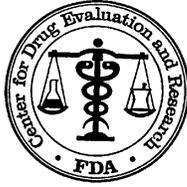


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125559Orig1s000

STATISTICAL REVIEW(S)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL MEMORANDUM

BLA Number: 125559 (SDN 32, eCTD Seq. No. 0032)
Drug Name: Alirocumab (Proposed Trade name: PRALUENT)
Indication(s): Treatment of primary hypercholesterolemia or mixed dyslipidemia
Applicant: Sanofi
Document Reviewed: Applicant's response to FDA information request
Date(s): April 15, 2015 (Document Date)
May 1, 2015 (Request to Biometrics)
July 24, 2015 (PDUFA Goal Date)
Review Priority: Priority
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Keywords: low LDL, new onset diabetes mellitus, propensity scores, post-randomization subgroup analyses

Introduction

This is a statistical memorandum by the Division of Biometrics VII (DBVII) in response to a consult, via email dated May 1, 2015, from the Division of Metabolism and Endocrinology Products (DMEP) to comment on the methodology and limitations of the subgroup analyses that were performed by Sanofi, the Applicant for Biologics License Application (BLA 125559, PDUFA Goal Date: July 24, 2015) for alirocumab (proposed trade name: PRALUENT). Alirocumab is a PCSK-9¹ inhibitor, which Sanofi proposes to be 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. Sanofi also proposes for alirocumab to be indicated for reduction in low-density lipoprotein cholesterol (LDL-C), total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, triglycerides, and lipoprotein (a), and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1. PRALUENT is proposed to be available in 75 mg/mL and 150 mg/mL pre-filled pens as well as 75 mg/mL and 150 mg/mL pre-filled syringes.

The Applicant's subgroup analyses, which are the subject of this document, were conducted in response to Questions 2 and 4 of an information request (IR) by the FDA dated March 15, 2015. Refer to the Appendix of this document for the specific statements of these questions. Note that in these questions the Applicant was asked to perform analyses for subgroups defined using baseline characteristics (e.g. normal glucose at baseline) as well as for subgroups defined post-randomization. The analyses were based on data from 12 phase 2 and 3 placebo- or active-controlled trials and performed in the following trial groupings for the respective questions:

- 5 phase 3 placebo-controlled trials (Question 2)
- 7 phase 2 and 3 placebo-controlled trials (Question 4)
- 5 phase 3 active-controlled trials only (Question 2)
- 10 phase 3 placebo- and active-controlled trials (Question 2)
- All 14 trials (Question 4)

The subgroup analyses by baseline characteristics were conducted using Cox models, stratified by trial, for estimating the hazard ratios (alirocumab to control) as well as the 95% confidence intervals for each of the outcomes of interest. The Applicant's subgroup analyses by baseline characteristics are acceptable and consistent with good statistical principles set forth in ICH E9². Therefore, no further discussion of these analyses is presented in this document.

There are concerns with any analyses performed by subgroups defined post-randomization. Of note, analyses by post-randomization subgroups are generally not advised because the treatment effect influences classification of the subgroup, which poses difficulties in interpretation of any

¹ The proprotein convertase subtilisin/kexin type 9, also known as PCSK-9, gene helps regulate the amount of cholesterol in the bloodstream.

² Internal Conference on Harmonization Harmonized Tripartite Guideline. "Statistical Principles for Clinical Trials E9" dated February 1998.

apparent subgroup findings. This document focuses on the Applicant's methods for analyzing post-randomization subgroups based on Cox models adjusted for propensity scores³.

In general, a propensity score represents the probability to be treated with the product under investigation. Propensity score methods have been widely used in observational studies, i.e. studies lacking randomization, to balance treatment arms in terms of baseline characteristics and to account for measured confounding. The score is usually estimated for all patients in the study, irrespective of treatment received, e.g. from a logistic regression model adjusted for baseline covariates. The statistical analysis method of choice (e.g. Cox modelling) for estimating the treatment effect then proceeds by accounting for the propensity score, for example, after matching treatment arms on propensity score or stratification by propensity score.

Summary of the Applicant's Subgroup Analyses using Propensity Scores

The following post-randomization subgroups were requested in the IR:

- Alirocumab LDL-C < 25 (low-LDL): patients with two consecutive LDL-C < 25 mg/dL
- Alirocumab LDL-C ≥ 25: patients without 2 two consecutive LDL-C < 25 mg/dL

For Question 2, the analyses were conducted within the alirocumab arm to compare LDL-C < 25 to LDL-C ≥ 25 for patients with normal glucose at baseline or without diabetes at baseline in the specified trial groupings. For Question 4, the analyses were conducted for all patients, irrespective of baseline glucose or diabetes status, within the alirocumab arm for the trial groupings specified.

Reviewer's Comment: As noted, findings from analyses of post-randomization subgroups are difficult to interpret; moreover, findings from such post-randomization subgroup analyses of subgroups defined at baseline are also questionable.

The Applicant's post-randomization subgroup analyses attempted to account for differences in baseline characteristics for patients with LDL-C < 25 that may put them at greater risk for the outcomes of interest in comparison to patients with LDL-C ≥ 25. The following points summarize the steps in the analyses as described in Appendix 1 of the response document:

1. Estimate the propensity score: The Applicant identified the baseline characteristics which were prognostic factors⁴ for achieving low LDL among all alirocumab patients in all phase 3 trials, irrespective of their baseline glucose or diabetes status. The Applicant notes that only data from the phase 3 trials were used in this step because some factors such as medical history were not available from phase 2 trials. Potential factors were first selected with p-values < 0.15 obtained in univariate analyses and then a multivariate

³ Everett, M. B. et al. *Safety Profile of Subjects Treated to Very Low Low-Density Lipoprotein Cholesterol Levels (<30 mg/dL) with Rosuvastatin 20 mg Daily (from JUPITER)*. The American Journal of Cardiology. 2014 Dec 1;114(11):1682-9.

⁴ Refer to Table 1 (page 7) of Appendix 1 of the Applicant's response document, dated April 15, 2015, for list of prognostic factors for achieving low LDL.

logistic regression was performed with stepwise selection using a 0.15 level to determine the final list of prognostic factors. The final multivariate logistic regression model yields the probability of achieving low LDL, that is, a “propensity score”.

2. Perform time to event analyses: The Applicant used Cox models, stratified by propensity score quintile (i.e. five strata whereby patients in each stratum should have similar propensity score) and including an indicator variable for low LDL (yes/no), were used to estimate the hazard ratios (alirocumab LDL-C < 25 to alirocumab LDL-C \geq 25) as well as 95% confidence intervals for the outcomes of interest in the specified trial groupings. P-values from these analyses were provided where requested. For low LDL patients, only the follow-up period after the patients achieved the first of 2 consecutive low LDL measurements was considered and for other patients the entire treatment emergent adverse event (TEAE) period, that is time from first treatment to last treatment + 70 days, was considered.

Comments Regarding Applicant’s Subgroup Analyses using Propensity Scores

The Applicant’s subgroup analyses using propensity score attempts to account for any differences between the two groups of interest (alirocumab LDL-C < 25 or alirocumab LDL-C \geq 25) in order to limit biases associated with comparing post-randomization subgroups. However, several concerns about the methodology limit the ability to rely on such analyses for making regulatory decisions as described below.

Firstly, there is a potential for bias to be introduced when considering different follow-up periods for the LDL-C < 25 and the LDL-C \geq 25. This arises as the LDL-C < 25 group includes only follow-up time after achieving two consecutive LDL-C < 25 whereas the LDL-C group includes all follow-up time after randomization. The direction of this bias is uncertain and thus, its impact on the subgroup findings is unknown. *This point is applicable for all subgroup analyses conducted by the Applicant using post-randomization subgroups, including analyses without the use of propensity scores.* For example, the bias could favor the low LDL group as fewer outcomes may be considered in the analyses (e.g. outcomes that occur shortly after treatment such as injection site reactions). On the other hand, the bias could disfavor the low LDL group because the follow-up period is shorter in comparison to the non-low LDL patients. Not knowing which direction the bias occurs makes it difficult to interpret if the hazard ratios obtained from the Applicant’s analyses over- or under-estimate the risks for the outcomes under investigation. Note that the Applicant did not provide any assessments of the potential for bias nor did they provide information on the distribution of follow-up time for the two groups.

Another concern is whether the propensity score analyses have adequately accounted for confounding between the alirocumab LDL-C < 25 and alirocumab LDL-C \geq 25 groups. Typically with propensity score analyses, diagnostics are performed to assess how well the analyses have achieved its goal, i.e. to create balanced groups in terms of baseline characteristics for the comparisons. Such diagnostics have not been provided in the Applicant’s response document. Therefore, there remains uncertainty whether subgroup findings are due to achieving

low LDL or if due to inherent baseline characteristics of the patients that caused them to experience the outcomes analyzed.

Finally, the process for variable selection in the propensity score estimating model may not be optimal. In these analyses, prognostic factors for achieving low LDL were determined using a logistic regression model with stepwise selection for identifying factors for inclusion in the model. Stepwise selection methods have been criticized⁵ for yielding inaccurate estimates of parameters and their variances. This could thereby impact the estimation of the propensity scores and lead to misclassification of patients into the quintiles used in the stratified Cox model. The consequences being inaccuracies in the hazard ratio estimates.

Given concerns with the Applicant's propensity score analyses, and concerns with analyses of post-randomization subgroups in general, there is uncertainty about the reliability of findings from these exploratory analyses. Therefore, we recommend that the findings from these exploratory analyses be interpreted cautiously.

⁵ Harrell, F. E. Regression modelling strategies: With applications to linear models, logistics regression, and survival analysis. 2001. Springer-Verlag. New York.

Appendix

Below are the specific questions from the FDA information request dated March 15, 2015 that motivated the Applicant's subgroup analyses which are evaluated in this document.

Question 2

Provide a time to event analysis including a Kaplan-Meier curve of time to new onset of impaired fasting glucose (combining data from both AEs [adverse events] and laboratory values): (1) by treatment group and (2) within alirocumab-treated patients only, by two consecutive LDL-C values < 25mg/dL vs. others. Provide these plots for both the global pool as well as separately for the placebo and ezetimibe pools.

Please provide this same analysis with time to new onset diabetes (by AE or laboratory values).

Question 4

Please provide in tables using the format in ISS appendix 1.4.5.4 (global pool) and 1.4.5.5 (placebo pool) TEAEs by HLGT [high level group term], HLT [high level term], and PT [preferred term] in control patients, alirocumab patients, alirocumab-treated patients with LDL-C ≥ 25 mg/dL and patients with 2 consecutive LDL-C < 25 mg/dL. Please provide p-values for the following comparisons of interest 2 LDL-C < 25mg/dL versus ≥ 25 mg/dL within alirocumab group; 2 LDL-C < 25mg/dL alirocumab versus control or placebo; and LDL-C ≥ 25 mg/dL versus control or placebo. (We recognize that this post hoc testing is exploratory and that the comparisons being made are not randomized comparisons since the subgroups are defined by post-randomization data.)

Please provide a table using this same format and analyses described above listing AEs of special interest (e.g. diabetic CMQ, neurologic, neurocognitive, hepatic, etc.)

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/s/

JANELLE K CHARLES
06/22/2015

MATTHEW J SOUKUP
06/22/2015
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA# 125559
Drug Name: Praluent (alirocumab)
Indication(s): Hyperlipidemia and mixed dyslipidemia
Applicant: Sanofi-Aventis
Date(s): Stamp date: November 24, 2014
Review due date: April 24, 2015
PDUFA date: July 24, 2015
Review Priority: Priority

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Keywords: subgroup analyses

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1 EXECUTIVE SUMMARY

This review examined existing data to assess the treatment effect of Praluent on percent change in LDL-C at week 24 within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Praluent on percent change in LDL-C at week 24 differs by sex, age, race, or ethnicity. We acknowledge that the analyses provided in this review are exploratory and the trials were not designed to support such investigations. Despite possible statistical limitations, these investigations were undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

This review concludes that there was statistical evidence of beneficial effects of Praluent on percent change in LDL-C at week 24 within all subgroups examined (by sex, age, race, and ethnicity), and the estimated effects were relatively consistent across these subgroups (range of subgroup-specific effects based on analyses integrating all five studies: -43% to -58%). In specific, this review concludes that

- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for each sex. There is an indication that the effect for Praluent on the percent change in LDL-C at week 24 is larger in males than females; however, it is unclear whether this difference between sexes in the effect on a surrogate endpoint will translate into an important difference between sexes in the clinical cardiovascular outcome.
- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for both age groups examined (below 65 years and 65 years and above). Available data did not give a strong indication that the treatment effect for Praluent is larger in one age group than the other.
- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for all races examined (White, Black or African American, Asian, American Indian or Alaska Native, and other). Available data did not give a strong indication that the treatment effect for Praluent is different for any race.
- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for both ethnicities examined (Hispanic or Latino and Not Hispanic or Latino). Some of the available data provides a possible indication that the treatment effect for Praluent is larger in patients who are not of Hispanic or Latino ethnicity; however, this result is not consistent across studies and is not considered reliable.

2 INTRODUCTION

This document is written as part of a pilot partnership between Division of Biometrics 2 and the Patient Advocacy and Stakeholder Engagement (PASE) group. The objective of this statistical review is to advise PASE in using existing data to understand the effects of Praluent within age,

sex, racial, and ethnic subgroups and whether these effects differ across subgroups. This objective is different from the objective of the original Statistical Review and Evaluation of this submission

(http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000StatR.pdf) and is in supplement to that document. The reader is referred to that document for the full statistical evaluation of the efficacy of the current Praluent submission.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Available Data

The applicant proposed and the Agency has approved¹ Praluent as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C.

The applicant provided results of ten phase 3 trials conducted to evaluate Praluent for LDL-C reduction at week 24 in different patient populations and across different levels of background statin intensity (maximally tolerated dose, less than maximally tolerated dose, and without statin). All 10 trials were randomized, double-blind, parallel-group, placebo- or active-controlled with treatment periods ranging from 6 to 24 months. Five trials (FH I, FH II, HIGH FH, COMBO I, LONG TERM) were placebo controlled (Table 1). These randomized a total of 3499 subjects 2:1 to Praluent or placebo on top of maximally tolerated background statin with or without other lipid modifying therapies. FH I, FH II and HIGH FH were done exclusively in patients with heterozygous familial hypercholesterolemia (heFH). LONG TERM was done in patients with heFH and non-familial hypercholesterolemia (FH). LONG TERM was the largest trial with 2341 subjects randomized. LONG TERM and HIGH FH were the only trials that studied the 150 mg dose throughout the treatment period. The primary efficacy endpoint for all studies was the percent change in calculated LDL-C from baseline to week 24. Findings in the overall study group using the preferred FDA analysis, which assumed LDL-C values after stopping treatment early would return to baseline levels, are provided in Table 2. Consistent with product labeling, these five placebo controlled trials are the basis of the efficacy portion of the “drug snapshot” and the evaluation of whether treatment effects vary across subgroups.

