events in the alirocumab groups combined, the data cannot be considered definitive. The OUTCOMES study is expected to provide sufficient data for more robust analyses of these rare events. To this end, we have made neurocognitive events an AESI in the OUTCOMES study. This means that there will be enhanced documentation on these events. Moreover, we are enlisting a group of outside experts to advise us on the blinded collection of data during the study. This group will issue quarterly reports for the DMC and provide analyses of the data after they are unblinded at the end of the study.

Table 29: **Number (%) of Patients with Neurocognitive Disorder TEAE(s) in Placebo-controlled and Ezetimibe-controlled Pools**

	Placebo-controlled pool[a] (on top of statins)		Ezetimibe-controlled pool (+/- statin)		LONG TERM[a] (on top of statins)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)	Placebo N=788	Alirocumab N=1550
Sponsor's CMQ						
TEAEs	9 (0.7%)	21 (0.8%)	6 (1.0%)	8 (0.9%)	4 (0.5%)[b]	18 (1.2%)[b]
Rate per 100 PY	0.6	0.7	1.3	1.1	0.3	0.8
HR (95% CI)	1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)		2.28 (0.77 to 6.75)	
SAEs, n (%)	2 (0.2%)	3 (0.1%)	1 (0.2%)	1 (0.1%)	1 (0.1%)	3 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	0	2 (0.3%)	0	1 (0.1%)	0
FDA's CMQ						
TEAEs	11 (0.9%)	21 (0.8%)	6 (1.0%)	7 (0.8%)	6 (0.8%)	16 (1.0%)
Rate per 100 PY	0.8	0.7	1.3	1.0	0.5	0.7
HR (95% CI)	0.96 (0.46, 2.00)		0.80 (0.26, 2.40)		1.35 (0.53 to 3.46)	
SAEs, n (%)	4 (0.3%)	3 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	3 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	0	2 (0.3%)	0	1 (0.1%)	0

[a] LONG TERM study is the largest of four 78-week studies included in the placebo-controlled pool.
[b] Robinson 2015.[42]
PY = Patient Years at Risk

Table 30: **Number (%) of Patients with Neurocognitive Disorders TEAE(s) (Sponsor's CMQ)**

	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)		Global Alirocumab Pool[a] (+/- statin)	
PT: Preferred Term	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)	LDL-C ≥ 25mg/dL (N=2544)	2 LDL-C < 25mg/dL[b] (N=796)
Any event	**9 (0.7%)**	**21 (0.8%)**	**6 (1.0%)**	**8 (0.9%)**	**24 (0.9%)**	**5 (0.6%)**
Confusional state	1 (<0.1%)	6 (0.2%)	2 (0.3%)	2 (0.2%)	7 (0.3%)	1 (0.1%)
Amnesia	2 (0.2%)	5 (0.2%)	2 (0.3%)	1 (0.1%)	5 (0.2%)	1 (0.1%)
Memory impairment	1 (<0.1%)	5 (0.2%)	0	3 (0.3%)	7 (0.3%)	1 (0.1%)
Disturbance in attention	1 (<0.1%)	2 (<0.1%)	2 (0.3%)	0	2 (<0.1%)	0
Confusion postoperative	0	1 (<0.1%)	0	0	1 (<0.1%)	0
Dementia	2 (0.2%)	1 (<0.1%)	0	0	0	1 (0.1%)
Disorientation	0	1 (<0.1%)	0	0	1 (<0.1%)	0
Frontotemporal dementia	0	1 (<0.1%)	0	0	0	1 (0.1%)
Transient global amnesia	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	0	1 (<0.1%)	0
Aphasia	0	0	0	1 (0.1%)	1 (<0.1%)	0
Delirium	1 (<0.1%)	0	0	0	0	0
Dementia Alzheimer's type	1 (<0.1%)	0	0	1 (0.1%)	1 (<0.1%)	0
Hallucination	0	0	0	1 (0.1%)	1 (<0.1%)	0

[a] Patients receiving alirocumab in the global safety pool.
[b] Patients from the global alirocumab pool with two consecutive LDL‑C < 25mg/dL during the treatment period. 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.

Table 31:   Summary of Neurocognitive Events in Phase 2/3 Studies

Patient with any neurocognitive disorders	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any TEAE	9 (0.7%)	21 (0.8%)	6 (1.0%)	8 (0.9%)
Any treatment emergent SAE	2 (0.2%)	3 (0.1%)	1 (0.2%)	1 (0.1%)
AnyTEAE leading to death	1 (<0.1%)	0	0	0
Any TEAE leading to permanent treatment discontinuation	2 (0.2%)	0	2 (0.3%)	0

9.9.4.1.   Placebo-Controlled Pool

Overall, neurocognitive events were of mild to moderate severity, with a single severe event reported in the placebo group (dementia with a fatal outcome in a patient with multiple morbidities and recent traumas).

The mean age of patients who experienced neurocognitive events was 64 years for alirocumab patients and 67 years for placebo patients and thus these patients were older than the average study patient (overall mean age 59 years).

Serious neurocognitive events were reported in 3 (0.1%) patients in the alirocumab group (2 reports of dementia [one of which was frontotemporal in nature] and 1 report of confusion) and 2 (0.2%) patients in the placebo group (severe dementia with fatal outcome mentioned above, and dementia of unknown etiology).

9.9.4.2.   Ezetimibe-Controlled Pool

All neurocognitive events recorded in the ezetimibe-controlled pool were of mild or moderate intensity.

The mean age of patients who have experienced neurocognitive events was 70 years for alirocumab patients and 68 years for ezetimibe patients, and thus higher than the overall mean age of 59 years.

In each of the 2 groups, a single patient experienced a serious neurocognitive event: Alzheimer's dementia in the alirocumab group and confusional state in the ezetimibe group. Permanent treatment discontinuation due to a neurocognitive TEAE did not occur in the alirocumab group while it occurred in 2 (0.3%) patients in the ezetimibe group due to mental impairment in 1 patient and memory loss with confusion in the other patient.

9.9.5.   Musculoskeletal Related Events

Musculoskeletal related events have been associated with use of statins. Since all patients were taking concomitant statins, and in the Phase 3 studies, were on their maximally tolerated dose, these types of events are described in this section. Musculoskeletal related events were an AESI for a single study (ALTERNATIVE) that specifically enrolled patients with documented statin intolerance and included a statin-rechallenge arm as a calibrator.

Skeletal muscle-related events were identified by a CMQ which consisted of PTs most commonly associated with skeletal muscle-related events in statin intolerant patients. These

terms were selected by a subject matter expert with extensive experience in the diagnosis and treatment of statin intolerant patients. The CMQ terms were selected prior to database lock and the analysis performed on ALTERNATIVE and the placebo-controlled pool only. The analysis on musculoskeletal related events was not performed on the ezetimibe-controlled pool since the great majority of events in this pool were from the ALTERNATIVE study.

Clinically meaningful changes in creatinine phosphokinase levels were not associated with alirocumab use (Table 32).

Rare cases of rhabdomyolysis were reported in 2 patients in the alirocumab group. The first patient with rhabdomyolysis was an 81 year-old man who experienced the event after a fall, from which he could not rise for several hours. Although he was hospitalized with several concurrent SAEs, he recovered from the events. In this case, the rhabdomyolysis was almost certainly caused by the fall. The second patient was a 54 year-old woman who experienced a modest, asymptomatic elevation in creatinine phosphokinase (CPK) 5X ULN and no renal changes. The investigator discontinued study drug because of the CPK elevation and later downgraded the diagnosis to "myositis".

Additionally, evaluation of changes in the laboratory data for CPK levels did not show any relevant changes associated with alirocumab.

Table 32: **Number (%) of Patients with Abnormalities in CPK Levels in Placebo-controlled and Ezetimibe-controlled Pools**

Creatinine Kinase	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
>3 ULN	56 (4.5%)	77 (3.2%)	13 (2.2%)	19 (2.3%)
>10 ULN	8 (0.6%)	12 (0.5%)	2 (0.3%)	0 (0.0%)

9.9.5.1. Placebo-Controlled Pool

In the placebo-controlled pool, 15.1% patients in the alirocumab group versus 15.4% patients in the placebo group experienced a skeletal muscle-related TEAE.

The rate of patients who experienced a serious skeletal muscle-related TEAE was 0.2% (4 patients) in the alirocumab group and <0.1% (1 patient) in the placebo group. The rate of patients who experienced a skeletal muscle-related TEAE leading to permanent treatment discontinuation was 0.4% in the alirocumab and 0.5% in the placebo group. No fatal cases of skeletal muscle-related TEAEs were reported in any treatment group.

9.9.5.2. ALTERNATIVE Study

A description of the ALTERNATIVE study design and the definition of statin intolerance is provided in Section 7.2.3. Overall in ALTERNATIVE, there were fewer patients with skeletal muscle-related TEAEs in the alirocumab group than the atorvastatin (HR 0.61 [0.38 to 0.99]) or ezetimibe (HR 0.71 [0.47 to 1.06]) groups based on the CMQ (Figure 30).

An analysis of skeletal muscle-related TEAEs was performed by events reported on a check-box for skeletal muscle-related AEs on the electronic-Case Report Form (e-CRF). Similar to the

incidence based on the CMQ, skeletal muscle-related TEAEs based on the e-CRF definition occurred in fewer patients in the alirocumab group compared to the atorvastatin (HR 0.64 [0.39 to 1.04]) or ezetimibe (HR 0.68 [0.44 to 1.03]) groups.

Figure 30: **Kaplan-Meier Incidence Curve of Musculoskeletal AEs by Treatment Group Based on the CMQ in ALTERNATIVE Study**
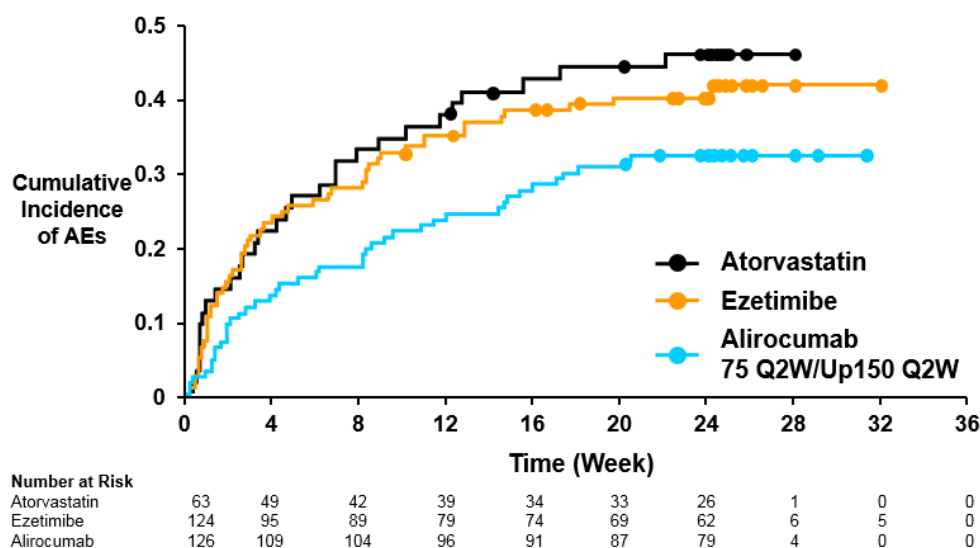
Patients in the alirocumab treatment group had a longer time to first occurrence of a skeletal muscle-related TEAE than patients in the atorvastatin and ezetimibe groups. The majority of all skeletal muscle-related TEAEs were mild to moderate in severity and the severity of skeletal muscle-related TEAEs was similar between treatment groups. No skeletal muscle-related TEAEs in any treatment group were considered SAEs. A lower percentage of patients in the alirocumab treatment group (15.9%) experienced skeletal muscle-related TEAEs that led to permanent IMP discontinuation than patients in the atorvastatin treatment group (22.2%) and the ezetimibe treatment group (20.2%).

9.9.6. Diabetes Mellitus

Increases in HbA_{1c} and fasting serum glucose levels have been reported with statins in recent CV outcomes trials. Given these data, the potential relationship of alirocumab use with worsening glycemic control was analyzed in the safety database. The approach used a variety of methods: analysis of TEAEs related to diabetes mellitus and diabetic complications, overall changes in mean levels of HbA_{1c}, and shifts in glucose control categories as determined by changes in levels of fasting glucose and HbA_{1c}. Overall, the data do not suggest a clinically meaningful effect on glycemic control.

9.9.6.1. Diabetes TEAEs

TEAEs related to diabetes were infrequent events, with a hazard ratio for alirocumab versus control of 1.07 and 0.71 in the placebo-controlled and ezetimibe-controlled pools, respectively (Table 33). Overall, the data do not suggest an effect of treatment on the incidence of investigator reports of diabetes or diabetic complication TEAEs.

Table 33: Number (%) of Patients with Diabetes Mellitus or Diabetic Complications TEAE(s) in the Placebo-controlled and Ezetimibe-controlled Studies

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any diabetes mellitus or diabetic complications TEAE				
n (%)	49 (3.8%)	103 (4.2%)	22 (3.6%)	25 (2.9%)
N events per 100 patient-years[a]	3.4	3.7	4.8	3.5
Hazard ratio versus control (95% CI)[b]	1.07 (0.76 to 1.50)		0.71 (0.40 to 1.26)	
Diabetes mellitus or diabetic complications TEAE n(%)				
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 incr.	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%)

[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.