¹ http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125559Orig1s000ltr.pdf

Table 1. Summary of study designs

Study	Population	Design	Primary Endpoint/ Treatment duration	Treatment arms (N randomized)
Background therapy: Maximally tolerated dose of statin ± other LMTs (Praluent add-on)				
FH I* (EFC12492)	heFH	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 75 mg/150 mg Q2W ¹ (n=323) - Placebo Q2W (n=163)
FH II* (R727-CL-1112)	heFH	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 75 mg/150 mg Q2W ¹ (n=167) - Placebo Q2W (n=82)
HIGH FH* (EFC12732)	heFH with LDL-C ≥ 160 mg/dL	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 150 mg Q2W (n=72) - Placebo Q2W (n=35)
COMBO I (EFC11568)	High CV risk with hypercholesterolemia	R, DB, PC, PG	LDL-C at week 24/ 12 months	- 75 mg/150 mg Q2W ¹ (n=209) - Placebo Q2W (n=107)
LONG TERM* (LTS11717)	heFH or non-FH with hypercholesterolemia	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 150 mg Q2W (n=1553) - Placebo Q2W (n=788)

LMTs – Lipid-modifying therapy; FH –familial hypercholesterolemia; heFH – heterozygous familial hypercholesterolemia; CV – cardiovascular; R – randomized; DB – double-blind; PC – placebo-controlled; AC – active-controlled; PG – parallel-group; DD – double-dummy;

¹Possible up-titration of dose from 75 mg to 150 mg at week 12 depending on LDL-C values at week 8, according to the level of CV risk

* Ongoing as of the August 31, 2014 data cutoff.

Source: Original FDA Statistical Review and Evaluation of this submission

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000StatR.pdf

Table2. % LDL-C change at week 24 by trial (ITT population; preferred FDA analysis)

	Baseline (mg/dL)	LS Mean: % Change	Difference: Praluent -Control (95% CI)
FH I (EFC12492)			
Aliro 75mg/150mg (N=323)	145	-47%	
Placebo (N=163)	144	9%	-56% (-62, -51)
FH II (R727-CL-1112)			
Aliro 75mg/150mg (N=167)	135	-47%	
Placebo (N=82)	134	3%	-50% (-57, -43)
HIGH FH (EFC12732)			
Aliro 150mg (N=72)	196	-43%	
Placebo (N=35)	201	-7%	-36% (-49, -24)
COMBO I (EFC11568)			
Aliro 75mg/150 mg (N=209)	100	-44%	
Placebo (N=107)	105	-2%	-43% (-50, -35)
LONG TERM (LTS11717)			
Aliro 150mg (N=1553)	123	-58%	
Placebo (N=788)	122	1%	-58% (-61, -56)

Source: Original FDA Statistical Review and Evaluation of this submission

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000StatR.pdf

3.2 Statistical Methods for Assessing Differences in Treatment Effect across Subgroups

In planning analyses to assess differences in treatment effect across subgroups, the merits of combining studies to provide increased power for small subgroups were weighed against the merits of analyzing all studies separately so as not to miss possible clinical settings where differences in treatment effect across subgroups differ for different populations or doses. While we acknowledge that differences in the treatment effect across differing populations and/or doses are possible, even likely, we note that consistency in the treatment effect across studies is not needed to justify combining studies for the purpose of identifying subgroups where the treatment effect differs. The objective of this review and these analyses is different from assessing the overall efficacy of the product. It is to characterize the differences in treatment effect across subgroups. What is necessary for this type of analysis is that if there are differences in the way the treatment acts in certain subgroups these differences by subgroup must extend to the other disease populations and doses. For example if the treatment effect for Praluent in males is larger than that of females in patients with heFH combining this study with a study of patients with hypercholesterolemia is more agreeable if the treatment effect for Praluent is also larger for males than females in patients with hypercholesterolemia. We believe that in general this type of assumption is much more likely to be true than the former.

As a result of the afore-mentioned considerations, subgroup analyses of each study and dose were considered individually. In addition the following combinations of studies were considered: FHI and FHII since both studies were conducted in the heFH population at the same dose; COMBO I and LONG TERM since both studies included hypercholesterolemia patients but albeit examined different doses; FHI, FHII, and HIGH FH since these studies included heFH patients but albeit examined different doses; and all five studies together despite differences in population and doses studied. In all cases where studies are combined, analyses are adjusted or stratified by study and dose to account for differences in population and dose across studies. We also note that the primary endpoint, the percent change in LDL-C at week 24, provides a pseudo-adjustment for differences in populations across studies by dividing by the subject's baseline score and possibly making differences in population less important. Tests for treatment-by-subgroup interaction were used to quantitatively assess whether there is evidence that the treatment effect differs by subgroup.

We acknowledge that these analyses are exploratory and the trials were not designed to support such investigations. In general, these comparisons may be limited by multiplicity on one hand and low power considerations on the other. Consistency in the differences in treatment effect across subgroups by study is qualitatively examined as a means to minimize (but albeit not eliminate) possible type I errors due to multiple analyses. Limitations due to low power are somewhat mitigated for this application in that the effect of Praluent on percent change in LDL-C is large and measurement of the endpoint is precise so that differences between Praluent and placebo are detectable even with the relatively small sample sizes

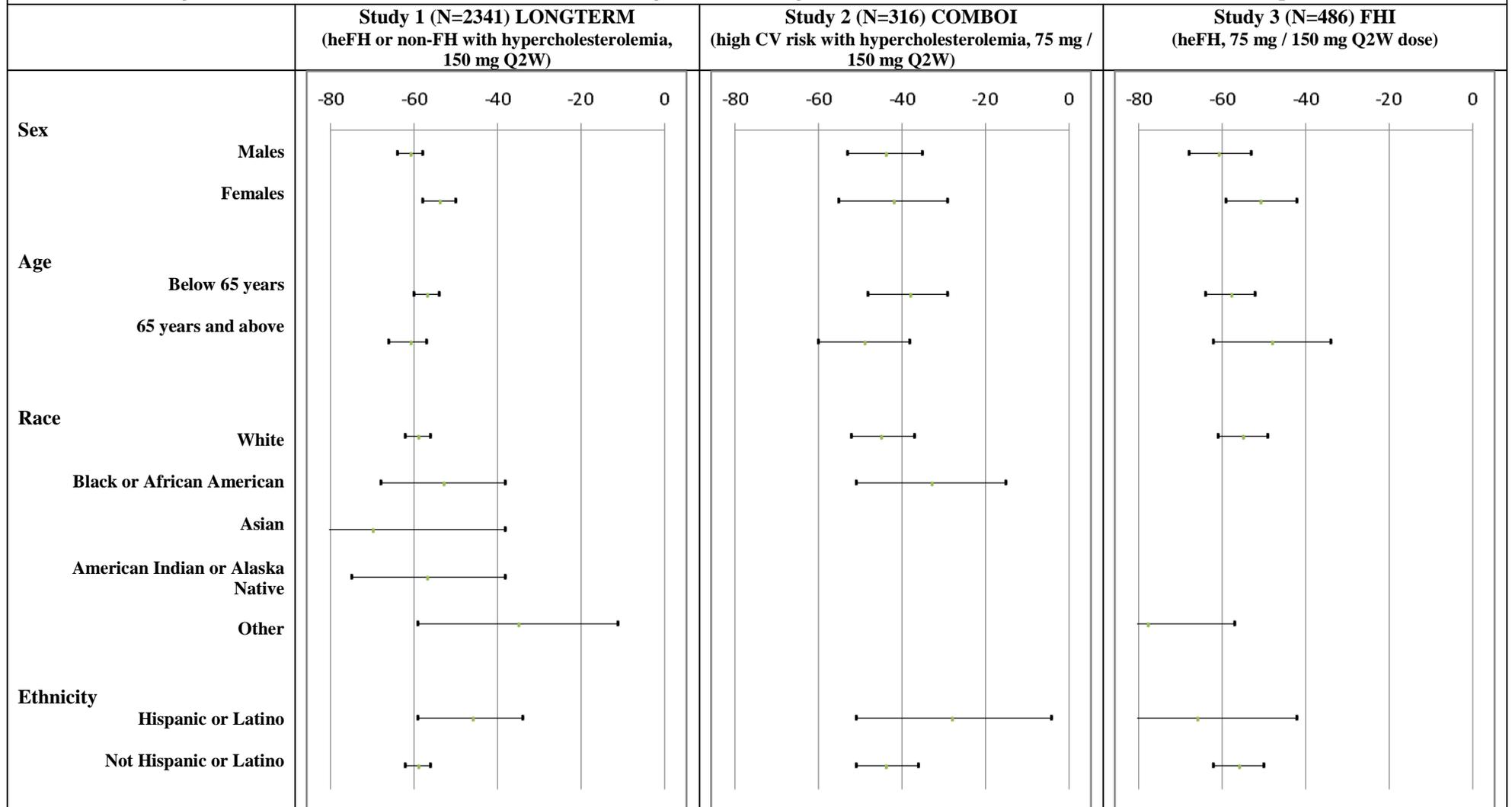
available within each age, sex, race, and ethnicity subset. Despite these possible statistical limitations associated with multiplicity and low power, these investigations are undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

All subgroup analyses presented in this review (as well as overall analyses presented in Table 2) rely on the FDA preferred statistical methods designed to appropriately account for missing data developed as part of the original review of the application. The approach used a Pattern-Mixture Model (PMM) with mixed imputation in the randomized population. To account for the uncertainty in the missing data, missing values were imputed using multiple imputation. A total of 100 imputed datasets were created. Results from the imputed datasets were combined using Rubin's method. In the PMM different imputation strategies were applied to missing LDL-C values during the on-treatment period and after treatment discontinuation, defined as after the day of last injection + 21 days. For missing values occurring during the on-treatment period it was assumed that patients would continue to show benefit. Missing LDL-C values during this period were considered missing at random (MAR) and imputed based on other on-treatment measurements. For patients that stopped their study treatment it was assumed they would no longer benefit from study drug, and their LDL-C values would return to baseline. For these patients the imputed LDL-C values were centered on the patient's baseline value. Patients not treated or with missing data before taking study medication also had their LDL-C values imputed based on their baseline value.

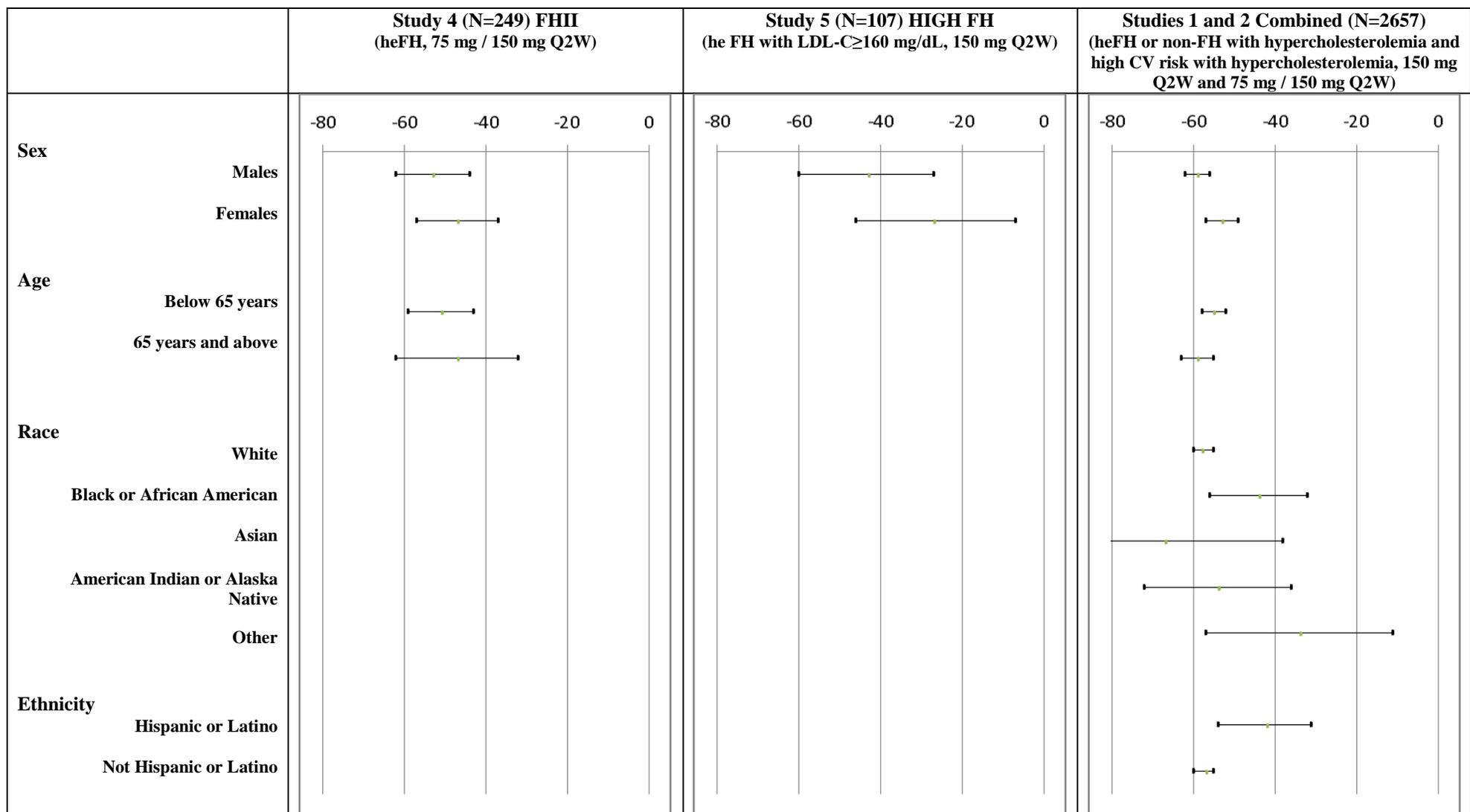
3.3 Results by Sex, Race, Age, and Ethnicity

This section provides estimates of the difference between Praluent and placebo in the mean percent change from baseline in LDL-C by sex, race, age, and ethnicity subgroups. Tests for the treatment-by-subgroup interaction are also provided. Figure 1 displays results for each study and dose considered individually as well as the following combinations of studies: FHI and FHII since both studies were conducted in the heFH population at the same dose; COMBO I and LONG TERM since both studies included hypercholesterolemia patients but albeit examined different doses; FHI, FHII, and HIGH FH since these studies included heFH patients but albeit examined different doses; and all five studies together despite differences in population and doses studied.