Selection of PTs based on the primary and secondary HLGT 'diabetic complications', HLT 'diabetes mellitus', HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased', and PT 'hyperglycemia' Table sorted by decreasing incidence of PT within each SMQ in the alirocumab group of placebo-controlled pool.

9.9.6.2. Shift Analysis of Diabetes

Analyses were also performed to evaluate shifts in patients' glucose control status. Patients' glucose control status was categorized at baseline as either normal, impaired glucose control (IGC), or diabetic based on a combination of medical history and baseline laboratory values (Table 34). During the study, patients were assigned to the "worst" category based on meeting the definition at any time in the study. For example, a patient with fasting plasma glucose (FPG) ≥126 mg/dL on 2 consecutive occasions was assigned to the "diabetes" category during the study regardless of whether subsequent values were normal.

Only 3 patients in the program, 1 in the placebo group and 2 in the alirocumab group, shifted from the normal category to the diabetes category. For all 3 patients, the shift from a normal fasting glucose control to a diabetes category was based on transient changes in fasting glucose that were not associated with a change in HbA1c values. In one patient ,the change was associated with the development of B cell lymphoma and in a second with IV corticosteroid treatment.

An analysis of patient shifts from the IGC category at baseline to the diabetes category is provided in Table 35. Most patients who met the IGC criteria at baseline continued to meet those criteria during the studies. A small number of patients shifted at some time in the studies

to the diabetes category: 5.7% in the alirocumab group and 3.8% in the placebo group. The 2%-age point difference in shifts to diabetes, with more shifts in the alirocumab group, is mirrored by a greater number of shifts to the normal category in the alirocumab group compared to the placebo group. This suggested the possibility that at least some of the shifts in category were due to small changes in laboratory values near the borders between these categories.

To further explore the data in greater detail, we determined which criteria accounted for these shifts from IGC to diabetes (Table 36). Patients who met multiple criteria were assigned to the highest (in the table) criterion that they met. More than half of the shifts were due only to changes in FPG and not to changes in either the investigator's assessment of the patient or to changes in HbA_{1c}. When looked at individually, these shifts were mostly due to small changes close to the thresholds at baseline.

Table 34: **Definition of Baseline Glucose Control Categories Based on Medical History and Laboratory Values**

- Diabetes was defined as:
  - Type 1 or 2 diabetes reported in the medical history; or
  - Baseline HbA_{1c} ≥6.5%; or
  - Two values of fasting plasma glucose (FPG) (at screening and randomization) ≥126 mg/dL.
- Impaired glucose control was defined as:
  - Specific terms reported in the medical history; or
  - Baseline HbA_{1c} ≥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.

Table 35: **Change in Glucose Control Category –Patients with Impaired Glucose Control at Baseline (Phase 3 Placebo and Ezetimibe-controlled Pools)**

	Placebo-controlled pool		Ezetimibe-controlled pool	
Glucose Control Status	Placebo (N=420)	Alirocumab (N=865)	Ezetimibe (N=243)	Alirocumab (N=333)
Improved to normal	18.1%	20.6%	31.7%	28.2%
Remained with impaired glucose control	78.1%	73.8%	65.0%	67.9%
Worsened to diabetes	3.8%	5.7%	3.3%	3.9%

Table 36: **Shift to the Diabetes Category by AE or Lab – Patients with Impaired Glucose Control at Baseline (Phase 3 Placebo-controlled Pool)**

Criteria	Placebo (N=420)		Alirocumab (N=865)	
	n	%	n	%
Total	16	3.8%	49	5.7%
Assessment by Adverse Events	6	1.4%	16	1.8%
Assessment by Laboratory Results only				
HbA$_{1c}$ > 6.5[a]	6	1.4%	16	1.8%
Fasting glucose > 126 mg/dL (only)	4	1.0%	17	2.0%

[a] HbA$_{1c}$ with or without elevated glucose

9.9.6.3. New Onset or Worsening Diabetes in Subgroups of Patients with or without Medical History of Diabetes at Baseline

To evaluate further whether the shifts noted above were detecting clinically meaningful changes in glycemic status, we also looked at a prespecified subgroup analysis of diabetes-related TEAEs in patients with and without a medical history of diabetes at baseline. In the patients without diabetes at baseline (Table 37), diabetes-related TEAEs reflected the new onset of clinical diabetes or clinically meaningful laboratory values as assessed by the investigator. There was no increase in the incidence of diabetes-related TEAEs in patients without diabetes at baseline or in the analysis of patients with diabetes at baseline (Table 38).

Table 37: **Number (%) of Patients with Diabetes-related TEAE(s) – Patients without Diabetes at Baseline in the Safety Population in the Placebo-controlled and Ezetimibe-controlled Pools**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=909)	Alirocumab (N=1766)	Ezetimibe (N=428)	Alirocumab (N=582)
Any diabetes mellitus or diabetic complications TEAE				
n (%)	18 (2.0%)	28 (1.6%)	9 (2.1%)	9 (1.5%)
N events per 100 patient-years[a]	1.8	1.4	2.8	1.8
Hazard ratio versus control (95% CI)[b]	0.79 (0.44 to 1.43)		0.55 (0.22 to 1.41)	
Diabetes mellitus or diabetic complications TEAE n(%)				
Diabetes mellitus or diabetic complications (CMQ)	18 (2.0%)	28 (1.6%)	9 (2.1%)	9 (1.5%)
Type 2 diabetes mellitus	9 (1.0%)	20 (1.1%)	2 (0.5%)	5 (0.9%)
Diabetes mellitus	5 (0.6%)	6 (0.3%)	2 (0.5%)	2 (0.3%)
Glucose tolerance decreased	0	1 (<0.1%)	0	0
Hyperglycemia	2 (0.2%)	1 (<0.1%)	2 (0.5%)	1 (0.2%)
Blood glucose increased	1 (0.1%)	0	3 (0.7%)	1 (0.2%)
Glycosylated hemoglobin increased	1 (0.1%)	0	0	0

[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

Selection of PTs based on the primary and secondary HLGT 'diabetic complications', HLT 'diabetes mellitus', HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased', and PT 'hyperglycemia'
Table sorted by decreasing incidence of PT within each SMQ in the alirocumab group of placebo-controlled pool.

Table 38: **Number (%) of Patients with Diabetes-related TEAE(s) - Patients with Diabetes at Baseline in the Safety Population in the Placebo-controlled and Ezetimibe-controlled Pools**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=367)	Alirocumab (N=710)	Ezetimibe (N=190)	Alirocumab (N=282)
Any diabetes mellitus or diabetic complications TEAE				
n (%)	31 (8.4%)	75 (10.6%)	13 (6.8%)	16 (5.7%)
N events per 100 patient-years[a]	7.6	9.4	9.4	7.1
Hazard ratio versus control (95% CI)[b]	1.20 (0.79 to 1.83)		0.82 (0.39 to 1.72)	
Diabetes mellitus or diabetic complications TEAE n(%)				
Diabetes mellitus or diabetic complications (CMQ)	31 (8.4%)	75 (10.6%)	13 (6.8%)	16 (5.7%)
Diabetes mellitus	9 (2.5%)	26 (3.7%)	8 (4.2%)	5 (1.8%)
Diabetes mellitus inadequate control	7 (1.9%)	12 (1.7%)	1 (0.5%)	3 (1.1%)
Type 2 diabetes mellitus	3 (0.8%)	11 (1.5%)	0	0
Hyperglycemia	4 (1.1%)	8 (1.1%)	1 (0.5%)	2 (0.7%)
Diabetic neuropathy	1 (0.3%)	6 (0.8%)	1 (0.5%)	3 (1.1%)
Blood glucose increased	3 (0.8%)	5 (0.7%)	2 (1.1%)	0
Diabetic retinopathy	2 (0.5%)	5 (0.7%)	0	1 (0.4%)
Glycosylated hemoglobin incr.	1 (0.3%)	5 (0.7%)	0	1 (0.4%)
Diabetic foot	0	2 (0.3%)	0	1 (0.4%)
Diabetic nephropathy	0	2 (0.3%)	1 (0.5%)	1 (0.4%)

[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

Selection of PTs based on the primary and secondary HLGT 'diabetic complications', HLT 'diabetes mellitus', HLT 'carbohydrate tolerance analyses (incl diabetes)' excluding PT 'Blood glucose decreased', and PT 'hyperglycemia' Table sorted by decreasing incidence of PT within each SMQ in the alirocumab group of placebo-controlled pool

9.9.6.4.   Hemoglobin A_{1c}

To further assess any effect of treatment on glycemic control, mean HbA_{1c} was compared across treatment groups within the patient subgroups defined in Table 34. No effect of treatment was seen in any of the subgroups in either the placebo-controlled or ezetimibe-controlled pool (Figure 31).

Figure 31: **HbA$_{1c}$ by Treatment Group and Baseline Diabetes Status (Normal/Impaired Glucose Control/Diabetic) in the Placebo-Controlled and Ezetimibe-Controlled Pools**
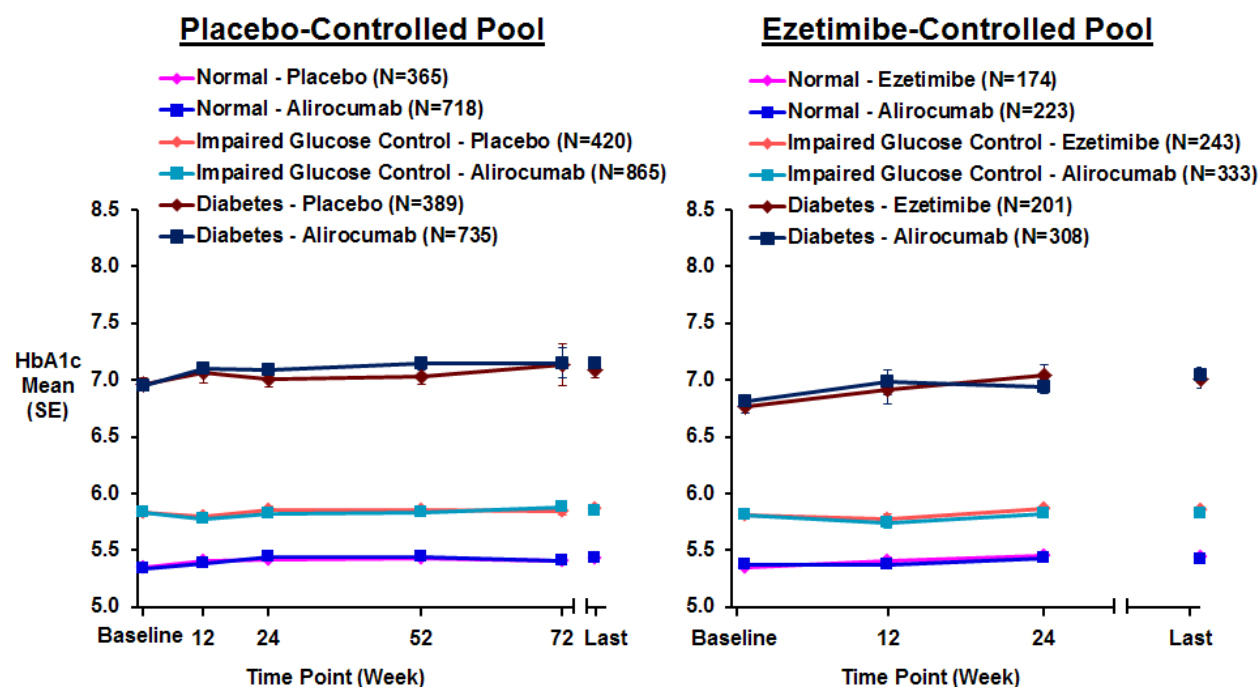
9.9.6.5. Diabetes Conclusion

The data do not suggest an effect of alirocumab on glycemic control. Clinically meaningful changes in glycemic control were infrequently observed in the safety database and at similar rates in the alirocumab and control groups. However, effects of statins on glycemic control were not observed until data from the large outcomes studies were available. This topic will be studied further in the CV OUTCOMES study.

9.9.7. Ophthalmologic Events

Ophthalmologic TEAEs were infrequent events reported at slightly higher rates in the alirocumab groups compared with the control groups in both the placebo- and the ezetimibe-controlled pool. Incidence rates per 100 patient-years were 1.6 in the alirocumab group and 1.2 in the placebo group in the placebo-controlled pool and 1.0 in the alirocumab group and 0.6 in the ezetimibe group in the ezetimibe-controlled pool. A difference in the incidence of cataracts was seen in alirocumab-treated patients who had 2 or more consecutive LDL-C values < 25 compared to alirocumab-treated patients who did not have these low LDL-C values (see Section 9.12.4). However, the apparent difference should be interpreted cautiously because the baseline characteristics are different between these post-randomization subgroups. Moreover, there was no difference in the incidence of cataracts in alirocumab-treated patients compared to the control groups in either the placebo-controlled or ezetimibe-controlled pools. Thus, the data do not suggest a direct effect of alirocumab treatment. We will continue to assess this in additional datasets as they become available.