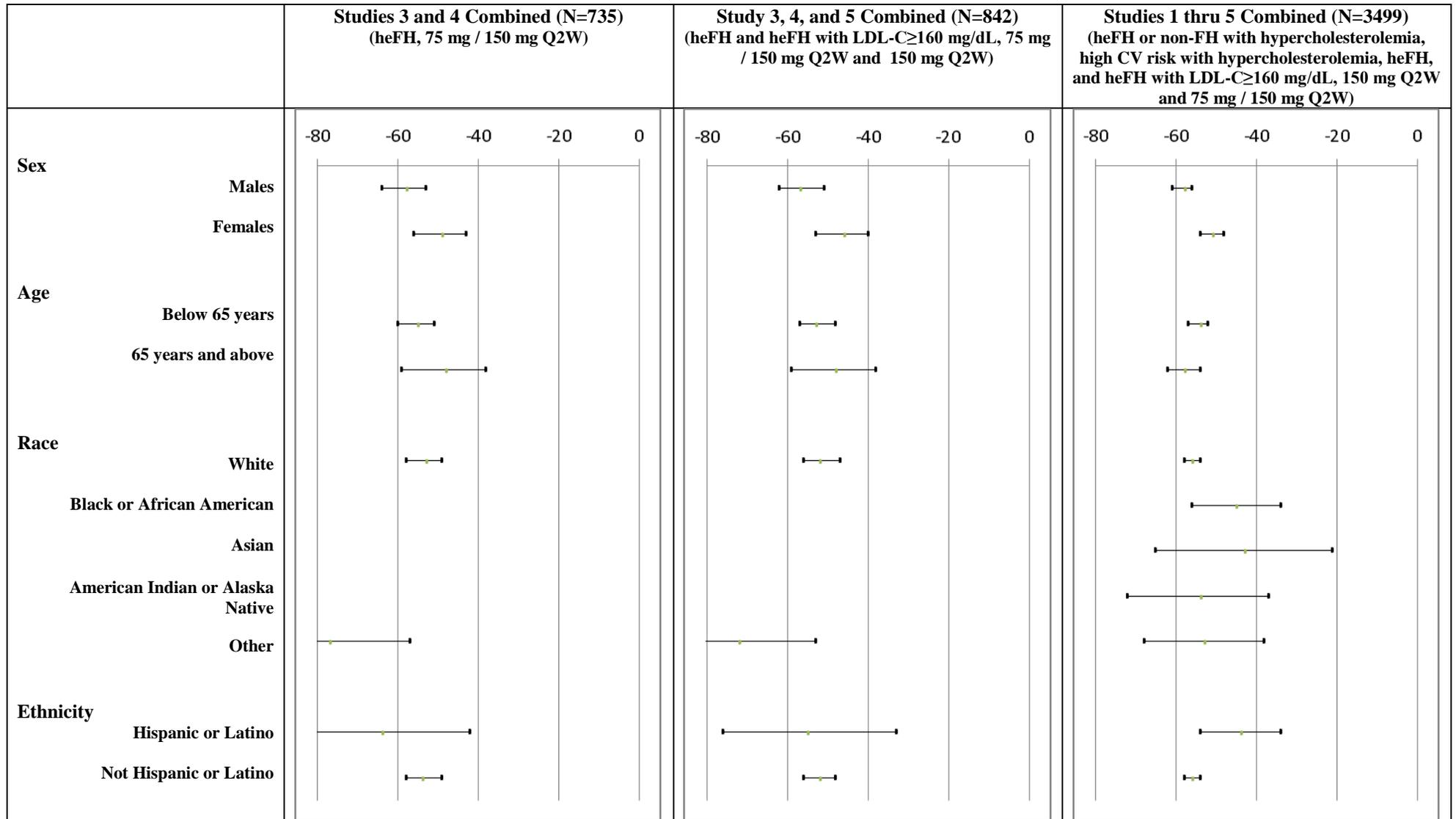
Figure 1: Difference (95% Confidence Interval) in Average Percent Change from Baseline in LDL-C at Week 24 (Praluent minus placebo)



P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for studies 1, 2, and 3, respectively: Sex: 0.01, 0.7, and 0.08; Age: 0.1, 0.1, and 0.2; Race: 0.3, 0.2, and 0.04; Ethnicity: 0.05, 0.2, and 0.4



P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for studies 4, 5, and 1 and 2 combined, respectively: Sex: 0.4, 0.2, and 0.02; Age: 0.6, NA, and 0.1; Race: NA, NA, and 0.057; Ethnicity: NA, NA, and 0.01



P-value for statistical test measuring whether the treatment effect differs across subgroups (i.e., p-value for test of treatment-by-subgroup interaction) for studies 3 and 4 combined, 3, 4, and 5 combined, and all studies combined, respectively: Sex: 0.04, 0.01, and 0.001; Age: 0.2, 0.4, and 0.1; Race: 0.03, 0.04, and 0.3; Ethnicity: 0.4, 0.8, and 0.02

Examination of treatment effect by sex: Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 within each sex. Study 1, the largest available single study, gives a strong indication that the effect for Praluent is larger in males than females as is evidenced by a p-value associated with the treatment-by-sex interaction of 0.01. Setting aside issues with multiplicity, the result for the treatment-by-sex interaction observed in study 1 would be considered statistically significant. This trend is not contradicted and is somewhat supported by consistent numerical differences in the point estimates for the treatment effect for males and females in the other studies and combinations of studies making it less likely that the result demonstrated in study 1 is in fact a type I error. However, it is unknown whether the small difference in the treatment effect of Praluent for males and females on this surrogate endpoint, percent change in LDL-C at week 24, would translate into a meaningful difference in effect for males and females on cardiovascular risk. Therefore, while this difference in effect in males and females on the surrogate endpoint is likely real, it may not be of clinical importance. Display of data to describe the effect of Praluent in males versus females on percent change in LDL-C at week 24 could reliably be achieved by displaying results from study 1 alone as it is the largest study (including approximately 2/3 of patients) or by display of analyses of the combined studies 1 thru 5 as the differences in the treatment effect for males and females are quite consistent across populations and doses.

Examination of treatment effect by age: Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for both age groups examined (below 65 years and 65 years and above). None of the studies give a strong indication that the treatment effect for Praluent is larger in one age group than the other as is evidenced by the p-values associated with the treatment-by-sex interaction. In addition, numerical differences in the point estimates for the treatment effect for the two age groups are not consistent across studies and combinations of studies and appear to be indicative of normal variation in point estimates with no underlying difference in the treatment effect for the two age groups. Display of data to describe the effect of Praluent in the two age groups could reliably be achieved by displaying results from study 1 alone as it is the largest study (including approximately 2/3 of patients) or by display of analyses of the combined studies 1 thru 5 which indicate that even with very large numbers of subjects, the effect of Praluent appears consistent in both age groups.

Examination of treatment effect by race: Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for all races examined (White, Black or African American, Asian, American Indian or Alaska Native, and other). Of the studies available, study 1 provides the most information regarding the treatment effect of Praluent by race as studies 2 thru 5 included almost exclusively white patients. Study 1, the largest available single study with approximately 2/3 of patients, does not give a strong indication that the treatment effect for Praluent is different for any race as is evidenced by the p-values associated with the treatment-by-sex interaction in each of the individual studies. However, setting issues of multiplicity aside, the p-values for the treatment-by-race interaction in the

analysis of studies 3 and 4 combined and 3, 4, and 5 combined, are what would be considered borderline statistically significant. But patients in these studies were primarily white and so provide only an assessment of whether the treatment effect differs for whites and non-whites (i.e., little practical information regarding differences in treatment effect for a variety of races is available). In addition, numerical trends in the results of studies 3 and 4 combined and 3, 4, and 5 combined that seem to suggest that Praluent may have a smaller treatment effect in whites are contradicted by results of study 1 where numerically, the effect for Praluent in whites is comparable to or even larger than that of the other races and suggesting that there may in fact be no difference in the treatment effect for different races. Display of data to describe the effect of Praluent in the two age groups could reliably be achieved by displaying results from study 1 alone as it is the largest study (including approximately 2/3 of patients) with the most information available about a variety of races or for the sake of consistency with other subgrouping factors examined in this review, by display of analyses of the combined studies 1 thru 5 as this is driven primarily by the largest study, study 1.

Examination of treatment effect by ethnicity: Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for both ethnicities examined (Hispanic or Latino and Not Hispanic or Latino). Of the studies available, only studies 1, 2, and 3 provide information regarding ethnicity. Study 1, the largest available single study with approximately 2/3 of patients, provides a possible indication that the treatment effect for Praluent is larger in patients who are not of Hispanic or Latino ethnicity as is evidenced by a p-value associated with the treatment-by-sex interaction in study 1 of 0.05. Setting aside issues with multiplicity, the result for the treatment-by-sex interaction observed in study 1 would be considered borderline statistically significant. However, numerical trends in the results of studies 2 and 3 suggest that Praluent may have a comparable or even smaller treatment effect in patients who are not of Hispanic or Latino ethnicity. Display of data to describe the effect of Praluent in the two ethnicity groups could reliably be achieved by displaying results from study 1 alone as it is the largest study (including approximately 2/3 of patients) or for the sake of consistency with other subgrouping factors examined in this review, by display of analyses of the combined studies 1 thru 5 as this is driven primarily by the largest study, study 1.

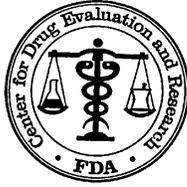
4 SUMMARY AND CONCLUSIONS

This review examined existing data to assess the treatment effect of Praluent on percent change in LDL-C at week 24 within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Praluent on percent change in LDL-C at week 24 differs by sex, age, race, or ethnicity. We acknowledge that the analyses provided in this review are exploratory and the trials were not designed to support such investigations. Despite possible statistical limitations, these investigations were undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using the available data.

This review concludes that there was statistical evidence of beneficial effects of Praluent on percent change in LDL-C at week 24 within all subgroups examined (by sex, age, race, and

ethnicity), and the estimated effects were relatively consistent across these subgroups (range of subgroup-specific effects based on analyses integrating all five studies: -43% to -58%). In specific, this review concludes that

- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for each sex. There is an indication that the effect for Praluent on the percent change in LDL-C at week 24 is larger in males than females; however, it is unclear whether this difference between sexes in the effect on a surrogate endpoint will translate into an important difference between sexes in the clinical cardiovascular outcome.
- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for both age groups examined (below 65 years and 65 years and above). Available data did not give a strong indication that the treatment effect for Praluent is larger in one age group than the other.
- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for all races examined (White, Black or African American, Asian, American Indian or Alaska Native, and other). Available data did not give a strong indication that the treatment effect for Praluent is different for any race.
- Praluent is statistically significantly better than placebo with respect to the percent change in LDL-C at week 24 for both ethnicities examined (Hispanic or Latino and Not Hispanic or Latino). Some of the available data provides a possible indication that the treatment effect for Praluent is larger in patients who are not of Hispanic or Latino ethnicity; however, this result is not consistent across studies and is not considered reliable.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA # 125559

Drug Name: Praluent (alirocumab)

Indication(s): Hyperlipidemia and mixed dyslipidemia

Applicant: Sanofi-Aventis

Date(s): Stamp date: November 24, 2014
Review due date: April 24, 2015
PDUFA date: July 24, 2015

Review Priority: Priority

Biometrics Division: II

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Keywords: Missing data, surrogate endpoints, risk-benefit

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1 EXECUTIVE SUMMARY

The applicant proposes Praluent (alirocumab) be indicated as an adjunct to diet, for the 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 (ApoB), triglycerides (TG), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A1 (ApoA1) either in combination with a statin or as monotherapy including in patients who cannot tolerate statins.

1.1 Conclusions and Recommendations

Ten phase 3 trials were conducted to evaluate LDL-C reduction at week 24 in different patient populations and across different levels of background statin intensity (maximally tolerated dose, less than maximally tolerated dose, and without statin). In all trials, alicumab had greater estimated LDL-C reduction than control (active or placebo). The excess reduction was statistically significant at the prespecified alpha level for all primary hypotheses tested in nine trials and for two of four tested in the tenth trial. The findings were overall consistent across the applicant's primary efficacy analysis and our preferred analysis that more appropriately represented missing data for subjects after stopping treatment early. My review of the statistical evidence found that alicumab is a highly effective therapy for lowering LDL-C. However, the submission had too few outcome events to allow a robust evaluation of cardiovascular (CV) benefit. Because patients not on a maximally tolerated background statin have treatment options for additional LDL-C lowering with known clinical benefit (i.e., up-titrating the statin), I support the approval of alicumab in a more restricted population than the one proposed by the applicant. I consider that the CV and efficacy data reviewed in this submission support approval for alicumab when used in combination with a maximally tolerated dose of a statin. An expanded population should be revisited once the ongoing CV outcomes trial has completed and the data have been reviewed.

1.2 Brief Overview of Clinical Studies

Ten phase 3 trials were reviewed for this BLA submission. All 10 trials were randomized, double-blind, parallel-group, placebo- or active-controlled with treatment periods ranging from 6 to 24 months. In total, there were 5296 subjects randomized across the trials, with 3188 assigned to receive alicumab. Two alicumab treatment regimens were studied. Each study investigated only one dosing regimen. One regimen had the 150 mg dose administered throughout the study duration. The other regimen had the 75 mg dose up-titrated to 150 mg if LDL-C at week 8 was not below a study-specific threshold.

Five trials (FH I, FH II, HIGH FH, COMBO I, LONG TERM) randomized a total of 3499 subjects 2:1 to alicumab or placebo on top of maximally tolerated background statin with or without other lipid modifying therapies. FH I, FH II and HIGH FH was done exclusively in patients with heterozygous familial hypercholesterolemia (heFH). LONG TERM was done in

patients with heFH and non-familial hypercholesterolemia (FH). LONG TERM was the largest trial with 2341 subjects randomized. LONG TERM and HIGH FH were the only trials that studied the 150 mg dose throughout the treatment period.

Five trials were active-controlled (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE and MONO). Ezetimibe 10 mg was an active-control in all five trials; OPTIONS I and OPTIONS II had statin up-titration as additional active-controls. Active-controlled trials were performed in different patient populations and on different background statin intensities. COMBO II was done in patients with high CV risk on a background of maximally tolerated statin. OPTIONS I and OPTIONS II were done in heFH and FH patients with high CV risk on a less than maximal dose of statin. ALTERNATIVE and MONO both studied alicumab without a background statin; in ALTERNATIVE patients were considered to be statin intolerant.

1.3 Statistical Issues and Findings

In the 10 trials designed to evaluate efficacy of alicumab at week 24, alicumab consistently had greater LDL-C reduction than control (active or placebo). The excess reduction at week 24 for alicumab was statistically significant at the prespecified alpha level in nine trials and in the tenth trial statistically significant for two of the four primary comparisons. The overall findings were found to be consistent across the applicant’s primary efficacy analysis and our preferred analysis (Table 1) that more appropriately represented missing data for subjects that stopped treatment early. The difference between analyses was the applicants’ assumed subjects would continue to sustain treatment benefit after stopping treatment early, which was not consistent with data from the phase 2 and phase 3 trials that showed levels would return to baseline.

Table 1. Summary of trials findings at week 24 for placebo and ezetimibe comparisons

Control arm / Background therapy		Study	Applicant’s primary analysis	FDA preferred analysis
			Alirocumab - Control (95%† CI)	Alirocumab - Control (95% CI)
Placebo				
Maximally tolerated dose of statin ± other LMTs	FH I		-58% (-63, -53)	-56% (-62, -51)
	FH II		-51% (-58, -45)	-50% (-57, -43)
	HIGH FH		-39% (-51, -27)	-36% (-49, -24)
	COMBO I		-46% (-52, -39)	-43% (-50, -35)
	LONG TERM		-62% (-64, -59)	-58% (-61, -56)
Ezetimibe				
Maximally tolerated dose of statin ± other LMTs	COMBO II		-30% (-34, -25)	-28% (-33, -23)
	OPTIONS I: Atorva 20 mg		-24% (-40, -7)	-21% (-35, -7)
	OPTIONS I: Atorva 40 mg		-31% (-47, -16)	-28% (-40, -15)
	OPTIONS II: Rosuva 10 mg		-36% (-52, -21)	-28% (-40, -16)
	OPTIONS II: Rosuva 20 mg		-25% (-51, 1)	-23% (-42, -3)
LMT (no statin)	ALTERNATIVE		-30% (-36, -24)	-30% (-37, -24)
None	MONO		-32% (-40, -23)	-31% (-40, -22)

† 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Based on our preferred analysis, the estimated excess reduction in LDL-C ranged between 36% and 58% compared to placebo when added to a maximally tolerated statin with or without other LMTs. Compared to ezetimibe, the estimated excess reduction was 28% when added to a maximally tolerated statin alone, between 21% and 23% when added to a less than maximal statin dose, and about 30% when given without a statin.