9.10. Laboratory Data of Interest

9.10.1. ALT Increase and Hepatic Disorders

The incidence of hepatic disorder TEAEs including single elevations of ALT reported as a TEAE was somewhat higher in the alirocumab plus statin group compared to the placebo plus statin group (Table 39). In contrast, it was somewhat lower in the alirocumab (± statin) group compared to the ezetimibe (± statin) group. For the serious hepatic disorder TEAEs and TEAEs leading to permanent treatment discontinuation, confounding factors or alternative causes (e.g., viral hepatitis) were identified in a majority of cases.

In addition, the descriptive and potentially clinically significant abnormality (PCSA) analyses of liver function tests (ALT, aspartate aminotransferase [AST], and bilirubin) did not reveal any hepatic safety concern associated with the use of alirocumab (Table 40). Three patients with combined increase of ALT and bilirubin were identified and none were considered cases of Hy's law. Two patients were in the placebo group; the one patient in the alirocumab group had acute hepatitis E. Overall, no safety concern related to liver disorders is associated with the use of alirocumab.

Table 39: **Number (%) of Patients with TEAE(s) Related to Hepatic Disorders by PT in Pools of Placebo-controlled and Ezetimibe-controlled Pools**

Adverse Event	Placebo-controlled pool (on top of statins)		Ezetimibe-controlled pool (+/- statin)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Any related to hepatic disorders TEAE				
n (%)	23 (1.8%)	61 (2.5%)	14 (2.3%)	16 (1.9%)
N events per 100 patient-years	1.6	2.2	3.1	2.2
Hazard ratio versus control (95% CI)	1.36 (0.84 to 2.20)		0.69 (0.34 to 1.43)	
SAEs, n (%)	1 (<0.1%)	8 (0.3%)	0	1 (0.1%)
Leading to discontinuation, n (%)	2 (0.2%)	9 (0.4%)	1 (0.2%)	4 (0.5%)
Related to hepatic disorders TEAE, n (%)				
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
Transaminases increased	0	1 (<0.1%)	1 (0.2%)	2 (0.2%)
Blood bilirubin increased	0	0	2 (0.3%)	2 (0.2%)
Hepatic cyst	1 (<0.1%)	0	1 (0.2%)	2 (0.2%)
Liver function test abnormal	1 (<0.1%)	0	0	2 (0.2%)

Note: only events occurring in at least 0.2% of patients in any group are shown.

Table 40: **Number (%) of Patients with Abnormalities in ALT, AST, Alkaline Phosphatase, and Combined ALT and Total Bilirubin Levels in Placebo-controlled and Ezetimibe-controlled Pools**

Parameter	Placebo-controlled pool (on top of statins)				Ezetimibe-controlled pool (+/- statin)			
	Placebo (N=1276)		Alirocumab (N=2476)		Ezetimibe (N=618)		Alirocumab (N=864)	
ALT								
>3 ULN	18	(1.4%)	41	(1.7%)	1	(0.2%)	9	(1.1%)
>5 ULN	7	(0.6%)	8	(0.3%)	0		5	(0.6%)
AST								
>3 ULN	18	(1.4%)	28	(1.1%)	0		10	(1.2%)
>5 ULN	5	(0.4%)	7	(0.3%)	0		4	(0.5%)
Alkaline Phosphatase								
>1.5 ULN	13	(1.0%)	11	(0.4%)	6	(1.0%)	7	(0.8%)
Combined ALT and Total Bilirubin								
ALT > 3 ULN and BILI > 2 ULN	2	(0.2%)	1	(<0.1%)	0		0	

9.10.1.1. Placebo-Controlled Pool

Hepatic disorders TEAEs were mostly laboratory abnormalities, among which ALT increased was the most frequently reported.

Serious hepatic disorder TEAEs were reported in 8 (0.3%) patients in the alirocumab group compared to 1 (<0.1%) in the placebo group. Many of these SAEs in the alirocumab group were transaminase elevations, however the incidence of transaminase elevations were similar between treatment groups (Table 40). Hepatic disorder TEAEs leading to permanent treatment discontinuation were reported in 9 (0.4%) patients the alirocumab group and 2 (0.2%) patients in the placebo group.

9.10.1.2. Ezetimibe-Controlled Pool

A single serious hepatic disorder TEAE (hepatitis E) was reported in the alirocumab group in this pool. Four (0.5%) patients permanently discontinued treatment in the alirocumab group and 1 (0.2%) in the ezetimibe group.

9.10.2. Steroid Hormones

A theoretical risk of impaired gonadal or adrenal peripheral hormonal synthesis, due to low levels of LDL-C, was evaluated. In humans, cholesterol required for adrenal, ovarian, and testicular steroid biosynthesis is partially derived from uptake of circulating LDL-C by high affinity LDL receptors, with additional sources derived from de novo synthesis and uptake from the circulating HDL-C by the human homolog of the scavenger receptor class B type 1 (SR-B1).[43]

To assess whether reductions in LDL-C with alirocumab impacted levels of gonadal or adrenal hormones, total testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were evaluated in males and cortisol was measured in males and females in the LONG TERM study.

Although significant reductions in LDL-C were achieved, no relevant changes were observed in the mean changes from baseline for total testosterone, LH, or FSH. Changes from baseline in total testosterone, LH, and FSH over time are shown in Figure 32. The percentage of patients with abnormalities in gonadal hormones was comparable between the alirocumab and placebo groups. There was no apparent correlation between calculated LDL-C and total testosterone, LH, and FSH.

Figure 32:   **Change from Baseline in Gonadal Hormones in Males in the LONG TERM Study**
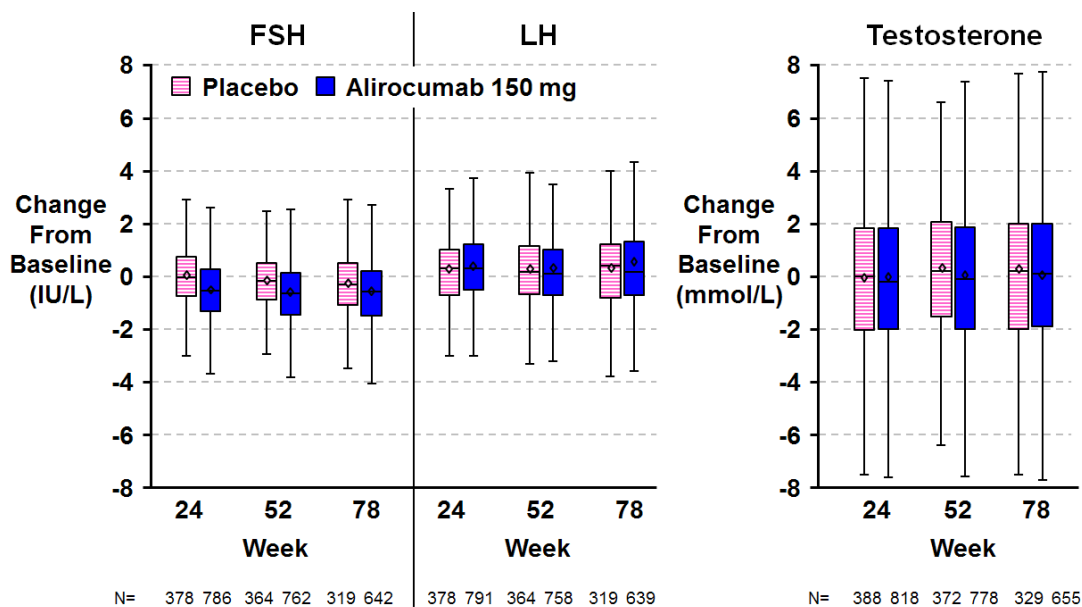
Cortisol (preferably an early morning sample, if possible) was evaluated in males and females in the LONG TERM study. If cortisol was less than the lower limit of normal range (LLN), then an adrenocorticotropic hormone (ACTH) level was measured on a blood specimen obtained at the same time point. If ACTH was greater than the upper limit of normal (ULN), then the patient underwent a 0.25 mg ACTH stimulation test. A single patient in the alirocumab group had a cortisol value < LLN and ACTH>ULN. However, no TEAE was reported for the patient considering that this occurred on the first day of the study. On Day 15, an abnormal ACTH stimulation test was reported and the patient was diagnosed with Addison's disease. Another patient in the alirocumab group had a reported TEAE of decreased blood cortisol because her cortisol level decreased during the study from 350 nmol/L (8AM baseline sample) to 233 nmol/L (unknown time of day, study day 167) (normal range >138 nmol/L). Neither patient had an LDL-C < 25 mg/dL.

No relevant differences between treatment groups for cortisol levels were observed during the study.

9.11.   **Cardiovascular Events Confirmed by Adjudication**

In Phase 3 studies, suspected CV events and all deaths that occurred from time of randomization until the follow-up visit were adjudicated by the CEC.

Analyses of the events confirmed by adjudication were performed on the global pool, placebo-controlled pool, and ezetimibe-controlled pool. The data from the adjudication are presented below with primary focus on MACE events (CHD death, nonfatal MI, fatal or nonfatal ischemic stroke, and unstable angina requiring hospitalization). The MACE composite endpoint represents hard events and therefore is generally considered the most appropriate and rigorous one to assess cardiovascular outcomes. It is the primary endpoint of the OUTCOMES study as agreed to by regulatory authorities. A broader composite of MACE plus CHF and revascularization (referred to as Treatment-Emergent CV Events Confirmed by Adjudication) is also presented.

The analyses of cardiovascular events confirmed by adjudication which include all data through the 4-month safety update report and, for the LONG TERM study, are the same as reported by Robinson et al. in The New England Journal of Medicine.[42]

9.11.1. Global Pool of Phase 3 Studies

The composite endpoints Treatment-Emergent MACE Confirmed by Adjudication and a broader composite of MACE plus CHF and revascularization (referred to as Treatment-Emergent CV Events Confirmed by Adjudication) were both prespecified in the integrated safety analysis plan.

9.11.1.1. MACE

Overall, there were fewer treatment-emergent MACE in the alirocumab arm when compared to placebo. There is study-by-study variability, consistent with the small number of events in some of the studies. Greater variability in estimating the HR was observed in the pool of ezetimibe-controlled studies likely due to the fact that in this pool there are relatively few events. The confirmed MACE composite endpoint occurred in 58 (1.8%) patients in the alirocumab group and in 36 (2.0%) patients in the control group (Table 41) with an associated HR of 0.82 (95% CI: 0.54 to 1.25). Results by study are shown in Figure 33.

Table 41: **Treatment-Emergent MACE Confirmed by Adjudication in Global Pool of Phase 3 Studies**

Category of Adjudication	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent MACE event		
n (%)	36 (2.0%)	58 (1.8%)
95% mid-p CI	1.4% to 2.7%	1.4% to 2.3%
Events per 100 patient-years	1.7	1.5
95% CI	1.2 to 2.4	1.1 to 1.9
Hazard ratio versus control (95% CI)	0.82 (0.54 to 1.25)	
Endpoint components		
CHD death (including undetermined cause)	10 (0.6%)	10 (0.3%)
Non-fatal MI	25 (1.4%)	33 (1.0%)
Fatal and non-fatal ischemic stroke[a]	3 (0.2%)	13 (0.4%)
Unstable angina requiring hospitalization	1 (<0.1%)	2 (<0.1%)

[a] Includes strokes not otherwise specified
Based on analyses of all data in the 4-month safety update, which include final data from the completed studies, LONG TERM and FH1.

Figure 33: **Forest Plot of Hazard Ratio for Treatment-Emergent MACE versus Control by Study in Phase 3 Placebo-controlled and Ezetimibe-controlled Studies**

Based on analyses of all data in the 4-month safety update, which include final data from the completed studies, LONG TERM and FH I.

9.11.1.2. Treatment-Emergent CV Events Confirmed by Adjudication (MACE, CHF Hospitalization, or Revascularization)

Treatment-emergent CV events confirmed by adjudication were reported in 121 (3.8%) patients in the alirocumab group and 59 (3.3%) patients in the control group, with an associated HR of 1.07 (95% CI: 0.78 to 1.46) (Table 42). Non-MACE cardiac events included congestive heart failure requiring hospitalization and coronary revascularization procedures. The latter was reported with somewhat higher frequency in the alirocumab group than in the control group. This will be further evaluated in the ongoing OUTCOMES study.

Table 42: **Treatment Emergent CV Events Confirmed by Adjudication in Global Pool of Phase 3 Studies**

Category of Adjudication	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent CV event confirmed by adjudication		
n (%)	59 (3.3%)	121 (3.8%)
95% mid-p CI	2.5% to 4.2%	3.2% to 4.5%
Events per 100 patient-years	2.8	3.1
95% CI	2.2 to 3.7	2.6 to 3.7
Hazard ratio versus control (95% CI)	1.07 (0.78 to 1.46)	
Endpoint components		
CHD death (including undetermined cause)	10 (0.6%)	10 (0.3%)
Non-fatal MI	25 (1.4%)	33 (1.0%)
Fatal and non-fatal ischemic stroke[a]	3 (0.2%)	13 (0.4%)
Unstable angina requiring hospitalization[b]	1 (<0.1%)	2 (<0.1%)
Congestive heart failure requiring hospitalization	6 (0.3%)	12 (0.4%)
Ischemia driven coronary revascularization procedure	35 (2.0%)	80 (2.5%)

[a] Includes strokes not otherwise specified
[b] With evidence of progressive ischemic condition
Based on analyses of all data in the 4-month safety update, which include final data from the completed studies, LONG TERM and FH1.