The amount of missing data ranged between 6% and 13% at week 24 across trials. Given the amount of missing data and the magnitude of the treatment effect, it is unlikely missing data could be such that it would alter the study conclusions.

An interaction appears to exist for sex, with the estimated effect being larger in all 10 trials for males than the estimated effect for females. Baseline LDL-C levels were not found to be systematically different for males and females across trials.

A total of 93 adjudicated major adverse cardiovascular events or MACE (CHD death, fatal and non-fatal and myocardial infarction, fatal and non-fatal ischemic stroke, or unstable angina requiring hospitalization) were observed in 10 trials, 58 in the alicumab group and 35 in the control arms. The majority of events came from LONG TERM (52 MACE), with fewer MACE observed for alicumab compared to placebo (1.7% vs. 3.2%). In an integrated analysis of placebo-controlled trials, the frequency of MACE was smaller for alicumab (1.8% vs. 2.4%). There were too few MACE in the trials reviewed to conclude with high statistical confidence that alicumab provides CV benefit.

None of the 10 trials can support an evaluation of either the dose-response relationship or the effect of up-titrating to the 150 mg dose from 75 mg. Any comparison of the different doses relies on post-randomization factors or cross-study comparisons.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Praluent (alirocumab) is a fully human monoclonal antibody and a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor. According to the applicant, by inhibiting the binding of PCSK9 to low-density lipoprotein receptors (LDLR), alicumab increases the number of LDLR available to clear LDL-C, thereby lowering LDL-C. No other products in the PCSK9 class are currently FDA approved.

The applicant propose alicumab be indicated as an adjunct to diet, for the 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, ApoB, TG, and Lp(a), and to increase HDL-C and ApoA1 either in combination with a statin or as monotherapy including in patients who cannot tolerate statins.

Alicumab is intended for biweekly subcutaneous injections. The proposed doses are 75 mg/mL and 150 mg/mL available either in a pre-filled pen or a pre-filled syringe.

2.1.2 History of Drug Development

Sanofi-Aventis and Regeneron Pharmaceuticals are developing alicumab. (b) (4)

The End-of-Phase 2 (EOP2) meeting was held on February 21, 2012. FDA stated that the decision to approve alicumab for the proposed indication would be based on surrogate endpoints. FDA subsequently stated that if data in the BLA submission raise concern about alicumab's potential efficacy to reduce cardiovascular (CV) events or raise significant concerns about safety, they may require results from a completed cardiovascular outcomes trial (CVOT) prior to approval; data from the ongoing CVOT EFC11570 (OUTCOMES) were not included in this submission. FDA also stated that results from the CVOT IMPROVE-IT, which investigated adding ezetimibe (a non-statin) to simvastatin, may also influence the decision on whether the CVOT needs to be completed prior to approval¹.

¹ Top-line results (released 11/17/2014) are that adding ezetimibe to simvastatin led to statistically significantly fewer major adverse cardiovascular events (CV death, nonfatal stroke, nonfatal myocardial infarction, re-hospitalization for angina, or coronary revascularization occurring at least 30 days after randomization) than simvastatin alone (HR = 0.936, p = 0.016). Data from this study has not yet been reviewed by FDA; Merck plans to submit data to FDA mid-2015. Source: <http://www.mercknewsroom.com/news-release/prescription-medicine-news/vytorin-ezetimibesimvastatin-significantly-reduced-cardiovas>

FDA also conveyed at the EOP2 meeting data from trials designed to demonstrate superiority of LDL-C reduction to ezetimibe or statin up-titration would not be added to the label until the CVOT was completed and provided a very robust assessment of the long-term safety and efficacy profile. FDA did not believe a trial of LDL lowering of several weeks duration would be adequate to claim superiority when compared to an agent that has proven cardiac risk reduction. Similar reservations were communicated in an April 24, 2012 advice letter regarding data from a trial in patients with a statin intolerance. In this case FDA stated it would be a review issue whether data would be included in a label prior to results from the CVOT.

Statistical approaches for the analysis of primary and key secondary efficacy endpoints were discussed in several correspondences between 2013 and 2014. For the applicant's primary analysis model for the primary and several key secondary efficacy endpoints, FDA conveyed their concern that by ignoring treatment adherence when addressing missing data that the analysis may not provide a clinically meaningful estimate of the treatment effect. In response the applicants implemented as a sensitivity analysis a pattern mixture model to account for possible non-random missingness. This model was only fit for the primary efficacy endpoint, and is the FDA's preferred analysis.

On June 9, 2015 an advisory committee meeting is scheduled to discuss this BLA.

2.1.3 Specific Studies Reviewed

Ten phase 3 trials were reviewed for this BLA submission (Table 2). All the trials were randomized, double-blind, parallel-group, placebo- or active-controlled with treatment periods ranging from 6 to 24 months. Five trials were completed as of the August 31, 2014 database lock. In the ongoing trials all subjects have at least 12 months of follow-up; the trial duration for these trials duration ranged between 18 and 24 months. Five trials compared alicumab to placebo when added to a background dose of maximally tolerated statin. The other five trials were active-controlled, with two studying alicumab without a background statin. Ezetimibe was an active-control in all five trials; two trials also included statin up-titration as a control.

Eight trials evaluated alicumab 75 mg Q2W with up-titration to 150 mg Q2W at week 12 if the predefined LDL-C target was not achieved by week 8. Two trials investigated the 150 mg dose for the entire study duration.

The primary efficacy endpoint in all ten trials was percent change in LDL-C from baseline to week 24.

Table 2. Summary of study designs

Study	Population	Design	Primary Endpoint/ Treatment duration	Treatment arms (N randomized)
Background therapy: Maximally tolerated dose of statin ± other LMTs (alirocumab add-on)				
FH I* (EFC12492)	heFH	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 75 mg/150 mg Q2W (n=323) - Placebo Q2W (n=163)
FH II* (R727-CL-1112)	heFH	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 75 mg/150 mg Q2W (n=167) - Placebo Q2W (n=82)
HIGH FH* (EFC12732)	heFH with LDL-C ≥ 160 mg/dL	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 150 mg Q2W (n=72) - Placebo Q2W (n=35)
COMBO I (EFC11568)	High CV risk with hypercholesterolemia	R, DB, PC, PG	LDL-C at week 24/ 12 months	- 75 mg/150 mg Q2W (n=209) - Placebo Q2W (n=107)
LONG TERM* (LTS11717)	heFH or non-FH with hypercholesterolemia	R, DB, PC, PG	LDL-C at week 24/ 18 months	- 150 mg Q2W (n=1553) - Placebo Q2W (n=788)
Background therapy: Maximally tolerated dose of statin alone (alirocumab add-on)				
COMBO II* (EFC11569)	High CV risk with hypercholesterolemia	R, DB, DD, AC, PG	LDL-C at week 24/ 24 months	- 75 mg/150 mg Q2W (n=479) - Ezetimibe 10 mg (n=241)
Background therapy: Less-than-maximal dose of statin (alirocumab add-on)				
OPTIONS I (R727-CL-1110)	High CV risk with non- FH or heFH	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W + atorvastatin 20 mg (n=57) - 75 mg/150 mg Q2W + atorvastatin 40 mg (n=47) - Ezetimibe 10 mg + atorvastatin 20 mg (n=55) - Ezetimibe 10 mg + atorvastatin 40 mg (n=47) - Atorvastatin 40 mg (n=57) - Atorvastatin 80 mg (n=47) - Rosuvastatin 40 mg (n=45)
OPTIONS II (R727-CL-1118)	High CV risk with non- FH or heFH	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W + rosuvastatin 10 mg (n=49) - 75 mg/150 mg Q2W + rosuvastatin 20 mg (n=54) - Ezetimibe 10 mg + rosuvastatin 10 mg (n=48) - Ezetimibe 10 mg + rosuvastatin 20 mg (n=53) - Rosuvastatin 20 mg (n=48) - Rosuvastatin 40 mg (n=53)
Background therapy: None or LMT other than statin or ezetimibe (alirocumab monotherapy or add-on)				
ALTERNATIVE (R727-CL-1119)	Hypercholesterolemia (heFH and non-FH) at moderate or high CV risk and intolerant to statins	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W (n=126) - Ezetimibe 10 mg (n=125) - Atorvastatin 20 mg (n=63)
MONO (EFC11716)	Moderate CV risk with LDL-C ≥ 100 mg/dL and ≤ 190 mg/dL	R, DB, DD, AC, PG	LDL-C at week 24/ 6 months	- 75 mg/150 mg Q2W (n=52) - Ezetimibe 10 mg (n=51)

LMTs – Lipid-modifying therapy; FH –familial hypercholesterolemia; heFH – heterozygous familial hypercholesterolemia; CV – cardiovascular; R – randomized; DB – double-blind; PC – placebo-controlled; AC – active-controlled; PG – parallel-group; DD – double-dummy;

* Ongoing as of the August 31, 2014 data cutoff.

2.2 Data Sources

The data and final study report were submitted electronically as an eCTD submission. The submission, organized as an .enx file, is archived at the following link:

<\\CDSESUB1\evsprod\BLA125559\125559.enx>

The following documents were used to support this review.

Document	Source
EOP 2 meeting minutes	eCTD: Section 1.6.3
April 24, 2012 advice letter	eCTD: Section 1.6.3
Clinical summary of efficacy	eCTD: Section 2.7.3
Introduction to summary	eCTD: Section 2.2
May 19, 2014 Advice letter on statistical methods	eCTD: Section 1.6.3
Individual trial protocols	eCTD: Section 5.3.5.1
November 17, 2011 advice letter	eCTD: Section 1.6.3
Supporting statistical documentation	eCTD: Section 5.3.5.1

All results presented in this review were derived from the submitted datasets by this reviewer except for the applicant's prespecified analysis of TG and Lp(a), and the analysis of LDL-C using a pattern-mixture model. All tables and figures in this review were created by this reviewer unless noted otherwise.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

I found the submission to be of high quality. There was extensive study documentation, which included documentation for the analysis programs. I was able to reproduce the applicant's primary efficacy results presented in the individual study reports.

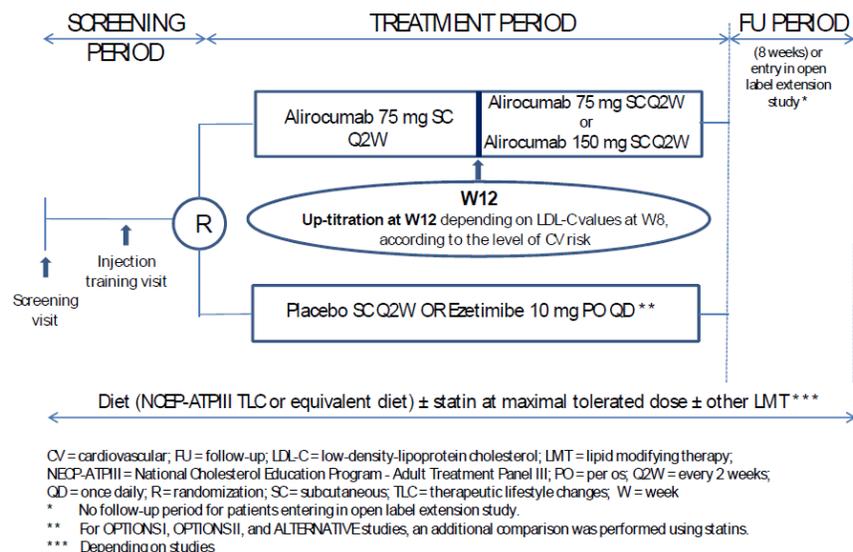
3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study Design

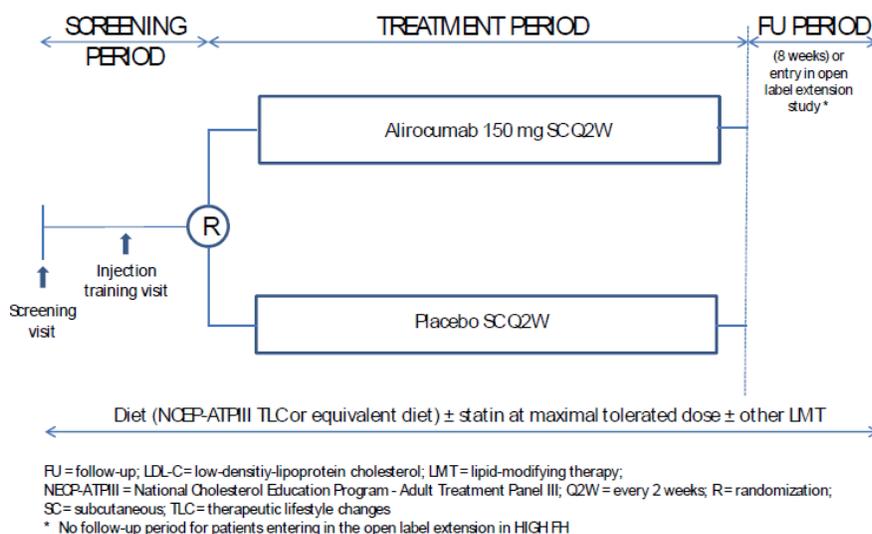
Design features of the 10 trials reviewed in this submission are displayed above in Table 2 above. All the trials were randomized, double-blind, parallel-group, placebo- or active-controlled with treatment periods ranging from 6 to 24 months. Five of the 10 trials are completed; the ongoing trials (FH I, FH II, HIGH FH, LONG TERM, COMBO II) all had at least 12 months of follow-up data for subjects. Two different dosing regimens were investigated. Separate study design schematics for the different dosing regimens are shown below.

Figure 1. General study design for trials with 75 mg/150 mg Q2W dosing



Source: Clinical summary of efficacy (eCTD, Section 2.7.3)

Figure 2. General study design for trials with 150 mg Q2W dosing



Source: Clinical summary of efficacy (eCTD, Section 2.7.3)

The screening period ranged from 2 to 6 weeks, where patients were trained to self-inject study drug. There was an additional run-in period for OPTIONS I, OPTIONS II and ALTERNATIVE prior to randomization. In ALTERNATIVE patients entered a 2 week washout period to eliminate ezetimibe, statins, and red yeast rice. Patients then entered a 4 week, single-blind placebo run-in period. Patients that did not experience skeletal muscle-related AEs were eligible to be randomized. In OPTIONS I, at the discretion of the investigator, patients underwent an open-label 4 week atorvastatin (20 mg or 40 mg) run-in period if they had 1) not been on a stable dose of atorvastatin (20 mg or 40 mg) for 4 weeks, 2) were being switched from another statin to

atorvastatin, or 3) were not receiving a statin, but should have according to local guidance. The run-in period for OPTIONS II was similar to OPTIONS I.