9.11.2. LONG TERM Study

Most of the MACE events occurred in the LONG TERM study, a 78-week placebo-controlled study of high CV risk patients taking a maximally tolerated dose of statin as background therapy. All patients in the active arm received alirocumab 150 mg Q2W. Cardiovascular events confirmed by adjudication are shown in Table 43 and a post-hoc analysis of MACE in Figure 34.

Table 43: **CV Events Confirmed by Adjudication in LONG TERM Study (final data)**

Cardiovascular events of interest, n(%)	Placebo (N=788)	Alirocumab 150 Q2W (N=1550)
Death from coronary heart disease, including death from unknown cause	7 (0.9%)	4 (0.3%)
Non-fatal MI	18 (2.3%)	14 (0.9%)
Fatal and non-fatal ischemic stroke	2 (0.3%)	9 (0.6%)
Unstable angina requiring hospitalization[a]	1 (0.1%)	0
Congestive heart failure requiring hospitalization	3 (0.4%)	9 (0.6%)
Ischemia-driven coronary revascularization procedure	24 (3.0%)	48 (3.1%)
Positively adjudicated CV events, including all CV adverse events listed above	40 (5.1%)	72 (4.6%)
Any patients with treatment emergent cardiovascular events confirmed by adjudication (MACE event)[b]	26 (3.3%)	27 (1.7%)

[a] With evidence of progressive ischemic condition
[b] Post-hoc analysis not specified in the study protocol. MACE=CHD death, non-fatal MI, ischemic stroke, or unstable angina (hospitalized)
Robinson et al., NEJM 2015.[42]

Figure 34:   MACE Confirmed by Adjudication in LONG TERM Study (final data) – Kaplan-Meier Analysis (Post-hoc Analysis)
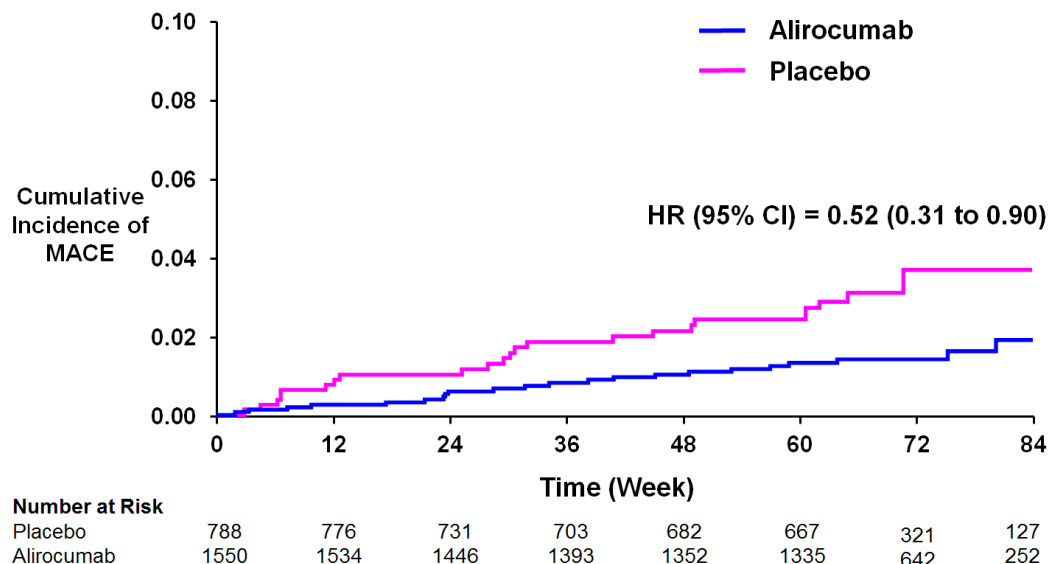
Robinson et. al., NEJM 2015.[42]

9.11.3.   Summary of CV Findings

Overall, there were fewer MACE confirmed by adjudication in the alirocumab arm when compared to placebo. Greater variability in estimating the HR was observed in the pool of ezetimibe-controlled studies likely due to the fact that in this pool there are relatively few events. When pooled together in the global pool of Phase 3 studies, the hazard ratio was 0.82 (95% CI: 0.54 to 1.25). For a broader endpoint that included CHF and revascularizations, the hazard ratio was 1.07 (95% CI: 0.78 to 1.46).

Most MACE events were in the largest placebo-controlled study, LONG TERM, a 78-week study comparing high CV risk patients treated with alirocumab 150 mg Q2W versus placebo on top of background maximally tolerated statin therapy. A post-hoc analysis of the LONG TERM data revealed a HR of 0.52 (95% CI: 0.31 to 0.90).

Definitive conclusions on the effect of alirocumab on CV morbidity and mortality cannot be drawn from these data. The effect on cardiovascular morbidity and mortality is being further evaluated in the ongoing OUTCOMES study. The primary endpoint of this study is MACE events confirmed by adjudication. The study will also provide additional data on the HRs for individual CV events confirmed by adjudication and other composite endpoints.

9.12.   Safety in Subgroups

9.12.1.   Safety Profile in Subgroups by Age

Significant (p<0.10) treatment-by-subgroup interactions were observed between the treatment groups and Age for 'General allergic events' in the placebo- and ezetimibe-controlled pools. The trend suggests a possible higher incidence of these reactions in patients <65 taking alirocumab

compared to control and a lower incidence in subjects ≥75. This may be a chance observation as the overall hazard ratio is approximately 1.

9.12.2.   Safety Profile in Subgroups by Sex

No interactions were observed between the treatment groups and sex and no pattern of TEAEs was identified according to sex.

9.12.3.   Safety Profile in Patients with Treatment-Emergent ADA Positive Response

In the global pool of Phase 3 studies, treatment-emergent TEAEs were reported in 112 (76.2%) patients with treatment emergent ADA positive responses compared to 2191 (75.9%) patients without treatment-emergent ADAs. Serious TEAEs were reported in 16.3% in patients with treatment-emergent ADA, compared to 14.1% patients without ADA.

Slight differences were seen in the safety profile of patients with a positive treatment-emergent ADA response at the level of individual PTs, compared to patients negative for treatment-emergent ADAs. Higher incidence rates (per 100 PYs) of TEAEs (events reported at incidence rates ≥5.0 and with a ≥1.0 difference between groups) were observed in patients with treatment-emergent ADA compared to patients without treatment-emergent ADA for the following TEAEs: 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).

There was no relationship between particular TEAEs and the development of neutralizing antibodies. Also, as had been discussed in Section 6.1.2, there was no consistent correlation between the development of neutralizing antibodies and LDL-C lowering.

9.12.4.   Adverse Events Among Patients with LDL-C <25 mg/dL and LDL <15 mg/dL

The controlled studies for alirocumab were designed to evaluate the safety of alirocumab in patients who achieved low LDL-C values. Safety was evaluated specifically in patients achieving two consecutive LDL-C values < 25 mg/dL since a level of ≥ 25 mg/dL has been hypothesized as sufficient for normal cell function[44] and because the safety of achieving such low LDL-C levels is unknown.

To ensure that an adequate number of patients achieved LDL-C values below 25 mg/dL, alirocumab was initiated at 150 mg every 2 weeks in the LONG TERM study which enrolled patients with high cardiovascular risk and LDL-C values >70 mg/dL. Additionally, down-titration was not permitted in any study.

In the global pool, a total of 796 (23.8%) patients had 2 consecutive values of LDL C<25 mg/dL. Approximately 70% of these patients were in the LONG TERM study, in which patients in the alirocumab arm received 150 mg of alirocumab throughout the duration of the study.

The overall rates of patients with at least 1 TEAE, treatment-emergent SAE, TEAE leading to death, and TEAE leading to treatment discontinuation were similar between patients with 2 consecutive values of LDL-C<25 mg/dL and 2 consecutive values of LDL-C<15 mg/dL and the overall alirocumab patient population (Table 44).

Table 44:   Adverse Experience Summary in Patients with LDL-C Values <25 mg/dL, <15 mg/dL, and ≥ 25 mg/dL in the Global Safety Pool

	Alirocumab-treated Patients in the Global Safety Pool			
	Overall Alirocumab (N=3340)	≥2 LDL-C <25 mg/dL (N=796)	≥2 LDL-C <15 mg/dL (N=288)	LDL-C ≥25 mg/dL (N=2544)
% of overall group	100%	23.8%	8.6%	76.2%
AEs (% of subgroup)				
Any TEAE	74.3%	68.2%	67.0%	73.4%
SAE	13.6%	13.1%	9.7%	13.1%
Death	0.4%	0.4%	0	0.5%
AE leading to discontinuation	6.2%	3.5%	4.9%	7.0%

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

An exploratory analysis was performed to describe the safety profile of patients with 2 consecutive LDL-C values <25 mg/dL (TEAEs occurring after the first LDL-C <25 mg/dL). For each TEAE occurring in these sub-populations at the MedDRA SOC and PT level, the corresponding incidence of TEAEs was compared to the overall alirocumab-treated population. A similar approach was used for patients with 2 consecutive LDL-C values <15 mg/dL (Table 45).

The data do not suggest a difference in the incidence of specific TEAEs in patients with 2 or more consecutive LDL-C values <25 mg/dL compared to patients with higher LDL-C values, with the possible exception of type 2 diabetes and cataracts. However, one needs to be cautious in interpreting these analyses because the baseline characteristics are different between these two post-randomization subgroups. Patients in our studies with 2 consecutive LDL-C < 25 mg/dL were more likely to be men, older than 65 years of age, with prior history of CHD or CHD risk equivalents, diabetic, with lower baseline LDL-C, Lp(a), HDL-C and with higher Triglycerides (TGs). 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. Those differences in baseline characteristics of patients in our studies 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. For example, risk factors for cataracts include age, male sex, diabetes, obesity, and hypertension (for additional information on cataracts, see Section 9.9.7).

Table 45: **Select TEAEs that Occurred in ≥ 2% of Patients in Any Group or of Special Interest with LDL-C Values <25 mg/dL, <15 mg/dL, and ≥25 mg/dL in the Global Safety Pool**

Primary system organ class, % Preferred term, %	Alirocumab-treated Patients in the Global Safety Pool			
	Overall Alirocumab (n=3340)	≥2 LDL-C <25 mg/dL (n=796)	≥2 LDL-C <15 mg/dL (n=288)	LDL-C ≥25 mg/dL (n=2544)
Infections and infestations	38.5%	34.0%	35.4%	37.2%
Nasopharyngitis	9.8%	8.3%	10.1%	9.2%
Upper respiratory tract infection	6.1%	4.5%	5.2%	6.0%
Urinary tract infection	4.1%	4.6%	4.9%	3.7%
Influenza	5.2%	3.6%	4.2%	5.5%
Bronchitis	3.8%	4.4%	3.1%	3.5%
Sinusitis	2.6%	2.6%	3.1%	2.5%
Lower respiratory tract infection	1.6%	2.0%	2.1%	1.4%
Gastroenteritis	1.9%	0.6%	1.0%	2.1%
Musculoskeletal and connective tissue disorders	24.2%	21.1%	20.1%	23.8%
Back pain	4.0%	4.3%	4.2%	3.7%
Arthralgia	4.0%	3.1%	2.1%	4.0%
Myalgia	4.9%	3.1%	3.8%	4.9%
Muscle spasms	2.8%	2.5%	3.5%	2.8%
Pain in extremity	2.4%	2.1%	1.4%	2.3%
Osteoarthritis	2.1%	1.8%	1.0%	2.0%
Musculoskeletal pain	1.9%	1.0%	1.0%	2.0%
Gastrointestinal disorders	17.0%	12.7%	10.1%	16.7%
Diarrhea	4.3%	3.0%	1.4%	4.0%
Nausea	2.2%	0.9%	1.0%	2.5%
General disorders and administration-site conditions	15.1%	10.2%	6.9%	15.5%
Injection-site reaction	5.7%	3.0%	3.5%	5.9%
Fatigue	2.8%	2.6%	2.4%	2.7%
Non-cardiac chest pain	1.6%	1.8%	0.3%	1.5%
Nervous system disorders	14.9%	10.3%	9.0%	15.1%
Dizziness	3.0%	1.8%	1.4%	3.2%
Headache	4.6%	1.8%	1.4%	4.8%
Hemorrhagic stroke	0.1%	0	0	0.1%
Metabolism and nutrition disorders	6.9%	7.0%	7.3%	6.4%
Type 2 diabetes mellitus	1.1%	1.8%	1.4%	0.8%
Diabetes mellitus	1.2%	1.5%	2.4%	1.1%
Eye disorders	4.6%	5.3%	6.9%	4.0%
Cataract	0.8%	1.5%	2.4%	0.5%
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2.5%	2.8%	2.4%	2.3%

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

To correct for this, a propensity analysis similar to the one done for the JUPITER CV Outcomes study[22] was performed. This analysis adjusts the risk of a patient developing a particular AE of interest using a propensity score based on that patient's baseline risk factors for developing low

LDL-C. The result is a hazard ratio and 95% CI for the risk of developing the AE of interest in alirocumab-treated patients with 2 or more LDL-C values < 25 mg/dL compared to the alirocumab-treated patients who did not achieve these low LDL-C values. This approach, performed in the global pool of Phase 3 studies, identified no excess risk for developing adverse events of interest in patients with LDL-C <25 mg/dL(Table 46).

Table 46: **Propensity Analysis[1] of the Risk of Certain AE of Interest in Patients with 2 or More Consecutive LDL-C Values <25 mg/dL**

AESI in Alirocumab Group	Hazard Ratio (95% CI) LDL < 25 versus ≥ 25 mg/dL
Local injection site reactions	0.87 (0.52 to 1.44)
General allergic TEAEs	0.81 (0.55 to 1.19)
Neurologic events	0.49 (0.26 to 0.93)
Neurocognitive events	0.38 (0.12 to 1.21)
Skeletal muscle TEAEs	0.79 (0.60 to 1.03)
Diabetes/glycemic control events	1.17 (0.74 to 1.83)
Ophthalmologic TEAEs	0.75 (0.35 to 1.62)
Hepatic disorders	0.56 (0.25 to 1.29)

Based on global safety pool.
[1] Everett et.al., Am J Cardiol 2014.[22]

One case was sufficiently unusual to merit further discussion. A 47 year old man, who had received alirocumab 150 mg since randomization, developed symptoms of gastroenteritis, followed by the Miller Fisher variant of Guillain-Barre syndrome on Day 190. His symptoms quickly began to resolve after IV immunoglobulin treatment, and completely resolved over 7 months. This patient's anti-drug antibody screening was positive only at Week 4. Notably, he achieved a calculated LDL value of 1.5 on Day 168. This case is typical of Miller-Fisher syndrome for which low LDL-C is not an acknowledged causative factor. A full narrative is provided in Section 13.5.

9.13. Safety Summary/Conclusions

In summary, a total of 5234 patients with hypercholesterolemia were included in the double-blind safety pool, among whom 3340 patients were treated with alirocumab at a dose of 75 or 150 mg administered SC once every 2 weeks. Treatment duration was up to 18 months, including 2408 patients exposed for at least 52 weeks, leading to an overall exposure of 3451 patient-years in the alirocumab group. This large safety database, with long-term exposure in the target patient population, allows a comprehensive assessment of the alirocumab safety profile.

All patients in the placebo-controlled pool and the majority of patients in the ezetimibe-controlled pool were at high or very high CV risk, with the majority of patients in both pools having a history of CHD (60 to 70% of patients). In addition, approximately 30% of patients reported a history of diabetes mellitus. The Phase 2/3 program included a significant number of elderly patients, with 1799 patients ≥65 years of age and 375 patients ≥75 years of age. Almost all patients in the placebo-controlled pool and 75–80% patients in the ezetimibe-controlled pool took study drugs on top of maximally tolerated concomitant statin usage.

The percentages of patients who experienced at least 1 TEAE, at least 1 treatment-emergent SAE and any TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups. The most common adverse reactions leading to treatment discontinuation in patients treated with alirocumab were local injection site reactions (0.2% patients in the alirocumab group versus 0.3% in control groups).

In a pooled analysis of Phase 3 studies, all-cause mortality was 0.6% in the alirocumab group and 0.9% in the control group. The primary adjudicated cause of death in the majority of these patients was CV events. There were no deaths in Phase 1 or 2 studies.

No difference in the safety profile was observed between the 2 doses (75 mg and 150 mg administered every 2 weeks) used in the Phase 3 program. There were no drug-drug interactions observed in the program which may have safety implication.

Common Adverse Events

Analyses of common adverse events across the placebo- and ezetimibe-controlled pools identified local injection site reactions and pruritus as more common on alirocumab than control.

Adverse Events of Interest

The AEs of interest included local injection site reactions, general allergic events, neurologic events including neurocognitive events, skeletal muscle-related AEs, diabetes mellitus, hepatic AEs/ALT increase, and ophthalmologic events. Increased frequency with alirocumab was only identified for local injection site reactions. There was a small imbalance in general allergic adverse events due to the increased incidence of pruritus in the alirocumab group.

No safety concern was identified with regard to skeletal muscle-related TEAEs. The incidence of the skeletal muscle-related TEAEs was similar between treatment groups (15.1% of the alirocumab group versus 15.4% of the placebo group). However, in ALTERNATIVE, there were fewer patients with skeletal muscle-related TEAEs in the alirocumab group than the atorvastatin (HR 0.61 [0.38 to 0.99]) or ezetimibe (HR 0.70 [0.47 to 1.06]) groups. Alirocumab represents an important therapeutic option for patients with documented statin intolerance who are unwilling to attempt another course of statin therapy.

None of the potential risks theoretically considered to be associated with low LDL-C levels were confirmed. The analysis of overall TEAEs in patients with 2 consecutive LDL-C values <25 mg/dL or <15 mg/dL did not reveal any specific effects.

Neurologic and neurocognitive events were reported overall at a low and comparable incidence rate in patients in the alirocumab and the placebo or ezetimibe control groups, although there was a higher incidence of neurocognitive events in one analysis of the LONG TERM study. With only 29 neurocognitive events in the combined alirocumab groups, the data cannot be considered definitive.

There was no increased incidence of diabetes-related TEAEs in an analysis of patients who achieved 2 or more LDL-C levels <25 mg/dL compared to those who did not. Clinically-meaningful changes in glycemic control were generally similar to placebo and ezetimibe in the pooled data

As with all therapeutic proteins, there is a potential for immunogenicity. In controlled clinical Phase 3 studies, 4.8% of alirocumab treated patients had a treatment-emergent ADA response as compared to 0.6% in the control group (placebo or ezetimibe). The majority of those patients exhibited transient low-titer ADA responses with no neutralizing activity. Compared to patients that were ADA negative, patients with an ADA positive status did not exhibit meaningful differences in alirocumab safety, except for a higher frequency of injection site reactions.

The impact of alirocumab on CV risk has been assessed in the Phase 3 program. In a pre-specified analysis of MACE in the global pool of Phase 3 studies, the hazard ratio was 0.82 (95% CI: 0.54 to 1.25). For a broader endpoint that included CHF and revascularizations that also had been prespecified, the hazard ratio was 1.07 (95% CI: 0.78 to 1.46). In a post-hoc analysis of MACE confirmed by adjudication in the largest study (LONG TERM), the hazard ratio was 0.52 (95% CI 0.31 to 0.90). Definitive conclusions on the effect of alirocumab on cardiovascular morbidity and mortality cannot be drawn from these data. CV risk reduction is being prospectively assessed in an ongoing 18000-patient OUTCOMES trial whose primary endpoint is MACE, confirmed by adjudication.

Overall, data from this large, double-blind safety database representing more than 3400 patient-years of exposure, demonstrated that alirocumab is well-tolerated and has a favorable safety profile.

10. RATIONALE FOR THE PROPOSED DOSING RECOMMENDATION

The alirocumab program evaluated two doses to flexibly meet patient's needs based on their baseline LDL-C and their target LDL-C. Data from outcomes studies with other drugs that lower LDL-C indicate that there is a benefit to lowering mean LDL-C values to <50 mg/dL. Post-hoc analyses from these outcome studies extend this benefit to somewhat lower LDL-C levels (approximately 40 mg/dL). However, the benefit/risk for considerably lower values of LDL-C (eg., <25 mg/dL) is unknown. The exposure in the alirocumab Phase 3 program to LDL-C <25 mg/dL is limited to 18 months in double-blind, placebo-controlled studies. By providing two doses of alirocumab, health care providers can more precisely target patients' individual goals with the potential to avoid markedly low LDL-C levels for which the benefit-risk has not been established.

Based on these considerations, we have designated the 75 mg dose as the usual starting dose and provide guidance that the 150 mg dose should be selected as a starting dose for those patients that need a larger (60%) reduction in LDL-C. The basis for the use of 60% as the threshold for utilizing 150 mg as a starting dose comes from two separate analyses of our Phase 3 data:

1. As shown in Figure 35, only 36% of patients started on the 75 mg dose can achieve a 60% or greater reduction in LDL-C. Therefore physicians looking to achieve 60% reduction in LDL-C for a given patient have only slightly better than a 1 in 3 chance of getting that level of reduction with 75 mg. By contrast, nearly 70% of patients started on the 150 mg Q2W can achieve a 60% or greater reduction in LDL-C.

2. Nearly 800 patients in the alirocumab Phase 3 program achieved 2 consecutive LDL-C levels <25 mg/dL. The majority of these (562) were observed in the ODYSSEY LONG TERM study where patients with LDL-C > 70 mg/dL were started and maintained up to 78 weeks on the 150 mg Q2W dose. Although no adverse effects were identified in patients who achieved these levels of LDL-C, out of an eminence of caution considering this is a new class of drugs, physicians may still wish to avoid very low LDL-C levels. Segregating the initial usage of the 150 mg to those patients that need 60% or more reduction in LDL-C to reach their desired LDL-C goal is a practical way to achieve this and is consistent with how physicians use lipid-lowering therapies. With the proposed 60% threshold, patients will only initiate treatment with the 150 mg dose if their baseline LDL-C is >2.5x their individual target level. For example, patients whose CV risk is thought to merit a 70 mg/dL LDL-C target will only be started on the 150 mg dose if their baseline LDL-C is >175 mg/dL (that is, before initiating alirocumab treatment but while taking their statin and other LMTs). An examination of the ODYSSEY Phase 3 data (Table 36) demonstrated that at these levels of baseline LDL-C only 6.2% of patients started on 150 mg Q2W achieved an LDL-C < 25 mg/dL. Importantly, by using a percent-reduction and not a fixed LDL-C threshold for initiating patients on the 150 mg dose, the dosing recommendation is flexible enough to allow physicians to weigh the potential risks and benefits of starting patients at the highest CV risk but with less severe elevations of LDL-C on the 150 mg dose if the physician

believes that the patient requires the lower LDL-C targets suggested by IMPROVE-IT or other recent studies.

Figure 35: **Rationale for 60% Efficacy Threshold for the Selection of the 150 mg Q2W Starting Dose**
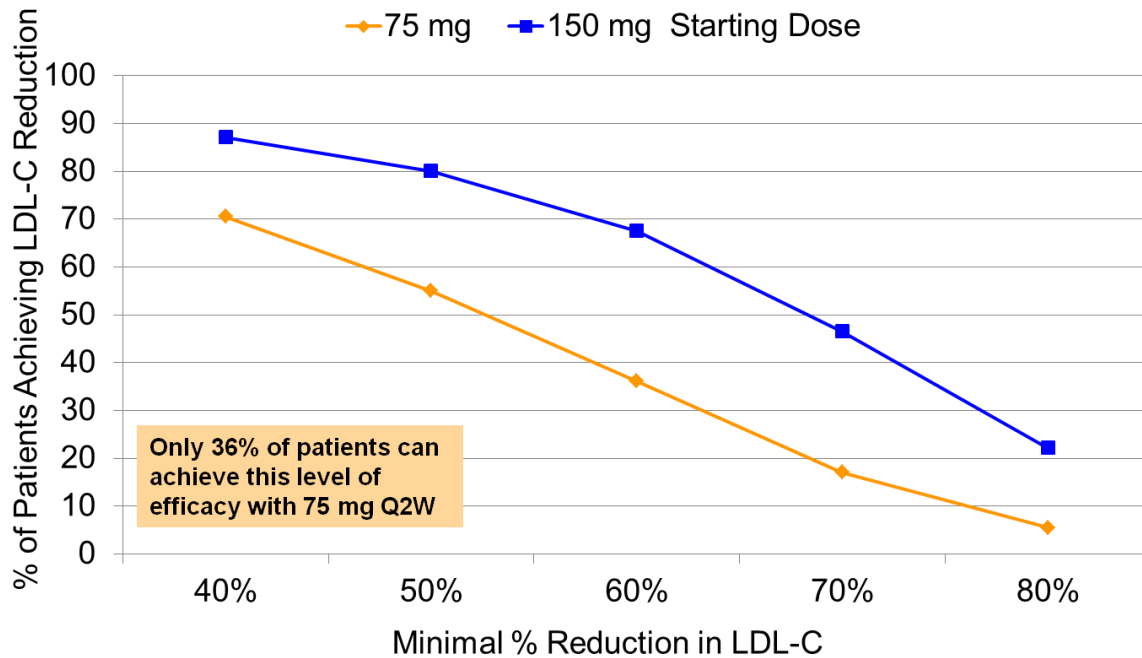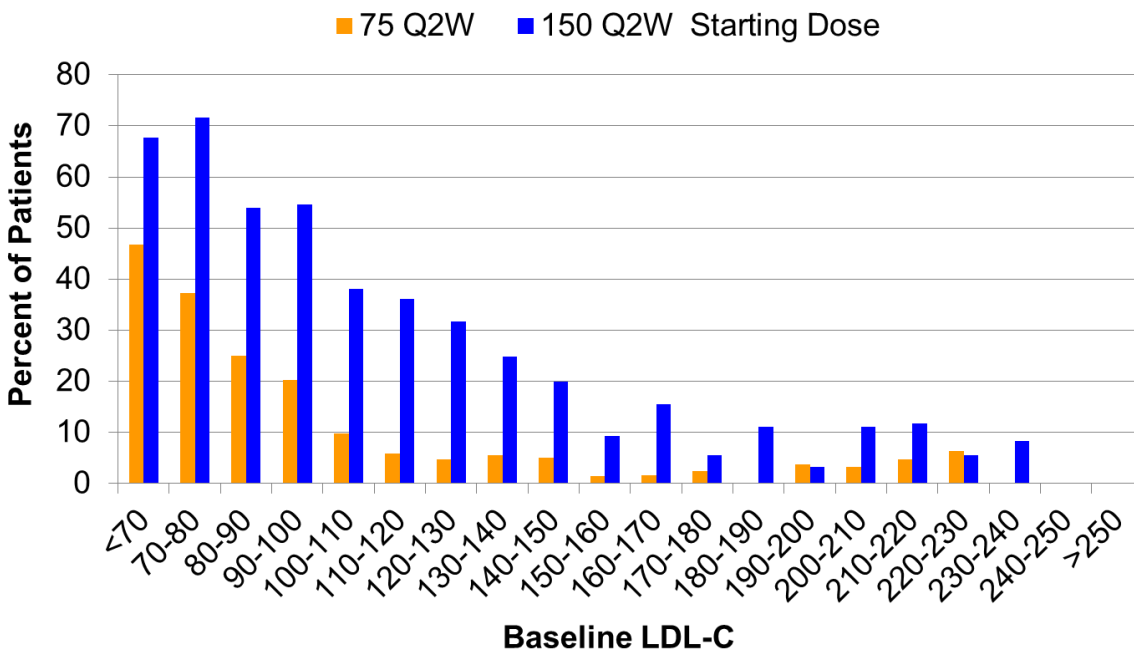