Scheduled follow-up visits during the double-blind treatment period are listed below for the individual trials. Subjects that prematurely discontinued study drug (and did not withdraw consent) were to remain in the study and undergo all study visits and procedures with the exception of dosing with study drug.

Table 3. Scheduled follow-up visits during double-blind treatment period

Trial	Scheduled follow-up visit (week)
FH I, FH II, HIGH FH, LONG TERM	0, 4, 8,12, 16, 24, 36, 52, 64, 78
COMBO I	0, 4, 8,12, 16, 24, 36, 52
COMBO II	0, 4, 8,12, 16, 24, 36, 52, 64, 78, 88, 104
OPTIONS I, OPTIONS II, ALTERNATIVE, MONO	0, 4, 8,12, 16, 24

In trials FH I, FH II, HIGH FH, COMBO I and LONG TERM patients that satisfied the trial's respective inclusion/exclusion criteria were randomized within stratum (Table 4) 2:1 to alicumab or placebo on top of their background maximally tolerated dose of statin with or without other lipid modifying therapies (LMT). Maximally-tolerated dose was defined as the following: rosuvastatin 20 mg or 40 mg daily; atorvastatin 40 mg or 80 mg daily; or simvastatin 80 mg daily. Patients not able to be on any of these doses, were to be treated with the dose of statin considered appropriate for the patients as per the investigator's judgment and concern. The treatment duration was either 12 months (COMBO I) or 18 months (FH I, FH II, HIGH FH, and LONG TERM).

Five trials were active-controlled (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE and MONO). Ezetimibe 10 mg was an active control in all five trials; two trials additionally included statin up-titration as a control (OPTIONS I and OPTIONS II). The active-controlled trials differed in important ways, including background therapy, patient populations, allocation ratios to study treatment, and number of treatment arms. In COMBO II patients were randomized 2:1 within stratum (Table 4) to alicumab or ezetimibe for 24 months on top of a background statin at the maximally tolerated level without any other LMT. Patients in ALTERNATIVE and MONO were not on a statin background, with those in ALTERNATIVE being statin intolerant.

In ALTERNATIVE, eligible statin intolerant patients were randomized 2:2:1 within stratum (Table 4) to alicumab, ezetimibe or atorvastatin 20 mg for 6 months; the atorvastatin arm was not included for efficacy evaluation but for assessing that the study population is truly statin intolerant. Statin intolerance was defined as the inability to tolerate at least 2 statins: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg or pitavastatin 2 mg), and another statin at any dose, due to skeletal muscle-related symptoms that began or increased during statin therapy and stopped when statin therapy was discontinued. Patients not receiving a daily regimen of a statin were eligible for study inclusion if they could not tolerate a cumulative weekly statin dose of 7 times the lowest approved tablet size and the criteria outlined above are also met.

In MONO patients were randomized 1:1 to alicocumab or ezetimibe for 6 months, administered as a monotherapy.

OPTIONS I and OPTIONS II both had 6 month treatment durations. Randomization was done within study stratum (Table 4) and background statin dose. OPTIONS I was conducted in patients not adequately controlled with atorvastatin 20 or 40 mg with or without other LMT (excluding ezetimibe). Patients on atorvastatin 20 mg regimen were randomized 1:1:1 to alicocumab plus atorvastatin 20 mg, atorvastatin 40 mg, or atorvastatin 20 mg plus ezetimibe. Patients on atorvastatin 40 mg regimen were randomized 1:1:1:1 to alicocumab plus atorvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 40 mg, or atorvastatin 40 mg plus ezetimibe. OPTIONS II was conducted in patients not adequately controlled with rosuvastatin 10 or 20 mg with or without other LMT (excluding ezetimibe). Patients on rosuvastatin 10 mg regimen were randomized 1:1:1 to alicocumab plus rosuvastatin 10 mg, rosuvastatin 20 mg, or rosuvastatin 10 mg plus ezetimibe. Patients on rosuvastatin 20 mg regimen were randomized 1:1:1 to alicocumab plus rosuvastatin 20 mg, rosuvastatin 40 mg, or rosuvastatin 20 mg plus ezetimibe.

Table 4. Randomization strata

Trial	Randomization strata
FH I, FH II, COMBO II	- Prior history of MI or ischemic stroke: yes; no - Statin treatment [†] : high dose; low/moderate dose - Geographic region: N. America; W. Europe; E. Europe; rest of world
HIGH FH, COMBO I	- Prior history of MI or ischemic stroke: yes; no - Statin treatment [†] : high dose; low/moderate dose
LONG TERM	- heFH: yes; no - Prior history of MI or ischemic stroke: yes; no - Statin treatment [†] : high dose; low/moderate dose - Geographic region: N. America; W. Europe; E. Europe; rest of world
OPTIONS I*, OPTIONS II*, ALTERNATIVE	- Prior history of MI or ischemic stroke: yes; no
MONO	- None

[†]High dose: Atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily; Low/moderate dose: Simvastatin (any dose), atorvastatin < 40 mg daily or rosuvastatin < 20 mg daily

* Randomization done within background dose of atorvastatin (OPTIONS I) or rosuvastatin (OPTIONS II).

The phase 3 trials were conducted in several patient populations that were either treated with or not treated with a statin. The population on statins included patients with heterozygous familial hypercholesterolemia (heFH) or non-familial hypercholesterolemia (non-FH), including patients with mixed dyslipidemia. Mixed dyslipidemia was defined as patients meeting the LDL-C entry criteria (Table 5) and having a baseline TG \geq 150 mg/dL. The population not on statins included patients that are considered statin intolerant (ALTERNATIVE) or have moderate CV risk (MONO). FH I, FH II and HIGH FH were done only in patients with heFH and trials LONG TERM, OPTIONS I, OPTIONS II and ALTERNATIVE were done in both FH and non-FH patients. All patients had elevated CV risk (very high, high, or moderate). All patients in MONO and a subset in ALTERNATIVE had moderate CV risk, defined as a 10-year risk of fatal CVD of \geq 1% and < 5% using Systematic Coronary Risk Estimation.

Except for HIGH FH and LONG TERM, the alicumab dosing regimen started at 75 mg Q2W with up-titration to 150 mg Q2W at week 12 if the predefined LDL-C target was not achieved by week 8 (Table 5). To preserve the blinding, lipid values were not communicated to study sites. In MONO the up-titration occurred at LDL-C \geq 70 mg/dL instead of the planned threshold of 100 mg/dL due to a reported error in specification form. In HIGH FH and LONG TERM alicumab was not up-titrated and the 150 mg dose was administered for the entire study duration.

An important limitation of the development program is that each trial investigated only one alicumab dosing regimen. The trials therefore do not support unconfounded inferences of the additional LDL lowering (if any) of either up-titrating or initiating treatment at 150 mg instead of 75 mg. Any comparisons of LDL reduction at different doses or follow-up visits within or across trials have to be interpreted cautiously as they are based on post-randomization factors or cross-study comparisons. This is particularly problematic since the titration algorithm is based on raw LDL-C values, which induces a systematic relationship with those with a larger baseline LDL-C being more likely to up-titrate. In my opinion, I do not consider this inherently bad as those with high LDL-C levels may require an increased dose to control LDL-C, it just makes the exploratory investigation more difficult to interpret.

Table 5. LDL-C threshold for alicumab up-titration

Trial	Baseline CV risk	LDL-C threshold in inclusion criteria	LDL-C threshold for uptitration
FH I, FH II, COMBO I, COMBO II	Prior CVD	\geq 70 mg/dL	\geq 70 mg/dL
	No prior CVD	\geq 100 mg/dL	\geq 70 mg/dL
OPTIONS I, OPTIONS II	VH	\geq 70 mg/dL	\geq 70 mg/dL
	H	\geq 100 mg/dL	\geq 100 mg/dL
ALTERNATIVE	VH	\geq 70 mg/dL	\geq 70 mg/dL
	H and M	\geq 100 mg/dL	\geq 100 mg/dL
MONO	M	\geq 100 mg/dL	\geq 70 mg/dL (actual)
			\geq 100 mg/dL (planned)

CVD-cardiovascular disease; VH-very high CV risk patient; H-high risk CV patient; M-moderate CV risk patient

Endpoints

The phase 3 trials all shared the same primary efficacy endpoint and investigated the same lipid parameters for key secondary endpoints. The primary efficacy endpoint is percent change in calculated LDL-C from baseline to week 24. Lipid parameters included as key secondary efficacy endpoints (evaluated at weeks 12, 24, and/or 52) are LDL-C, total-C, non-HDL-C, ApoB, TG, Lp(a), HDL-C and ApoA1.

Calculated LDL-C values were derived using Friedewald equation. However, due to accuracy concerns with the equation in patients with high fasting TG levels and at the low end of the LDL-C spectrum, LDL-C values were also measured directly using beta quantification at select visits in select trials. Measured LDL-C using beta-quantification was done at baseline, at weeks 12, 24, 52 and 78 in LONG TERM and at baseline and week 24 in seven other trials (FH I, FH II, COMBO I, COMBO II, OPTIONS I, OPTIONS II, and ALTERNATIVE). In addition, when TG values exceeded 400 mg/dL the central lab measured LDL-C using beta-quantification rather than calculating it. FDA also recommended (advice letter: November 17, 2011) for LONG

TERM only LDL-C values be directly measured when value LDL-C < 50 mg/dL. The applicants did not follow this advice.

All suspected CV events and deaths that occurred from randomization to the follow-up visit were adjudicated by a Clinical Events Committee (CEC). The events were adjudicated to the following categories as defined in the CEC charter: CHD death; non-fatal MI; fatal and non-fatal ischemic stroke; unstable angina requiring hospitalization; congestive heart failure requiring hospitalization; ischemia-driven coronary revascularization procedure.

3.2.2 Statistical Methodologies

Analysis populations

The two analysis populations used by the applicants were the intention-to treatment (ITT) population and the modified ITT (mITT) population. Population definitions were the same across the trials.

The ITT population was defined as all randomized patients that had 1) a baseline calculated LDL-C value, and 2) one post-baseline calculated LDL-C value up to week 24 that falls within one of the analysis windows. A limitation of this analysis population and the mITT are they depend on post-randomization events, resulting in statistical inferences possibly failing to preserve the integrity of randomization. I consider this to be an important issue. However, for this application, its impact is likely negligible given the size of the treatment effect and the small percentage of randomized subjects excluded from the analysis population (ITT: 98.5%; mITT: 97.7%). In our preferred analysis, described below, the analysis population preserves the integrity of randomization as it is applied to all randomized subjects with a baseline measurement.

The mITT population was defined as randomized patients that 1) took at least one dose or part of a dose of the study drug, 2) had a baseline calculated LDL-C value, and 3) one post-baseline calculated LDL-C value up to week 24 that falls within one of the analysis windows during the efficacy treatment period. The efficacy treatment period was the period from the first double-blind study drug injection up to the last day of injection + 21 days or the day of last capsule intake + 3 days, whichever came first; the capsule condition applied only to active control trials.

Estimands

The statistical parameters used to summarize the study intervention effects were prespecified by the applicant. These parameters are referred to as estimands. The specification of estimands follows recommendations from the 2010 National Academy of Science report entitled *The Prevention and Treatment of Missing Data in Clinical Trials*. In my opinion, specifying which estimands are of a priori interest is useful for several reasons. One reason is that when not all subjects adhere to study treatment, it clarifies which parameter the analysis is intending to estimate (e.g., the ITT effect or the effect during adherence). In turn, it will inform whether follow-up data after premature treatment discontinuation is or is not needed to support statistical inferences. For example, the ITT estimand requires knowing what happens at the endpoint for all

subjects, regardless of treatment adherence. Another reason is that, for a given estimand, it guides how missing data should be approached in the analysis. For example, for an ITT estimand, some subjects with missing data at week 24 will still be receiving study drug, while others will not. If treatment response is not sustained for those that stopped treatment early, it would be inappropriate to describe what happened to those that did not adhere to treatment using information from those that did adhere to treatment.

The applicant specified the ITT estimand and the on-treatment estimand as estimands of interest. The ITT estimand uses all data, regardless of treatment adherence. The on-treatment estimand uses only data from the efficacy treatment period (see definition above).

As discussed in detail below, I question whether 1) the primary statistical model provides a reliable estimate of the ITT effect, and 2) the on-treatment estimand is clinically relevant.

Statistical hypotheses

For each trial, the primary hypothesis that alirocumab has a greater average percent LDL-C reduction than control at week 24 is tested against the null of no difference, based on the ITT estimand.

In ALTERNATIVE the hypothesis was only evaluated for ezetimibe; atorvastatin served to evaluate whether the study truly included a statin intolerant population. For OPTIONS I and OPTIONS II the prespecified comparisons are as follows.

In OPTIONS I the five prespecified pairwise comparisons are:

- alirocumab + atorvastatin 20 mg vs. atorvastatin 40 mg
- alirocumab + atorvastatin 20 mg vs. ezetimibe + atorvastatin 20 mg
- alirocumab + atorvastatin 40 mg vs. atorvastatin 80 mg
- alirocumab + atorvastatin 40 mg vs. rosuvastatin 40 mg, and
- alirocumab + atorvastatin 40 mg vs. ezetimibe + atorvastatin 40 mg.

In OPTIONS II the four prespecified pairwise comparisons are:

- alirocumab + rosuvastatin 10 mg vs. rosuvastatin 20 mg
- alirocumab + rosuvastatin 10 mg vs. ezetimibe + rosuvastatin 10 mg
- alirocumab + rosuvastatin 20 mg vs. rosuvastatin 40 mg
- alirocumab + rosuvastatin 20 mg vs. ezetimibe + rosuvastatin 20 mg

Controlling study-wise type-I error

Study-wise type-I error rate was maintained at the two-sided 5% level by testing the primary and key secondary endpoints hierarchically according to the order in Table 6. Each hypothesis is defined by four quantities: the endpoint, weeks from randomization, analysis population (ITT or mITT) and statistical estimand (on-treatment or ITT). For OPTIONS I and OPTIONS II testing was done hierarchically within each pairwise comparison; in OPTIONS I each pairwise comparison was performed at the two-sided 1% alpha level and 1.25% level for OPTIONS II.