Figure 36: **Patients with 2x LDL-C <25 mg/dL as a Function of Alirocumab Starting Dose and Baseline LDL-C – Global Pool of Phase 3 Studies**

11.   BENEFIT/RISK ASSESSMENT

The data available to assess the efficacy and safety of 75 mg Q2W and 150 mg Q2W alirocumab were obtained from an extensive clinical program, including 5296 patients in the Phase 3 program, most observed for at least 52 weeks in double-blind studies. Alirocumab use was assessed in combination with best standard of care therapies (potent statins, with or without other LMT, at the maximally tolerated dose in the vast majority of the studies), as monotherapy and in combination with non-statin LMT. Studies were conducted in 3 main populations with significant unmet medical need: heFH patients, patients intolerant to statins, and patients with non-FH at high/very high CV risk, including patients with mixed dyslipidemia and patients with diabetes.

Robust and durable lipid-modifying efficacy

Across all Phase 3 studies, treatment with alirocumab, either as add-on to statin (with or without other LMTs), or as monotherapy (or as add-on to other non-statin LMT) was superior to placebo and to ezetimibe in reducing LDL-C. The 75 mg dose was associated with a mean reduction in LDL-C from baseline of 44.5% and the 150 mg dose with a reduction of 62.6%. This LDL-C lowering effect was sustained for 52 weeks, and up to 78 weeks (in the patients having completed the LONG TERM study). In all studies, the percentage of patients reaching pre-defined LDL-C targets was higher in the alirocumab group than in the control groups at both Week 12 (before up-titration, on the 75 mg Q2W dose only) and at Week 24 (primary efficacy time point in all studies). Depending on baseline LDL-C, up to 79.3% of alirocumab-treated patients achieved LDL-C <70 mg/dL at Week 24 regardless of background therapy. Even in studies where the mean baseline LDL-C level was greater than 190 mg/dL, approximately one third of patients were able to reach this target.

Given the large decrease in LDL-C observed with alirocumab, a specific analysis combining all treatment groups (alirocumab, ezetimibe, and placebo), was performed to evaluate whether the linear relationship between LDL-C and CV events is maintained even at low levels of LDL-C. In the Phase 3 studies, 83 CV events occurred in patients with very high CV risk and only 2 events in patients with high CV risk. Therefore, the analysis was performed only in patients with very high CV risk. Additionally, because of the entry criteria in the studies, this population had the highest probability of achieving lower levels of LDL-C. The incidence of treatment emergent MACE according to the average level of LDL-C achieved during the treatment period was analyzed by the following categories: < 40 mg/dL, $\geq$ 40 to <70 mg/dL, $\geq$ 70 to <100 mg/dL, $\geq$ 100 to <130 mg/dL, $\geq$ 130 to < 160 mg/dL, and $\geq$ 160 mg/dL.

In this analysis a correlation is observed between average LDL-C during the treatment period and MACE rate (Figure 37).

Figure 37: **Incidence of Treatment-emergent MACE in All Treatment Groups by Average LDL-C Achieved during the Treatment Period (Safety Population at Very High CV Risk)**
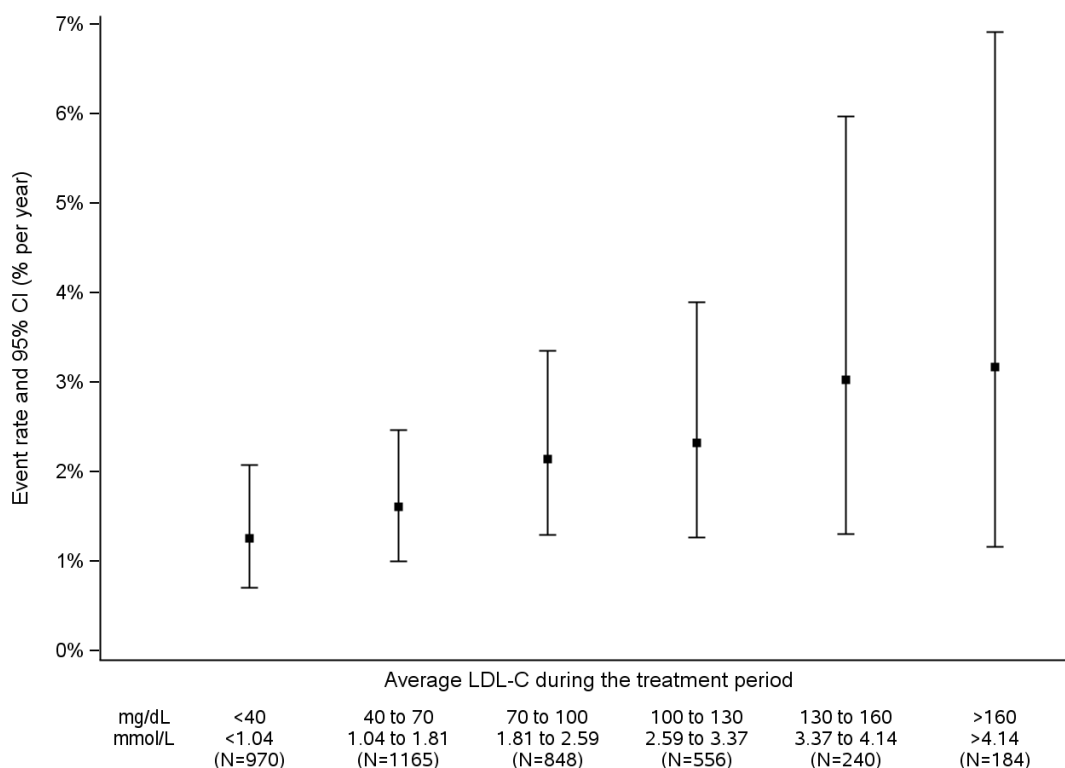
Analysis of patients at very high CV risk in FH I, FH II, HIGH FH, LONG TERM, COMBO I, COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, and MONO studies (all treatment groups combined).

Significant and clinically meaningful reductions were also observed in pro-atherogenic biomarkers including, non-HDL-C, Apo B, and Total-C. Alirocumab was also superior to placebo and to ezetimibe for the reduction in Lp(a) in all studies except MONO. Modest but consistent reductions in fasting TGs and increases in HDL-C were also observed with alirocumab treatment.

Consistent reductions in LDL-C were observed with alirocumab across age, BMI, race, baseline LDL-C levels, patients with heFH, and non heFH, patients with mixed dyslipidemia, and patients with diabetes. LDL-C reduction was consistent regardless of which statin was concomitantly used as well as statin dose. A slight difference (approximately 10%) was observed between men and women, although both sexes achieved meaningful LDL-C reduction.

Favorable safety profile

The information provided in the safety database of 3340 patients treated with alirocumab at the 75 or 150 mg Q2W doses (global exposure of 3451 patient-years) supports that the drug was well tolerated. The overall occurrences of SAEs and premature withdrawals were comparable between treatment groups. Deaths were rare and less frequently reported for alirocumab than control. In patients who had at least 2 consecutive values of LDL-C < 25 or <15 mg/dL, no safety effects were identified in analyses of the AEs of interest. Across all treatment groups in

the Phase 2/3 safety database, 1799 (34.4%) patients were ≥65 years of age and 375 (7.2%) were 75 years or older. There were no significant differences observed in safety and efficacy with increasing age or in other subgroups evaluated. The data suggest that alirocumab is not associated with hepatic effects or muscle-related AEs, common safety concerns associated with statins, nor with clinically meaningful effects on glycemic control. There were no differences in overall neurocognitive events in the safety pools although a difference was seen in one analysis of the LONG TERM study. With only 29 neurocognitive events in the combined alirocumab groups, the data cannot be considered definitive. The OUTCOMES study is expected to provide sufficient data for more robust analyses of these rare events.

There were few AEs judged to be associated with the use of alirocumab: injection site reaction and pruritus. Injection site reaction was the most commonly reported TEAE with a higher incidence in the alirocumab than the control groups. Most events were mild in intensity, transient in nature, did not necessitate treatment discontinuation and usually occurred within the first 24 weeks of initiation of treatment. Injection site reaction was the only adverse effect that was reported more frequently in patient positive (versus those negative) for treatment-emergent ADA. General allergic events were reported at slightly higher rates in the alirocumab group versus control in each of the placebo-controlled and ezetimibe-controlled pools. This difference was attributed to a higher incidence of pruritus (typically mild and transient) in the alirocumab groups. Discontinuations due to rare allergic adverse events (nummular eczema, hypersensitivity vasculitis) were reported in the alirocumab pool. These all resolved without clinical sequelae after discontinuation of alirocumab and, in some cases, treatment with a short course of corticosteroids.

Low level of immunogenicity

Treatment-emergent positive ADA responses were observed in 4.8% of patients in the alirocumab group. Most of the ADA positive samples exhibited low titers (≤240). Compared to patients without treatment-emergent ADA, patients with treatment-emergent ADA did not exhibit any difference in alirocumab exposure, efficacy or safety, except for increased injection site reactions. Only a few patients exhibited NAb, all of them in the alirocumab group. The data in these patients do not suggest a correlation between the presence of NAb and LDL-C lowering efficacy or safety.

Additional key elements of the development program

1) Allowed up- titration to attain individual patient goal

The 75 mg Q2W dose of alirocumab was associated with a mean reduction from baseline in LDL-C of 45-49% at week 12; the 150 mg Q2W dose with 63%. Up-titration from 75 to 150 mg Q2W was associated with an additional 14% mean reduction in LDL-C as add-on to statins. In patients not taking concomitant statins, up-titration of alirocumab resulted in an additional 3% mean reduction in LDL-C, with the majority of the effect seen in approximately 25% of patients who achieved at least an additional 10% LDL-C lowering after up-titration.

Both alirocumab doses showed significant efficacy and a similar favorable safety profile, with no evidence of any dose-dependent adverse effects. LDL-C reductions observed with 75 mg and 150 mg Q2W doses allow for initial dose selection to be individualized, taking into account baseline LDL-C levels and CV risk status, and the goal of therapy. The usual starting dose is

75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously every 2 weeks. Lipid levels can be assessed as early as 4 weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dosage adjusted accordingly. This treatment paradigm is in line with more individualized management of elevated LDL-C, as recommended by most recent therapeutic guidelines.

2) *Evaluation of efficacy and safety in statin intolerant patients*

In the ALTERNATIVE study in patients with a history of documented statin intolerance, patients in the alirocumab arm were less likely to have musculoskeletal TEAEs than patients in the statin re-challenge arm (HR 0.61 [95% CI: 0.38 to 0.99]). Patients in the alirocumab arm also had significantly greater reduction in LDL-C than patients in the ezetimibe arm. However, a substantial proportion of patients prospectively considered to be statin intolerant were able to tolerate a moderate dose of atorvastatin for at least 24 weeks. The results suggest that many patients reporting statin intolerance could try a similar course of statins under close medical supervision. However, for those patients who are truly statin intolerant or who are unwilling to be re-challenged, alirocumab provides a valuable alternative for lipid lowering.

3) *Adjudication of CV events in long-term double-blind studies in high and very high CV risk patients*

In this Phase 3 population predominantly at high/very high CV risk, with the majority of patients followed for at least 52 weeks, fewer MACE events in the alirocumab arm when compared to placebo was observed. Greater variability in estimating the HR was observed in the pool of ezetimibe-controlled studies likely due to the fact that in this pool there are relatively few events. In a pre-specified analysis of the global pool of Phase 3 studies, the HR was 0.82 (95% CI: 0.54 to 1.25). In a post-hoc analysis of MACE confirmed by adjudication in the largest study (LONG TERM), the hazard ratio was 0.52 (95% CI 0.31 to 0.90). A large CV outcomes trial is in progress.

Ongoing assessment of CV Outcomes and Adverse Events of Interest

ODYSSEY OUTCOMES is a placebo-controlled cardiovascular outcomes trial that began in 2012. It will enroll approximately 18,000 high-risk patients with recent acute coronary syndrome, who are being treated with maximum tolerated dose of a potent statin. The study will continue until a pre-specified number of events has accrued and the last patient enrolled has been followed for 2 years. The primary endpoint is major cardiac events confirmed by adjudication and the primary analysis is intention to treat. This study will have adequate statistical power to evaluate the potential benefit of alirocumab to reduce the incidence of MACE.

The ongoing cardiovascular outcomes study will also provide an extensive safety database for post-approval surveillance and opportunity to evaluate further AESI.

Benefit and Risk Conclusion

The ODYSSEY clinical program for alirocumab has demonstrated a consistent and significant effect on LDL-C lowering in all ten Phase 3 clinical studies as an add-on to statins, with or without other LMTs, or as monotherapy or add-on to non-statin LMT.

The recommended dosing regimens offer the flexibility of two doses with distinct degrees of robust LDL-C lowering that may be adjusted based on individual treatment goals and patient's response to treatment. A starting dose of 75 mg Q2W has demonstrated a mean reduction in LDL-C of -44.5 to -49.2% by Week 12 and most patients (73%) achieved their LDL-C goal with the 75 mg dose. Titrating up to 150 mg Q2W has shown to provide an additional 14.2% reduction when co-administered with a background statin or an additional 3.1% reduction when administered alone. Continuous dosing with 150 mg Q2W has shown to reduce LDL-C by approximately 60%.

It is worth emphasizing that the risk of developing very low LDL-C (i.e. less than 25 mg/dL) is a function of the patient's baseline LDL-C value and the starting dose of alirocumab. Although the safety data do not identify risks to patients from low LDL-C, physicians may still wish to avoid very low LDL-C levels over long periods of time. Segregating the initial usage of the 150 mg to those patients that need 60% or more reduction in LDL-C to reach their desired LDL-C goal is a practical way to achieve this and is consistent with how physicians use lipid-lowering therapies. Therefore, we propose that the usual starting dose is 75 mg Q2W which can be titrated to 150 mg Q2W based on individual treatment goals and patient's response to treatment. Patients requiring a larger LDL-C reduction (>60%) in LDL-C may be started at 150 mg Q2W.

The adverse events identified to date (injection site reaction and pruritus) were generally mild, transient and manageable; more significant serious allergic adverse events were very rare. The Phase 3 studies mostly enrolled patients at high/very high CV risk and were designed for long-term double-blind assessment of safety and efficacy. Although the studies were not powered to provide CV outcomes evidence, CV events were adjudicated, allowing an assessment of CV safety. The data are encouraging and support the safety of alirocumab. A cardiovascular outcomes study is ongoing.

The overall benefit-risk profiles of both 75 and 150 mg Q2W doses of alirocumab are positive and the product offers an innovative treatment option, particularly in those patients who are not well controlled despite their current therapies, including those receiving a maximally tolerated dose of statin. The lower rate of musculoskeletal TEAEs in the alirocumab group compared to the statin re-challenge arm (HR 0.61 [0.38 to 0.99]) and its superior LDL-C lowering capacity compared to ezetimibe suggests it could be a valuable alternative in patients who are unable or unwilling to take a statin. For all of these reasons, alirocumab is proposed for use as an adjunct therapy to diet, for long-term treatment in patients with primary hypercholesterolemia (non-FH and FH) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce LDL-C, Total-C, non- HDL-C, Apo B, TGs, and Lp(a), and to increase HDL-C and Apo A-1. It is proposed for use in patients with hyperlipidemia not appropriately controlled with a statin, as combination therapy with a statin, with or without other LMTs, or as monotherapy, or add-on to non-statin LMTs, including in patients who cannot tolerate statins.

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13. APPENDICES

13.1. Additional Study Design Tables

Table 47: Key Secondary Efficacy Variables in Phase 3 Studies

	Hierarchical Ordering of Secondary Efficacy Variables				
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 analysis)	1	1	1	1	-
Percent change in calculated LDL-C from baseline to Week 12 (ITT analysis)	2	2	2	2	1
Percent change in calculated LDL-C from baseline to Week 12 (on-treatment analysis)	3	3	3	3	-
Percent change in measured LDL-C from baseline to Week 24 (ITT analysis)	-	4	-	-	-
Percent change in Apo B from baseline to Week 24 (ITT analysis)	4	5	4	4	2
Percent change in Apo B from baseline to Week 24 (on-treatment analysis)	5	6	5	5	-
Percent change in non-HDL-C from baseline to Week 24 (ITT analysis)	6	7	6	6	3
Percent change in non-HDL-C from baseline to Week 24 (on-treatment analysis)	7	8	7	7	-
Percent change in Total-C from baseline to Week 24 (ITT analysis)	8	9	8	8	4
Percent change in Apo B from baseline to Week 12 (ITT analysis)	9	10	9	9	5
Percent change in non-HDL-C from baseline to Week 12 (ITT analysis)	10	11	10	10	6
Percent change in Total-C from baseline to Week 12 (ITT analysis)	11	12	11	11	7
Percent change in calculated LDL-C from baseline to Week 52 (ITT analysis)	12	13	12	-	-
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL or moderate[a] to high CV risk patients reaching calculated LDL-C < 100 mg/dL at week 24 (ITT analysis)	13	14	-	12	-
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL or moderate to high CV risk patients reaching calculated LDL-C < 100 mg/dL at week 24 (on-treatment analysis)	14	15	-	13	-

	Hierarchical Ordering of Secondary Efficacy Variables				
Key secondary endpoint	FH I, FH II, HIGH FH	LONG TERM	COMBO I, COMBO II	OPTIONS I, OPTIONS II, ALTERNATIVE	MONO
Proportion of patients reaching calculated LDL-C <100 mg/dL at Week 24 (ITT analysis)	-	-	-	-	8
Proportion of patients reaching calculated LDL-C <70 mg/dL at Week 24 (ITT analysis)	15	16	13	14	9
Proportion of patients reaching calculated LDL-C <70 mg/dL at Week 24 (on-treatment analysis)	16	17	14	15	-
Percent change in Lp(a) from baseline to Week 24 (ITT analysis)	17	18	15	16	10
Percent change in HDL-C from baseline to Week 24 (ITT analysis)	18	19	16	17	11
Percent change in fasting TGs from baseline to Week 24 (ITT analysis)	19	20	17	18	14
Percent change in Apo A-1 from baseline to Week 24 (ITT analysis)	20	21	18	19	16
Percent change in Lp(a) from baseline to Week 12 (ITT analysis)	21	22	19	20	13
Percent change in HDL-C from baseline to Week 12 (ITT analysis)	22	23	20	21	12
Percent change in fasting TGs from baseline to Week 12 (ITT analysis)	23	24	21	22	15
Percent change in Apo A-1 from baseline to Week 12 (ITT analysis)	24	25	22	23	17

[a] Moderate to high CV risk only applicable to ALTERNATIVE study

13.2.   Baseline Lipid Levels

Table 48:   Baseline Lipid Levels in Phase 3 Placebo-controlled Studies

Baseline Parameter	FH I (N=486)	FH II (N=249)	HIGH FH (N=107)	COMBO I (N=316)	LONG TERM (N=2341)
Calculated LDL-C (mg/dL), mean ± SD	144.6 ± 49.7	134.4 ± 41.1	197.8 ± 53.4	102.2 ± 31.6	122.4 ± 42.2
Calculated LDL-C, n (%)					
<70 mg/dL	6 (1.2%)	4 (1.6%)	0	34 (10.8%)	98 (4.2%)
≥70 to <100 mg/dL	64 (13.2%)	39 (15.7%)	2 (1.9%)	136 (43.0%)	622 (26.6%)
≥100 to <130 mg/dL	142 (29.2%)	93 (37.3%)	2 (1.9%)	98 (31.0%)	861 (36.8%)
≥130 to <160 mg/dL	136 (28.0%)	63 (25.3%)	14 (13.2%)	35 (11.1%)	419 (17.9%)
≥160 to <190 mg/dL	62 (12.8%)	23 (9.2%)	43 (40.6%)	6 (1.9%)	185 (7.9%)
≥190 mg/dL	76 (15.6%)	27 (10.8%)	45 (42.5%)	7 (2.2%)	156 (6.7%)
Measured LDL-C (mg/dL), mean ± SD	140.1 ± 47.6	131.8 ± 39.3	NA	96.6 ± 31.2	116.7 ± 38.7
Apo-B (mg/dL), mean ± SD	114.1 ± 30.0	107.9 ± 26.3	140.9 ± 31.0	91.0 ± 22.3	101.7 ± 27.6
Non-HDL-C (mg/dL), mean ± SD	170.1 ± 53.3	158.5 ± 44.4	226.4 ± 55.3	131.1 ± 36.0	152.4 ± 46.3
Total-C (mg/dL), mean ± SD	219.9 ± 53.0	211.6 ± 45.6	274.4 ± 54.0	179.7 ± 37.0	202.2 ± 47.3
Apo-B/Apo-A1 (ratio), mean ± SD	0.839 ± 0.277	0.762 ± 0.244	1.061 ± 0.323	0.651 ± 0.197	0.717 ± 0.261
Lp (a) (mg/dL), mean ± SD	50.2 ± 50.7	50.2 ± 66.1	41.2 ± 46.6	49.5 ± 50.0	43.0 ± 48.2
HDL-C (mg/dL), mean ± SD	49.8 ± 15.3	53.1 ± 15.7	48.1 ± 13.3	48.5 ± 13.8	49.9 ± 12.3
Apo-A1 (mg/dL), mean ± SD	141.1 ± 27.4	147.2 ± 29.4	137.5 ± 23.3	143.8 ± 24.5	146.8 ± 25.9
Fasting TGs (mg/dL), mean ± SD	127.8 ± 65.4	121.0 ± 65.4	149.8 ± 86.6	147.5 ± 84.6	150.9 ± 83.4
Total-C/HDL-C (ratio), mean ± SD	4.774 ± 1.785	4.272 ± 1.458	6.135 ± 2.119	3.932 ± 1.205	4.244 ± 1.343

Table 49: **Baseline Lipid Levels in Phase 3 Ezetimibe-controlled Studies**

Baseline Parameter	COMBO II (N=720)	OPTIONS I (N=355)	OPTIONS II (N=305)	ALTERNATIVE (N=314)	MONO (N=103)
Calculated LDL-C (mg/dL), mean ± SD	107.3 ± 35.7	105.1 ± 34.1	111.3 ± 39.0	191.3 ± 69.3	139.7 ± 25.8
Calculated LDL-C, n (%)					
<70 mg/dL	55 (7.6%)	24 (6.8%)	22 (7.2%)	NA	NA
≥70 to <100 mg/dL	307 (42.6%)	165 (46.5%)	117 (38.4%)	6 (1.9%)	7 (6.8%)
≥100 to <130 mg/dL	204 (28.3%)	96 (27.0%)	87 (28.5%)	38 (12.1%)	23 (22.3%)
≥130 to <160 mg/dL	95 (13.2%)	46 (13.0%)	44 (14.4%)	74 (23.6%)	50 (48.5%)
≥160 to <190 mg/dL	34 (4.7%)	12 (3.4%)	26 (8.5%)	61 (19.4%)	23 (22.3%)
≥190 mg/dL	25 (3.5%)	12 (3.4%)	9 (3.0%)	134 (42.7%)	2 (1.9%)
Measured LDL-C (mg/dL), mean ± SD	102.9 ± 34.9	101.4 ± 32.7	106.9 ± 38.1	183.2 ± 69.8	NA
Apo-B (mg/dL), mean ± SD	94.0 ± 23.1	90.8 ± 23.2	95.3 ± 24.1	139.8 ± 37.7	104.3 ± 18.7
Non-HDL-C (mg/dL), mean ± SD	138.3 ± 40.4	133.3 ± 38.8	141.1 ± 43.4	228.7 ± 78.3	165.7 ± 29.9
Total-C (mg/dL), mean ± SD	185.6 ± 41.4	182.0 ± 39.0	191.1 ± 44.7	278.7 ± 77.9	222.8 ± 31.9
Apo-B/Apo-A1 (ratio), mean ± SD	0.689 ± 0.208	0.650 ± 0.221	0.670 ± 0.208	0.956 ± 0.317	0.684 ± 0.180
Lp(a) (mg/dL), mean ± SD	43.6 ± 45.9	44.8 ± 47.9	51.5 ± 54.7	33.6 ± 42.3	24.8 ± 27.5
HDL-C (mg/dL), mean ± SD	47.3 ± 13.4	48.7 ± 13.4	50.0 ± 13.1	50.0 ± 14.3	57.1 ± 17.8
Apo-A1 (mg/dL), mean ± SD	140.5 ± 24.2	144.2 ± 23.8	146.2 ± 25.0	150.6 ± 24.6	158.4 ± 31.7
Fasting TGs (mg/dL), mean ± SD	155.7 ± 77.1	140.7 ± 71.0	149.5 ± 82.1	179.0 ± 99.0	129.9 ± 64.4
Total-C/HDL-C (ratio), mean ± SD	4.177 ± 1.373	3.976 ± 1.353	4.032 ± 1.327	5.973 ± 2.265	4.1841.168