Table 6. Testing sequence for primary and key secondary endpoints

Endpoint (week, analysis population, estimand)	FH I, FH II	HIGH FH	COMBO I, COMBO II, LONG TERM	OPTIONS I, OPTIONS II, ALTERNATIVE	MONO
% Δ LDL-C (24, ITT, ITT)	1	1	1	1	1
% Δ LDL-C (24, mITT, OT)	2	2	2	2	-
% Δ LDL-C (12, ITT, ITT)	3	3	3	3	2
% Δ LDL-C (12, ITT, OT)	4	4	4	4	-
% Δ Apo B (24, ITT, ITT)	5	5	5	5	3
% Δ Apo B (24, ITT, OT)	6	6	6	6	-
% Δ non HDL-C (24, ITT, ITT)	7	7	7	7	4
% Δ non HDL-C (24, ITT, OT)	8	8	8	8	-
% Δ total-C (24, ITT, ITT)	9	9	9	9	5
% Δ Apo B (12, ITT, ITT)	10	10	10	10	6
% Δ non HDL-C (12, ITT, ITT)	11	11	11	11	7
% Δ total-C (12, ITT, ITT)	12	12	12	12	8
% Δ LDL-C (52, ITT, ITT)	13	13	13	-	-
LDL-C response* (24, ITT, ITT)	14	14	-	13	-
LDL-C response* (24, ITT, OT)	15	15	-	14	-
LDL-C < 100 mg/dL (24, ITT, ITT)	-	-	-	-	9
LDL-C < 70 mg/dL (24, ITT, ITT)	16	24	14	15	10
LDL-C < 70 mg/dL (24, ITT, OT)	17	25	15	16	-
% Δ Lp(a) (24, ITT, ITT)	18	16	16	17	11
% Δ HDL-C (24, ITT, ITT)	19	17	17	18	12
% Δ TG (24, ITT, ITT)	20	18	18	19	15
% Δ Apo A-1 (24, ITT, ITT)	21	19	19	20	17
% Δ Lp(a) (12, ITT, ITT)	22	20	20	21	14
% Δ HDL-C (12, ITT, ITT)	23	21	21	22	13
% Δ TG (12, ITT, ITT)	24	22	22	23	16
% Δ Apo A-1 (12, ITT, ITT)	25	23	23	24	18

Sample size

All trials had sample sizes large enough to ensure sufficient statistical power (90% or 95%) to demonstrate either a 20% or 30% decrease in the primary study endpoint (Table 7). Except for OPTIONS I, OPTIONS II, and MONO, the sample size was increased beyond the number needed to demonstrate efficacy for safety considerations. For example, in FH I the sample size was increased from 45 subjects needed to show a 30% excess reduction in LDL-C to 471 subjects for safety purposes. The sizing of LONG TERM was done for safety considerations and has very high statistical power to evaluate efficacy.

Table 7. Sample size and power considerations

Trial	Expected Difference	Standard deviation	Power	Estimated sample size to demonstrate efficacy	Sample inflated*	Planned sample size
FH I	30%	25%	95%	45 (30 ALIRO;15 PLA)	Yes	471
FH II	30%	25%	95%	45 (30 ALIRO;15 PLA)	Yes	250
HIGH FH	30%	25%	95%	45 (30 ALIRO;15 PLA)	Yes	105
COMBO I	30%	25%	95%	45 (30 ALIRO;15 PLA)	Yes	306
COMBO II	20%	25%	95%	96 (64 ALIRO;32 PLA)	Yes	660
LONG TERM	NA	NA	NA	NA	NA	2100
OPTIONS I	20%	25%	95%	350 (50 per group)	No	350
OPTIONS II	20%	25%	90%	300 (50 per group)	No	300
ALTERNATIVE	20%	25%	95%	84 (42 ALIRO;42 EZE)	Yes	250
MONO	20%	25%	95%	100 (50 ALIRO;50 EZE)	No	100

ALIRO-alirocumab; PLA-placebo; EZE-ezetimibe

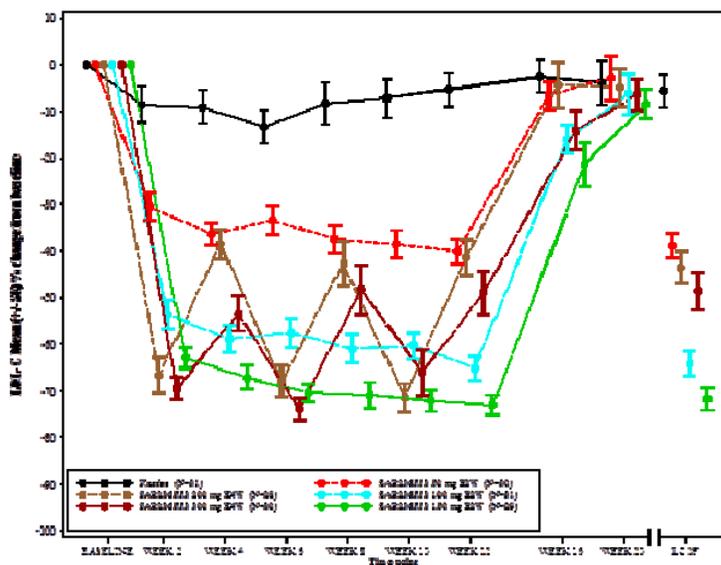
* Sample size inflated beyond number needed to demonstrate efficacy

Statistical analysis

Analysis of the primary efficacy endpoint: Percent change in LDL-C from baseline to week 24 was analyzed using a mixed model for repeated measures (MMRM). The model included the following variables as covariates: treatment, randomization strata, time point (up to week 52; see Table 3), treatment-by-time interaction, strata-by-time interaction, baseline LDL-C, and baseline LDL-C by time interaction. Parameters were estimated using restricted maximum likelihood; denominator degrees of freedom were estimated using Satterthwaite’s approximation. Missing LDL-C values were assumed to be missing at random (MAR) and were not imputed.

In my opinion, given that treatment adherence is not accounted for in the MMRM, the MAR assumption is questionable and likely leads to an over-estimate of the ITT effect. The problem with assuming that the statistical behavior of the missing data is the same as the statistical behavior of the observed data (conditional on covariates and observed responses) is that those with data are systematically different than those without data. In particular, those with data were primarily on study drug, whereas those without data were primarily no longer receiving study drug. The distinction is important as the LDL-C reduction achieved while on study drug was not sustained after stopping treatment, suggesting an attenuation of the treatment effect. This trend was observed in two phase 2 studies (Figure 3 and Figure 4) that followed patients after a 12 week treatment period and in LONG TERM, COMBO I and COMBO II, which had a sizable number of patients followed after stopping drug early. Mean profile plots for these phase 3 trials are displayed in Figure 13 to Figure 15 in the Appendix.

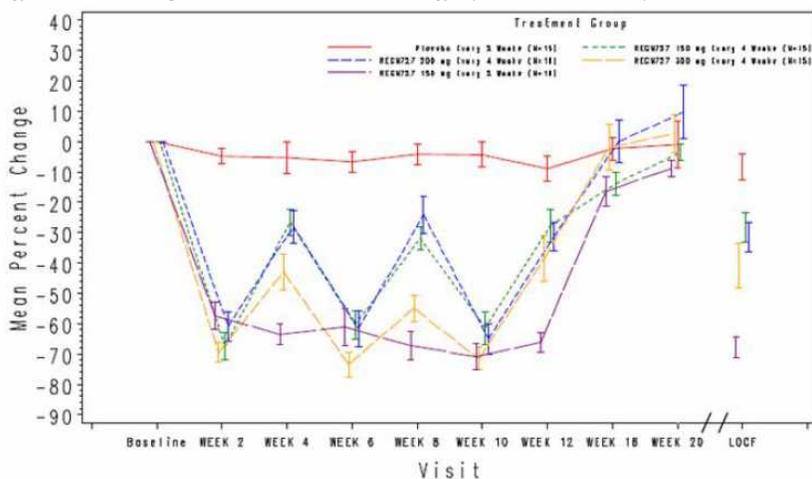
Figure 3. Mean profile: % LDL-C change (DFH11565)



Source: Supporting statistical documentation (eCTD: Section 5.3.5.1)

Note: The top (black) line corresponds to placebo. The other lines correspond to different alicumab doses

Figure 4. Mean profile: % LDL-C change (R727-CL-1003)



Source: Supporting statistical documentation (eCTD: Section 5.3.5.1)

Note: The top (red) line corresponds to placebo. The other lines correspond to different alicumab doses

Preferred analysis of the primary efficacy endpoint: In response to the concerns shared with the applicant regarding the handling of missing data in the primary efficacy analysis, they proposed an alternative approach that likely gives a more accurate estimate of the ITT effect. The approach used a Pattern-Mixture Model (PMM) with mixed imputation in the randomized population. To account for the uncertainty in the missing data, missing values imputed using multiple imputation. A total of 100 imputed datasets were created. Results from the imputed datasets were combined using Rubin’s method.

In the PMM different imputation strategies were applied to missing LDL-C values during the on-treatment period and after treatment discontinuation, defined as after the day of last injection + 21 days. For missing values occurring during the on-treatment period it was assumed that patients would continue to show benefit. Missing LDL-C values during this period were considered MAR and imputed based on other on-treatment measurements. For patients that stopped their study treatment it was assumed they would no longer benefit from study drug, and their LDL-C values would return to baseline. For these patients the imputed LDL-C values were centered on the patient's baseline value. Patients not treated or with missing data before taking study medication also had their LDL-C values imputed based on their baseline value.

Analysis of key secondary efficacy endpoints: Different statistical models were used for continuous secondary endpoints anticipated to have a normal and non-normal distribution. The two endpoints anticipated to have a non-normal distribution were TG and Lp(a).

Continuous endpoints assumed to be normally distributed were analyzed using the same MMRM that was used for the primary efficacy endpoint. Continuous endpoints assumed to have a non-normal distribution was analyzed using robust regression (M-estimation). The model included treatment, randomization strata and baseline value as predictor variables. Subjects missing the endpoint had a response imputed. The imputation model included treatment, baseline value, randomization strata, baseline characteristics and post-baseline values. The imputation did not follow the PMM approach. A total of 100 imputed datasets were created. Results from the 100 complete datasets were combined using Rubin's method. Binary endpoints were analyzed using logistic regression. The model included treatment and baseline value as covariates and randomization strata as a stratification factor. Missing responses were imputed using the approach described above for non-normally distributed continuous endpoints.

Comments on the applicants' use of robust regression: Different statistics can be used to summarize the difference in responses between treatment groups. In general, the chosen statistic should provide a meaningful summary of the difference between groups. The choice of a statistic can sometimes be influenced by attributes of the data. For example, the difference in means may or may not be preferred depending on the relevance of "extreme values." Medians are a popular alternative for describing central tendency.

Both TG and Lp(a) were analyzed using robust regression. Estimates of the mean treatment differences from robust regression are derived by down-weighting extreme values according to a weight function defined by some parameters. Each subject has an estimated weight, between 0 and 1, with those with weight 0 not contributing to the estimation. This is very different from an ANCOVA model, where each subject has weight 1. My issues with the robust regression approach are twofold. First, if you believe the mean difference is the appropriate statistic for characterizing the treatment difference (i.e., you believe extreme values are relevant), it is unclear to me why you would then reweight the data to minimize the impact of extreme values. Second, if you were to choose an alternative weight function or modify the weight function parameters, the results would change. The applicant did not justify their weight function including its parameters. Because of these points, I do not consider the results from the analysis readily interpretable. While I will include the applicants' results for completeness, I also include

median changes and the Hodges-Lehmann (HL) estimate of location shift. The HL estimate is the median of all paired differences between two treatment groups. Labels for other approved products have summarized treatment differences in TG using a HL estimate.

Comments on estimating the on-treatment estimand: The on-treatment estimand used data only during the on-treatment period. Thus, if a subject had a measurement after stopping study drug early, that value was not used in the analysis. In such a case the LDL-C value is not missing, although the MMRM assumes it is. Due to the MAR assumption made by the MMRM, statistical behavior of the missing data in the analysis is the same as the observed data. Because the model uses only on-treatment observations, the model is estimating the treatment effect assuming all subjects included in the mITT population adhered to randomized therapy, contrary to the fact some could not. The analysis therefore attempts to estimate a treatment effect under conditions that were not observed in the clinical trial. It is my opinion the on-treatment estimand lacks clinical relevance due to the underlying implausibility of achieving perfect treatment adherence.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

In this section data on patient disposition, alicumab up-titration, missing data, and demographic and baseline characteristics are summarized.

Patient disposition

In total, there were 5296 subjects randomized in the 10 phase 3 trials, with 3188 assigned to receive alicumab, 620 assigned to ezetimibe, and 1175 placebo. The other 313 subjects were randomized to statin up-titration (205) or another statin (108). Almost half (44%) of the randomized subjects were enrolled in one study, LONG TERM. LONG TERM and HIGH FH were the only two trials that studied the 150 mg dose throughout the treatment period. Of the 3188 subjects assigned to alicumab, 1563 (49%) were enrolled in trials that up-titrated alicumab from 75 mg to 150 mg.

Patient disposition is summarized below separately for the ongoing trials (FH I, FH II, HIGH FH, LONG TERM and COMBO II; Table 8) and the completed trials (COMBO I, OPTIONS I, OPTIONS II, ALTERNATIVE and MONO; Table 9). For ongoing trials the table summarizes the disposition at the time of the August 31, 2014 database lock. For the completed trials the proportion of completers varied across trials, ranging from 70% (ALTERNATIVE) to 85% (MONO); the percentage of completers was fairly similar across treatment arms in a given trial. The reasons for not completing the treatment period were fairly comparable across treatment arms.

In the ongoing trials there were similar percentages between treatment arms in a trial that have discontinued, along with the reasons for discontinuation.

Table 8. Patient disposition for ongoing trials (FH I, FH II, HIGH FH, LONG TERM and COMBO II)

	FH I*		FH II*		HIGH FH*		LONG TERM*		COMBO II	
	Aliro	Placebo	Aliro	Placebo	Aliro	Placebo	Aliro	Placebo	Aliro	EZE
Randomized	323	163	167	82	72	35	1553	788	479	241
Randomized and treated	322 (100%)	163 (100%)	167 (100%)	81 (99%)	72 (100%)	35 (100%)	1550 (100%)	788 (100%)	479 (100%)	241 (100%)
Completed trt period*	6 (2%)	1 (1%)	0 (0%)	0 (0%)	6 (8%)	4 (11%)	349 (22%)	176 (22%)	0	0
Treatment ongoing*	281 (87%)	144 (88%)	156 (93%)	78 (95%)	51 (71%)	25 (71%)	890 (57%)	466 (59%)	406 (85%)	206 (85%)
Died	4 (1%)	0	0	0	0	0	11 (1%)	8 (1%)	2 (0%)	4 (2%)
Did not complete trt period	36 (11%)	18 (11%)	11 (7%)	4 (5%)	15 (21%)	6 (17%)	314 (20%)	146 (19%)	73 (15%)	35 (15%)
Adverse event	12	8	5	1	3	1	98	44	36	13
Poor compliance with protocol	8	4	2	1	4	1	54	34	13	7
Physician decision	0	1	0	0	0	0	3	0	1	2
Moved	3	0	0	0	2	0	16	4	6	2
Withdrew consent	1	0	0	1	0	0	0	1	0	1
Related to IMP autoinjector	2	0	1	0	0	0	13	4	2	2
Other	11	5	3	1	6	4	130	58	15	8
Analysis Populations										
ITT	322 (100%)	163 (100%)	166 (99%)	81 (99%)	71 (99%)	35 (100%)	1530 (99%)	780 (99%)	467 (97%)	240 (100%)
mITT	321 (99%)	163 (100%)	166 (99%)	81 (99%)	71 (99%)	35 (100%)	1523 (98%)	777 (99%)	464 (97%)	235 (98%)

* As of the August 31, 2014 database cutoff.

Table 9. Patient disposition for the completed trials (COMBO I, ALTERNATIVE, MONO, OPTIONS I and OPTIONS II)

	COMBO I		ALTERNATIVE			MONO	
	Aliro	Placebo	Aliro	EZE	ATOR	Aliro	EZE
Randomized	209	107	126	125	63	52	51
Randomized and treated	207 (99%)	107 (100%)	126 (100%)	124 (99%)	63 (100%)	52 (100%)	51 (100%)
Completed trt period	156 (75%)	75 (70%)	96 (76%)	82 (66%)	42 (67%)	44 (85%)	44 (86%)
Died	3 (1%)	3 (3%)	0	0	0	0	0
Did not complete trt period	51 (24%)	32 (30%)	30 (24%)	43 (34%)	21 (33%)	8 (15%)	7 (14%)
Adverse event	13	8	23	31	16	5	4
Poor compliance with protocol	11	9	0	0	2	0	1
Physician decision	2	1	0	0	0	0	0
Moved	2	1	0	0	0	1	0
Withdrew consent	0	0	0	0	0	1	0
Related to IMP autoinjector	1	2	0	0	0	0	0
Other	24	11	7	12	3	1	2
Analysis Populations							
ITT	205 (98%)	106 (99%)	126 (100%)	122 (98%)	62 (98%)	52 (100%)	51 (100%)
mITT	204 (98%)	105 (98%)	123 (98%)	118 (94%)	60 (95%)	51 (98%)	50 (98%)
	OPTIONS I						
	Aliro + ATOR 20 mg	Aliro + ATOR 40 mg	EZE + ATOR 20 mg	EZE + ATOR 40 mg	ATOR 40 mg	ATOR 80 mg	ROSU 40 mg
Randomized	57	47	55	47	57	47	45 (100%)
Randomized and treated	57 (100%)	47 (100%)	55 (100%)	46 (98%)	57 (100%)	47 (100%)	45 (100%)
Completed trt period	46 (81%)	38 (81%)	40 (73%)	40 (85%)	44 (77%)	39 (83%)	39 (87%)
Died	0	0	2 (4%)	0	0	0	0
Did not complete trt period	11 (19%)	9 (19%)	15 (27%)	7 (15%)	13 (23%)	8 (17%)	6 (13%)
Adverse event	5	2	3	1	4	3	1
Poor compliance with protocol	0	1	4	0	2	0	0
Physician decision	0	1	0	1	0	0	0
Moved	1	1	0	0	0	0	0
Withdrew consent	0	0	0	0	0	0	0
Related to IMP autoinjector	0	0	0	1	0	0	0
Other	5	4	8	4	7	5	5
Analysis Populations							
ITT	55 (96%)	46 (98%)	53 (96%)	46 (98%)	53 (93%)	47 (100%)	45 (100%)
mITT	52 (91%)	46 (98%)	52 (95%)	46 (98%)	52 (91%)	47 (100%)	45 (100%)

	OPTIONS II					
	Aliro + ROSU 10 mg	Aliro + ROSU 20 mg	EZE + ROSU 10 mg	EZE + ROSU 20 mg	ROSU 20 mg	ROSU 40 mg
Randomized	49	54	48	53	48	53
Randomized and treated	49 (100%)	54 (100%)	48 (100%)	53 (100%)	48 (100%)	53 (100%)
Completed trt period	38 (78%)	41 (76%)	34 (71%)	44 (83%)	43 (90%)	45 (85%)
Died	0	0	0	1 (2%)	0	0
Did not complete trt period	11 (22%)	13 (24%)	14 (29%)	9 (17%)	5 (10%)	8 (15%)
Adverse event	3	2	6	2	2	3
Poor compliance with protocol	2	2	2	0	1	0
Physician decision	0	0	0	0	0	1
Moved	1	0	0	0	0	0
Other	5	9	6	7	2	4
Analysis Populations						
ITT	48 (98%)	53 (98%)	47 (98%)	50 (94%)	48 (100%)	52 (98%)
mITT	48 (98%)	51 (94%)	46 (96%)	50 (94%)	48 (100%)	50 (94%)

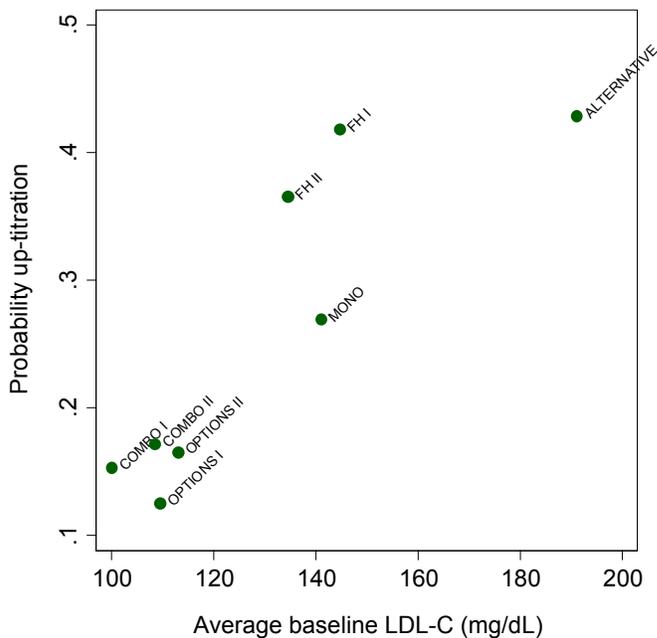
Up-titration

The proportion of subjects randomized to alirocumab that were titrated to 150 mg from 75 mg varied considerably across trials, from 7% to 43% (Table 10). As expected, there was a positive relationship between up-titrating and baseline LDL-C. In particular, trials with larger average baseline LDL-C were more likely to have a subject up-titrate (Figure 5), and within a trial, subjects with larger LDL-C values at baseline were more likely to be the ones that up-titrated (Figure 16 in Appendix).

Table 10. Summary of alirocumab up-titration

Trial	Randomized to Alirocumab N=	Up-titrated alirocumab dose		
		Yes n (%)	No n (%)	Status Missing n (%)
FH I	323	135 (42%)	176 (54%)	12 (4%)
FH II	167	61 (37%)	97 (58%)	9 (5%)
COMBO I	209	32 (15%)	159 (76%)	18 (9%)
COMBO II	479	82 (17%)	364 (76%)	33 (7%)
OPTIONS I: Aliro + Ator 20mg	57	4 (7%)	46 (81%)	7 (12%)
Aliro + Ator 40mg	47	9 (19%)	34 (72%)	4 (9%)
OPTIONS II: Aliro + Rosu 10 mg	49	7 (14%)	37 (76%)	5 (10%)
Aliro + Rosu 20 mg	54	10 (19%)	38 (70%)	6 (11%)
ALTERNATIVE	126	54 (43%)	55 (44%)	17 (13%)
MONO	52	14 (27%)	32 (62%)	6 (12%)

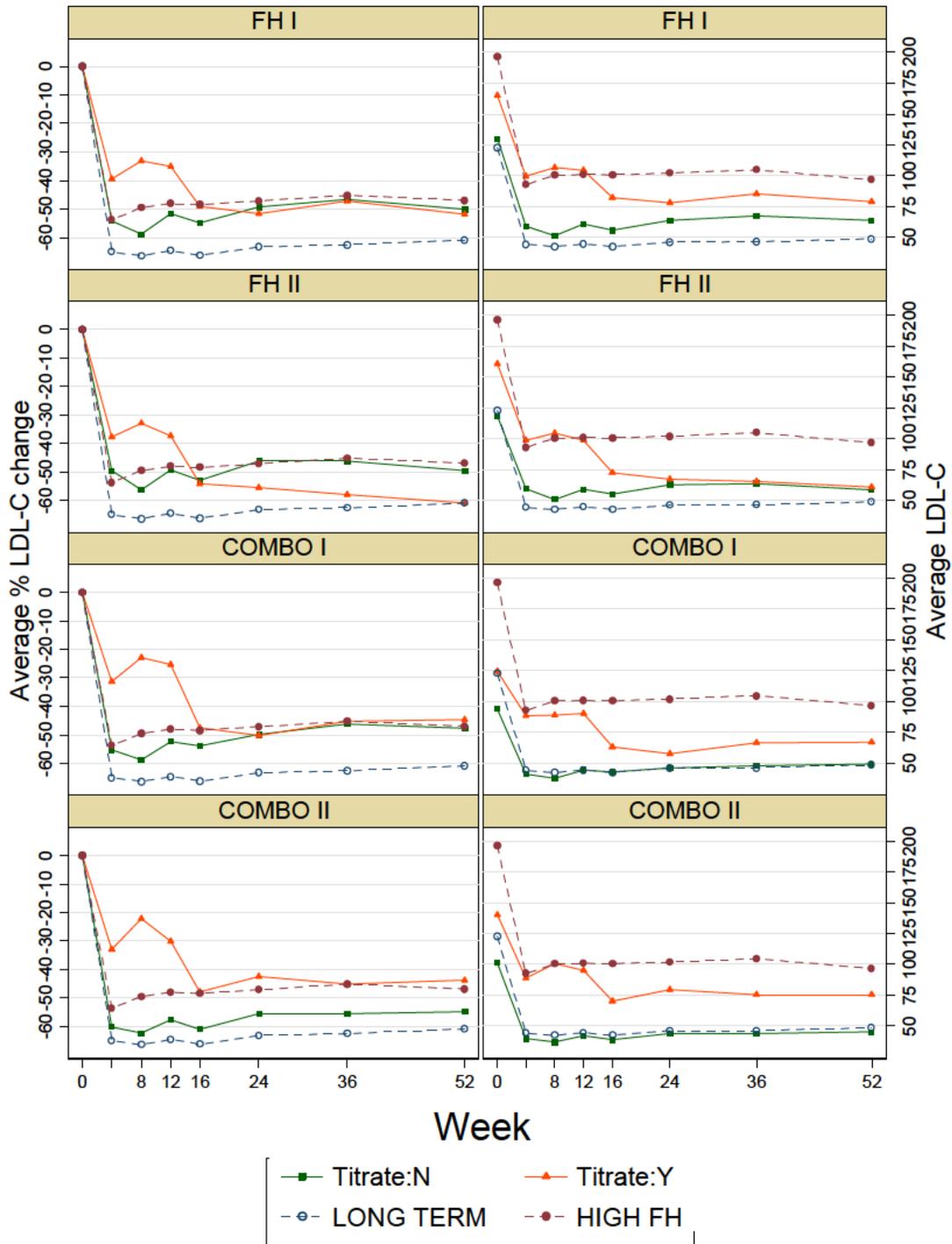
Figure 5. Scatterplot of the probability of up-titration and average baseline LDL-C (mg/dL)



Mean profile plots during treatment adherence were used to explore the impact of up-titration on LDL-C change for alirocumab. Since the comparison of different doses within a trial is not supported by the individual trial designs, the plots must be viewed with extreme caution. For

trials with a maximally tolerated statin as background, after the up-titration occurred, there was an apparent reduction in % LDL-C change from week 12 to 16 (Figure 6). Compared to those that did not up-titrate, there was no consistent trend across trials of greater % LDL-C reduction after week 12 for those that up-titrated. In some trials the % LDL-C reduction was greater for those that up-titrated, while in other instances it was similar or not as great. Similar observations regarding the apparent reduction in % LDL-C change after up-titrating was observed in the trials with less than maximal statin dose as background therapy (Figure 17 in Appendix) and the trials with no statin background therapy (Figure 18 in Appendix).

Figure 6. Mean profile plots of % LDL-C change (left panel) and LDL-C (mg/dL; right panel) by titration status for trials with a maximally tolerated statin as background therapy (FH I, FH II, COMBO I and COMBO II). Profiles for HIGH FH and LONG TERM are included for reference.



Missing Data

Most subjects had a week 24 calculated LDL-C value (Table 11). Across trials, the amount of missing data ranged from 6% to 13%. There did not appear to be systematically more missing data in either the experimental or control arms across trials. Most measurements came from subjects while on study drug. A respectable number of subjects had measurements after discontinuing study drug, suggesting efforts were made by study investigators to minimize missing data.

Of those with a LDL-C missing at week 24, most (61%) had stopped study drug prior to the beginning of the week 24 analysis window. However, there was substantial variability in the percentages within and across trials.

Mean profile plots of LDL-C change after stopping treatment early for COMBO I, COMBO II and LONG TERM are displayed in the Appendix (Figure 13 to Figure 15). After stopping treatment LDL-C values were not sustained and returned to approximately to baseline levels. In Section 3.2.2 the implications are discussed on this and treatment adherence status being differential among those with and without data as it relates the handling of missing data in the applicant's primary efficacy analysis.

Table 11. Ascertainment of LDL-C at week 24

Treatment arm	Not missing		Missing	
	n (%)	On study drug n (%)*	n (%)	Stopped treatment prior to week 24† n (%‡)
FH I (EFC12492)				
Aliro 75/150 (N=323)	290 (90%)	288 (99%)	33 (10%)	15 (45%)
Placebo (N=163)	149 (91%)	143 (96%)	14 (9%)	3 (21%)
FH II (R727-CL-1112)				
Aliro 75/150 (N=167)	157 (94%)	155 (99%)	10 (6%)	6 (60%)
Placebo (N=82)	78 (95%)	77 (99%)	4 (5%)	1 (25%)
HIGH FH (EFC12732)				
Aliro 150 (N=72)	63 (88%)	62 (98%)	9 (13%)	5 (56%)
Placebo (N=35)	33 (94%)	33 (100%)	2 (6%)	0 (0%)
COMBO I (EFC11568)				
Aliro 75/150 (N=209)	189 (90%)	181 (96%)	20 (10%)	17 (85%)
Placebo (N=107)	97 (91%)	92 (95%)	10 (9%)	9 (90%)
LONG TERM (LTS11717)				
Aliro 150 (N=1553)	1386 (89%)	1347 (97%)	167 (11%)	90 (54%)
Placebo (N=788)	708 (90%)	688 (97%)	80 (10%)	46 (58%)
COMBO II (EFC11569)				
Aliro 75/150 (N=479)	428 (89%)	415 (97%)	51 (11%)	30 (59%)
Ezetimibe (N=241)	221 (92%)	213 (96%)	20 (8%)	16 (80%)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75/150 + Atorva 20 (N=57)	50 (88%)	46 (92%)	7 (12%)	7 (100%)
Atorva 40 (N=57)	50 (88%)	43 (86%)	7 (12%)	5 (71%)
Ezetimibe + Atorva 20 (N=55)	43 (78%)	38 (88%)	12 (22%)	9 (75%)
Atorvastatin 40 mg stratum				
Aliro 75/150 + Atorva 40 (N=47)	41 (87%)	37 (90%)	6 (13%)	4 (67%)
Atorva 80 (N=47)	42 (89%)	37 (88%)	5 (11%)	3 (60%)
Ezetimibe + Atorva 40 (N=47)	44 (94%)	39 (89%)	3 (6%)	3 (100%)
Rosuva 40 (N=45)	44 (98%)	38 (86%)	1 (2%)	0 (0%)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75/150 + Rosuva 10 (N=49)	42 (86%)	37 (88%)	7 (14%)	5 (71%)
Rosuva 20 (N=48)	45 (94%)	42 (93%)	3 (6%)	1 (33%)
Ezetimibe + Rosuva 10 (N=48)	37 (77%)	33 (89%)	11 (23%)	8 (73%)
Rosuvastatin 20mg stratum				
Aliro 75/150 + Rosuva 20 (N=54)	45 (83%)	41 (91%)	9 (17%)	8 (89%)
Rosuva 40 (N=53)	48 (91%)	45 (94%)	3 (6%)	1 (33%)
Ezetimibe + Rosuva 20 (N=53)	47 (89%)	44 (94%)	6 (11%)	6 (100%)
ALTERNATIVE (R727-CL-1119)				
Aliro 75/150 (N=126)	112 (89%)	90 (80%)	11 (9%)	8 (73%)
Atorvastatin (N=63)	54 (86%)	40 (74%)	5 (8%)	3 (60%)
Ezetimibe (N=125)	106 (85%)	78 (74%)	16 (13%)	14 (88%)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	49 (94%)	43 (88%)	3 (6%)	2 (67%)
Ezetimibe (N=51)	46 (90%)	43 (93%)	5 (10%)	4 (80%)

* Percent of non-missing; † Percent among those with missing data at the endpoint; ‡ prior to beginning of week 24 analysis window

Demographic and baseline characteristics

Across trials differences in patient demographic and baseline characteristics were observed (Table 12) and reflective of the different patient populations studied. A greater percentage of patients in COMBO I, COMBO II and LONG TERM had a prior history MI or stroke compared to other trials (53% vs. 28%). All trials enrolled patients with diabetes, with notably fewer in FH I, FH II, HIGH FH and MONO (9%) compared with the other trials (36%). Across trials, the average LDL-C value ranged from 102 to 198 mg/dL.