13.3.   Demographics and Patient Characteristics of US Patients

Table 50:   Demographics and Patient Characteristics of US Patients in the Phase 3 Placebo-controlled Studies

Characteristic	FH I (N=109)	FH II (N=0)	HIGH FH (N=27)	COMBO I (N=316)	LONG TERM (N=485)
Age (years), mean ± SD	50.4 ± 13.0	0	48.7 ± 14.9	63.0 ± 9.3	61.4 ± 10.2
Age group					
<45	42 (38.5%)	0	8 (29.6%)	13 (4.1%)	29 (6.0%)
≥45 to <65	54 (49.5%)	0	18 (66.7%)	172 (54.4%)	265 (54.6%)
≥65 to <75	9 (8.3%)	0	1 (3.7%)	99 (31.3%)	141 (29.1%)
≥75	4 (3.7%)	0	0	32 (10.1%)	50 (10.3%)
Female, n (%)	43 (39.4%)	0	10 (37.0%)	108 (34.2%)	184 (37.9%)
Race, n (%)					
White	93 (85.3%)	0	20 (74.1%)	258 (81.6%)	413 (85.2%)
Black or African American	4 (3.7%)	0	2 (7.4%)	51 (16.1%)	63 (13.0%)
Asian	4 (3.7%)	0	5 (18.5%)	3 (0.9%)	2 (0.4%)
Other	5 (4.6%)	0	0	1 (0.3%)	7 (1.4%)
Hispanic or Latino ethnicity, n (%)	10 (9.2%)	0	4 (14.8%)	34 (10.8%)	24 (4.9%)
Weight (kg), mean ± SD	88.0 ± 18.2	0	83.4 ± 14.6	94.5 ± 21.2	91.7 ± 20.4
BMI (kg/m^2), mean ± SD	29.9 ± 4.9	0	28.8 ± 5.0	32.4 ± 6.6	31.5 ± 6.5
Region, n (%)					
North America	109 (100%)	0	27 (100%)	316 (100%)	485 (100%)
Hypertensive, n (%)	44 (40.4%)	0	11 (40.7%)	280 (88.6%)	406 (83.7%)
Type 2 diabetic, n (%)	20 (18.3%)	0	8 (29.6%)	136 (43.0%)	192 (39.6%)
Current smoker, n (%)	11 (10.1%)	0	4 (14.8%)	60 (19.0%)	93 (19.2%)
heFH, n (%)	109 (100%)	0	27 (100%)	0	59 (12.2%)
CV risk level, n (%)					
Very high	50 (45.9%)	0	11 (40.7%)	316 (100%)	471 (97.1%)
High	59 (54.1%)	0	16 (59.3%)	0	14 (2.9%)
Moderate	0	0	0	0	0

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Table 51:   Demographics and Patient Characteristics of US Patients in the Phase 3 Active-controlled Studies

Characteristic	COMBO II (N=217)	OPTIONS I (N=255)	OPTIONS II (N=183)	ALTERNATIVE (N=214)	MONO (N=49)
Age (years), mean ± SD	62.9 ± 10.3	64.1 ± 9.7	62.4 ± 10.3	64.9 ± 9.1	59.9 ± 5.2
Age group					
<45	8 (3.7%)	6 (2.4%)	6 (3.3%)	3 (1.4%)	0
≥45 to <65	111 (51.2%)	122 (47.8%)	96 (52.5%)	102 (47.7%)	40 (81.6%)
≥65 to <75	67 (30.9%)	92 (36.1%)	61 (33.3%)	74 (34.6%)	9 (18.4%)
≥75	31 (14.3%)	35 (13.7%)	20 (10.9%)	35 (16.4%)	0
Female, n (%)	67 (30.9%)	94 (36.9%)	72 (39.3%)	97 (45.3%)	38 (77.6%)
Race, n (%)					
White	187 (86.2%)	211 (82.7%)	148 (80.9%)	196 (91.6%)	39 (79.6%)
Black or African American	24 (11.1%)	37 (14.5%)	27 (14.8%)	12 (5.6%)	10 (20.4%)
Asian	4 (1.8%)	5 (2.0%)	5 (2.7%)	4 (1.9%)	0
Other	0	1 (0.4%)	0	1 (0.5%)	0
Hispanic or Latino ethnicity, n (%)	15 (6.9%)	34 (13.3%)	18 (9.8%)	5 (2.3%)	1 (2.0%)
Weight (kg), mean ± SD	93.0 ± 20.3	92.9 ± 22.6	93.1 ± 22.0	85.9 ± 20.0	84.4 ± 20.8
BMI (kg/m^2), mean ± SD	31.7 ± 6.0	32.0 ± 6.5	32.1 ± 7.1	29.9 ± 6.2	31.7 ± 7.6
Region, n (%)					
North America	217 (100%)	255 (100%)	183 (100%)	214 (100%)	49 (100%)
Hypertensive, n (%)	195 (89.9%)	215 (84.3%)	146 (79.8%)	151 (70.6%)	23 (46.9%)
Type 2 diabetic, n (%)	83 (38.2%)	136 (53.3%)	79 (43.2%)	53 (24.8%)	3 (6.1%)
Current smoker, n (%)	40 (18.4%)	51 (20.0%)	36 (19.7%)	13 (6.1%)	6 (12.2%)
heFH, n (%)	0	1 (0.4%)	2 (1.1%)	16 (7.5%)	0
CV risk level, n (%)					
Very high	217 (100%)	160 (62.7%)	125 (68.3%)	128 (61.8%)	0
High	0	95 (37.3%)	58 (31.7%)	54 (26.1%)	0
Moderate	0	0	0	25 (12.1%)	49 (100%)

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13.4. Patient Disposition

Table 52: Reasons for Treatment Discontinuation at BLA Cut-off Date

	Randomized and Treated	Did not complete study treatment period[a]		Discontinued due to adverse event		Discontinued due to poor protocol compliance		Discontinued due to other reasons	
FH I									
Placebo	163	18	(11.0%)	8	(4.9%)	4	(2.5%)	6	(3.7%)
Alirocumab 75/150 Q2W	322	36	(11.1%)	12	(3.7%)	8	(2.5%)	16	(5.0%)
FH II									
Placebo	81	3	(3.7%)	1	(1.2%)	1	(1.2%)	1	(1.2%)
Alirocumab 75/150 Q2W	167	11	(6.6%)	5	(3.0%)	2	(1.2%)	4	(2.4%)
High FH									
Placebo	35	6	(17.1%)	1	(2.9%)	1	(2.9%)	4	(11.4%)
Alirocumab 150 Q2W	72	15	(20.8%)	3	(4.2%)	4	(5.6%)	8	(11.1%)
COMBO I									
Placebo	107	32	(29.9%)	8	(7.5%)	9	(8.4%)	15	(14.0%)
Alirocumab 75/150 Q2W	207	51	(24.4%)	13	(6.2%)	10	(4.8%)	28	(13.4%)
COMBO II									
Ezetimibe 10	241	35	(14.5%)	13	(5.4%)	7	(2.9%)	15	(6.2%)
Alirocumab 75/150 Q2W	479	73	(15.2%)	36	(7.5%)	13	(2.7%)	24	(5.0%)
LONG TERM									
Placebo	788	146	(18.5%)	44	(5.6%)	34	(4.3%)	67	(8.5%)
Alirocumab 150 Q2W	1550	311	(20.0%)	98	(6.3%)	54	(3.5%)	159	(10.2%)
OPTIONS I									
Patients on atorvastatin 20 mg before randomization									
Atorvastatin 40	57	13	(22.8%)	4	(7.0%)	2	(3.5%)	7	(12.3%)
Ezetimibe 10 + atorvastatin 20	55	15	(27.3%)	3	(5.5%)	4	(7.3%)	8	(14.5%)
Alirocumab 75/150 Q2W + atorvastatin 20	57	11	(19.3%)	5	(8.8%)	0		6	(10.5%)
Patients on atorvastatin 40 mg before randomization									
Atorvastatin 80	47	8	(17.0%)	3	(6.4%)	0		5	(10.6%)
Rosuvastatin 40	45	6	(13.3%)	1	(2.2%)	0		5	(11.1%)
Ezetimibe 10 + atorvastatin 40	46	6	(12.8%)	1	(2.1%)	0		5	(10.6%)
Alirocumab 75/150 + atorvastatin 40	47	9	(19.1%)	2	(4.3%)	1	(2.1%)	6	(12.8%)

	Randomized and Treated	Did not complete study treatment period[a]		Discontinued due to adverse event		Discontinued due to poor protocol compliance		Discontinued due to other reasons	
OPTIONS II									
Patients on rosuvastatin 10 mg before randomization									
Rosuvastatin 20	48	5	(10.4%)	2	(4.2%)	1	(2.1%)	2	(4.2%)
Ezetimibe 10 + Rosuvastatin 10	48	14	(29.2%)	6	(12.5%)	2	(4.2%)	6	(12.5%)
Alirocumab 75/150 Q2W + Rosuvastatin 10	49	11	(22.4%)	3	(6.1%)	2	(4.1%)	6	(12.2%)
Patients on rosuvastatin 20 mg before randomization									
Rosuvastatin 40	53	8	(15.1%)	3	(5.7%)	0		5	(9.4%)
Ezetimibe 10 + Rosuvastatin 20	53	9	(17.0%)	2	(3.8%)	0		7	(13.2%)
Alirocumab 75/150 Q2W + Rosuvastatin 20	54	13	(24.1%)	2	(3.7%)	2	(3.7%)	9	(16.7%)
ALTERNATIVE									
Atorvastatin 20	63	21	(33.3%)	16	(25.4%)	2	(3.2%)	3	(4.8%)
Ezetimibe 10	124	42	(33.6%)	31	(24.8%)	0		11	(8.8%)
Alirocumab 75/150 Q2W	126	30	(23.8%)	23	(18.3%)	0		7	(5.6%)
MONO									
Ezetimibe 10	51	7	(13.7%)	4	(7.8%)	1	(2.0%)	2	(3.9%)
Alirocumab 75/150 Q2W	52	8	(15.4%0	5	(9.6%)	0		3	(5.8%)

[a] Includes patients who completed the planned treatment duration but who otherwise did not fulfill the strict CRF criteria for study treatment period completion.

13.5. Patient Narratives

Trigeminal neuralgia (#1) – A 54-year-old male patient with ongoing cervical dystonia and a history of a concussion 10 years prior, was receiving rosuvastatin 20 mg/day before alirocumab initiation. On Day 346 of the study, the patient had a new adverse event of moderate intensity, reported as trigeminal neuralgia. On that day, the patient reported 4-5 episodes of right sided facial pain within the past month that occurred spontaneously; these episodes lasted just for seconds and went away without residual. A neurological examination was performed with normal results. The patient was diagnosed with trigeminal neuralgia involving the V1 territory (intensity: severe). The patient was suggested to take Coenzyme Q-10 (coQ10) (200 mg/daily) for his symptoms. On Day 383 this episode worsened. On Day 385, the patient had 10-15 episodes of pain, which was not as sharp as in previous episodes but duration was increased 8-10 seconds with every episode. On Day 386, the patient underwent a neurology consultation (Office visit). The neurological examination was normal. No action was taken with the IMP. At the date of the last received information, the patient had not recovered from the event. This patient had several LDL-C < 25 mg/dL during the study (lowest LDL-C value was 4 mg/dL at D88).

Trigeminal neuralgia (#2) – A 57-year-old female patient with a history of anxiety and depression, was receiving simvastatin 40 mg/day before alirocumab initiation. On Day 43, the patient had a new adverse event reported of trigeminal neuralgia, which resolved by Day 70 with amitriptyline 10 mg/day. On Day 482, a second episode was reported. No corrective treatment was given. Approximately one month later, amitriptyline 5 mg/day was re-started for unspecified reasons following the last dose of alirocumab. Alirocumab and simvastatin were continued as planned through the end of the study. Of note, the patient also reported a common cold that started on Day 25 and resolved by Day 42. An event of transitory finger paresthesia was also reported on Day 187 that resolved approximately one month later. This patient had no LDL-C values <25 mg/dL and the lowest LDL-C value was 40 mg/dL.

Optic neuritis: A 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 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 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. Magnetic resonance imaging (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 alirocumab, statin, or other 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 (lowest values of LDL-C, 36 mg/dL and 30 mg/dL, occurred at Weeks 4 and 8, respectively). Vitamin E levels remained normal throughout the study. This patient had pre-existing positive ADA status.

Demyelination: 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 IMP and to statin, and not related to other LMT. No action was taken with the IMP. 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.

Myelitis transverse: 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 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 to 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.

Miller-Fisher syndrome: 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 gamma-globulin 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-gangliozide antibodies, and 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 medical product (IMP) 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.