Most subjects include in the trials were White (90%), followed by Black or African American (5%). The average age across trials was 60 years, with a range of 18 to 89 years. Most patients were male (62%); the average BMI was 30 kg/m², with 44% having values greater than 30 kg/m². Thirty five (35%) of subjects were enrolled in sites in the US. Subjects from the US were included in all trials except HIGH FH.

Table 12. Patient demographic and baseline characteristics by trial

	FH I N=486	FH II N=249	HIGH FH N=107	COMBO I N=316	LONG TERM N=2341	COMBO II N=720	OPTIONS I N=355	OPTIONS II N=305	ALTER- NATIVE N=314	MONO N=103
Gender: Males	274 (56%)	131 (53%)	57 (53%)	208 (66%)	1459 (62%)	530 (74%)	231 (65%)	187 (61%)	172 (55%)	55 (53%)
Age (years): mean (SD)	52 (13)	53 (13)	51 (13)	63 (9)	60 (10)	62 (9)	63 (10)	61 (10)	63 (9)	60 (5)
≥ 65	81 (17%)	51 (20%)	14 (13%)	131 (41%)	869 (37%)	286 (40%)	163 (46%)	117 (38%)	144 (46%)	19 (18%)
Race:										
White	444 (91%)	244 (98%)	94 (88%)	258 (82%)	2175 (93%)	610 (85%)	306 (86%)	256 (84%)	295 (94%)	93 (90%)
Black	5 (1%)	2 (1%)	2 (2%)	51 (16%)	77 (3%)	28 (4%)	38 (11%)	27 (9%)	12 (4%)	10 (10%)
Country: USA	109 (22%)	0 (0%)	27 (25%)	316 (100%)	486 (21%)	217 (30%)	255 (72%)	183 (60%)	214 (68%)	49 (48%)
Prior MI or Stroke: Yes	135 (28%)	55 (22%)	27 (25%)	181 (57%)	1125 (48%)	468 (65%)	116 (33%)	105 (34%)	65 (21%)	0 (0%)
heFH: Yes	486 (100%)	249 (100%)	107 (100%)	0 (0%)	417 (18%)	0 (0%)	32 (9%)	41 (13%)	47 (15%)	0 (0%)
Diabetes: Yes	56 (12%)	11 (4%)	15 (14%)	136 (43%)	832 (35%)	223 (31%)	178 (50%)	128 (42%)	75 (24%)	4 (4%)
High statin dose: Yes	396 (81%)	216 (87%)	78 (73%)	182 (58%)	1032 (44%)	480 (67%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mixed dyslipidemia: Yes	129 (27%)	53 (21%)	31 (29%)	123 (39%)	947 (40%)	304 (42%)	128 (36%)	116 (38%)	164 (52%)	30 (29%)
BMI (kg/m²): Mean (SD)	29 (5)	28 (5)	29 (5)	32 (7)	30 (6)	30 (5)	31 (6)	31 (7)	29 (6)	29 (6)
≥ 30	188 (39%)	73 (29%)	36 (34%)	188 (60%)	1057 (45%)	318 (44%)	181 (51%)	157 (51%)	116 (37%)	38 (37%)
Lipids (mg/dL):										
LDL-C: mean (SD)	145 (50)	134 (41)	198 (53)	102 (32)	122 (42)	107 (36)	105 (34)	111 (39)	191 (69)	140 (26)
Apo-B: mean (SD)	114 (30)	108 (26)	141 (31)	91 (22)	102 (28)	94 (23)	91 (23)	95 (24)	140 (38)	104 (19)
Apo-A1: mean (SD)	141 (27)	147 (29)	137 (23)	144 (25)	147 (26)	141 (24)	144 (24)	146 (25)	151 (25)	158 (32)
total-C: mean (SD)	220 (53)	212 (46)	274 (54)	180 (37)	202 (47)	186 (41)	182 (39)	191 (45)	279 (78)	223 (32)
HDL-C: mean (SD)	50 (15)	53 (16)	48 (13)	48 (14)	50 (12)	47 (13)	49 (13)	50 (13)	50 (14)	57 (18)
non-HDL-C: mean (SD)	170 (53)	158 (44)	226 (55)	131 (36)	152 (46)	138 (40)	133 (39)	141 (43)	229 (78)	166 (30)
Lp(a): mean (SD)	50 (51)	50 (66)	41 (47)	50 (50)	43 (48)	44 (46)	45 (48)	52 (55)	34 (42)	25 (27)
Q2 (Q1, Q3)	28 (11, 80)	22 (8, 75)	26 (10, 48)	33 (10, 80)	22 (7, 67)	25 (8, 66)	23 (8, 68)	28 (11, 79)	15 (7, 45)	16 (5, 37)
TG: mean (SD)	128 (65)	121 (65)	150 (87)	147 (85)	151 (83)	156 (77)	141 (71)	150 (82)	179 (99)	130 (64)
Q2 (Q1, Q3)	112 (83, 152)	104 (81, 141)	129 (94, 171)	127 (92, 186)	133 (94, 185)	137 (100, 195)	122 (89, 175)	128 (92, 185)	156 (108, 229)	117 (87, 153)

3.2.4 Results and Conclusions

This section is organized as follows. In the next section results for the primary endpoint are summarized. Section 3.2.4.2 summarizes CV outcomes data. In Section 3.2.4.3 the frequency of low LDL-C values are summarized. A comparison of calculated and measured LDL-C values is done in Section 3.2.4.4 and in Section 3.2.4.5 results from the secondary endpoints are summarized.

3.2.4.1 Analysis of the primary efficacy endpoint

Results from the applicant's primary analysis of % LDL-C change at week 24 for each of the phase 3 trials is shown in Table 13. Alirocumab had greater estimate % LDL-C reduction than control (active or placebo) in all trials. The excess reduction for alicocumab was statistically significant at the prespecified alpha level for all comparisons except two in OPTIONS II. The two non-statistically significant comparisons were both in the rosuvastatin 20 mg stratum and were tested at the two-sided 1.25% alpha level; the non-significant comparison were with rosuvastatin 40 mg (diff.: -20%, 98.75% CI = -46, 6; p-value = 0.045) and ezetimibe + rosuvastatin 20 mg (diff.: -25%, 98.75% CI = -51, 1; p-value = 0.014). Alirocumab met its prespecified primary study objective in 9 trials and two of four in the 10th trial.

In the placebo controlled trials, the excess % LDL-C reduction for alicocumab ranged from 39% to 62% across trials. The largest and smallest estimated reductions were in HIGH FH and LONG TERM, respectively, which used the 150 mg dosing regimen for the entire study duration. The reduction at week 24 is similar to the reduction at the first follow-up visit (week 4), which is sustained throughout the 52 week follow-up period (Figure 7).

In the active controlled trials, compared to ezetimibe, the excess % LDL-C reduction for alicocumab ranged from 24% to 36%. In trials without statin background (ALTERNATIVE and MONO), there was an excess reduction in % LDL-C in the alicocumab group of about 30%. Similar to the placebo controlled trials, the initial decrease in LDL-C at week 4 was sustained throughout follow-up period for alicocumab (Figure 8 and Figure 9).

Findings from the preferred FDA analysis (Table 14), which assumed LDL-C values after stopping treatment early would return to baseline levels, were aligned with the findings from the primary efficacy analysis. However, as expected, the estimated treatment effects were attenuated. On an absolute difference scale, the degree of attenuation ranged 0% to 8%. Given the magnitude of the treatment effect and the small amount of missing data, it is very unlikely that missing data could be such that it could alter study conclusions (i.e., the difference is not statistically significant).

Table 13. % LDL-C change at week 24 by trial (ITT population; applicants' primary efficacy analysis)

	n*	Baseline (mg/dL)	LS Mean: % Change	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	290	145	-49%	
Placebo (N=163)	149	144	9%	-58% (-63, -53)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	157	135	-49%	
Placebo (N=82)	78	134	3%	-51% (-58, -45)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	63	196	-46%	
Placebo (N=35)	33	201	-7%	-39% (-51, -27)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	189	100	-48%	
Placebo (N=107)	97	105	-2%	-46% (-52, -39)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	1386	123	-61%	
Placebo (N=788)	708	122	1%	-62% (-64, -59)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	428	108	-51%	
Ezetimibe (N=241)	221	104	-21%	-30% (-34, -25)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	50	103	-44%	
Atorvastatin 40mg (N=57)	50	101	-5%	-39% (-56, -22)
Ezetimibe + Atorvastatin 20mg (N=55)	43	101	-20%	-24% (-40, -7)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	41	117	-54%	
Atorvastatin 80mg (N=47)	42	109	-5%	-49% (-65, -34)
Ezetimibe + Atorvastatin 40mg (N=47)	44	99	-23%	-31% (-47, -16)
Rosuvastatin 40mg (N=45)	44	110	-21%	-33% (-48, -17)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	42	108	-51%	
Rosuvastatin 20mg (N=48)	45	106	-16%	-34% (-49, -19)
Ezetimibe + Rosuvastatin 10mg (N=48)	37	102	-14%	-36% (-52, -21)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	45	118	-36%	
Rosuvastatin 40mg (N=53)	48	114	-16%	-20% (-46, 6)
Ezetimibe + Rosuvastatin 20mg (N=53)	47	119	-11%	-25% (-51, 1)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	115	191	-45%	
Ezetimibe (N=125)	108	194	-15%	-30% (-36, -24)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	49	141	-47%	
Ezetimibe (N=51)	46	138	-16%	-32% (-40, -23)

† 99% CI for OPTIONS I and 98.75% CI for OPTIONS II; * N with baseline and week 24 data

Figure 7. % LDL-C change mean profile plots for placebo controlled trials along with number of subjects with a response at each visit (ITT population).

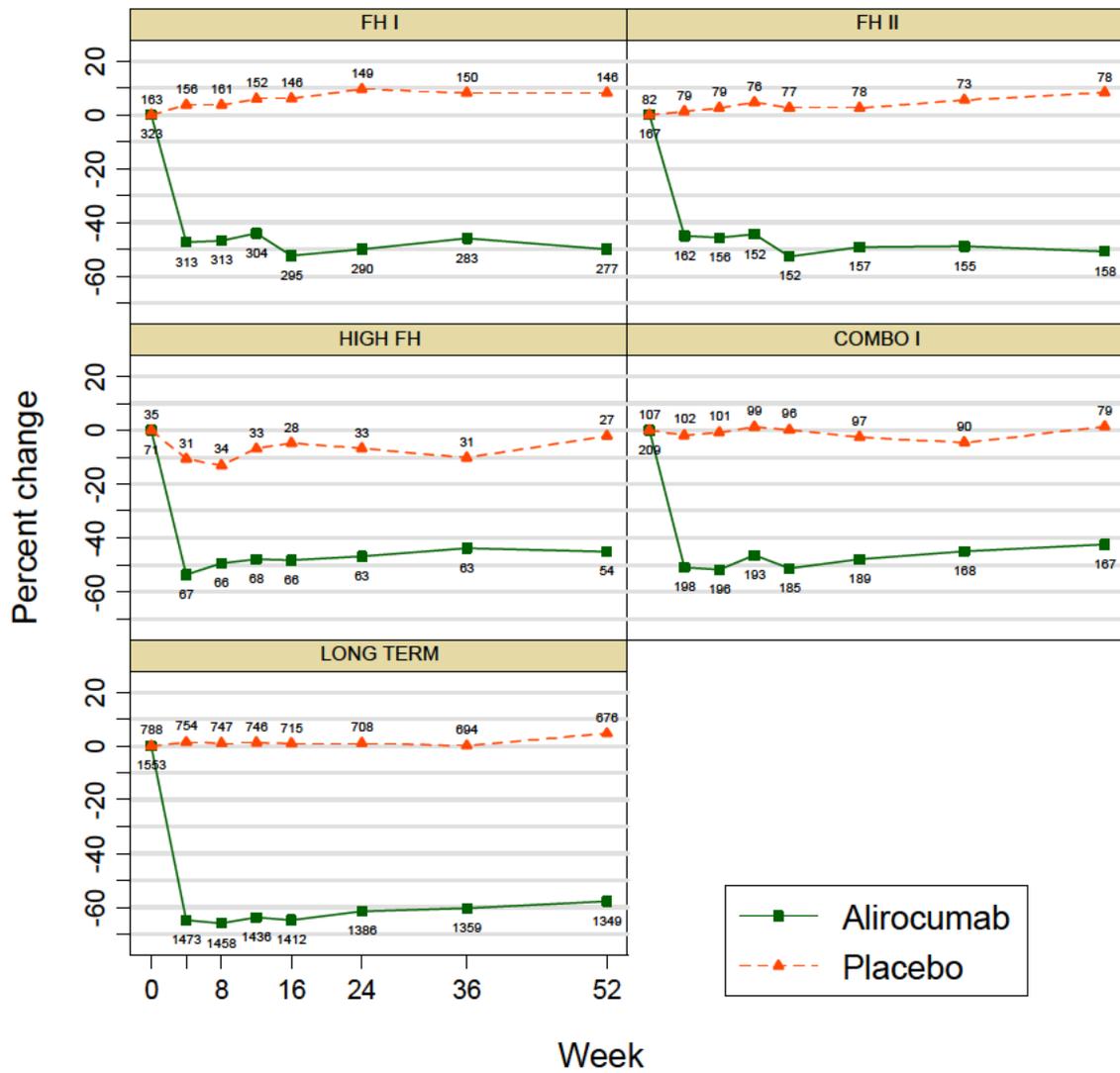


Figure 8. % LDL-C change mean profile plots for COMBO II, ALTERNATIVE and MONO along with number of subjects with a response at each visit (ITT population).

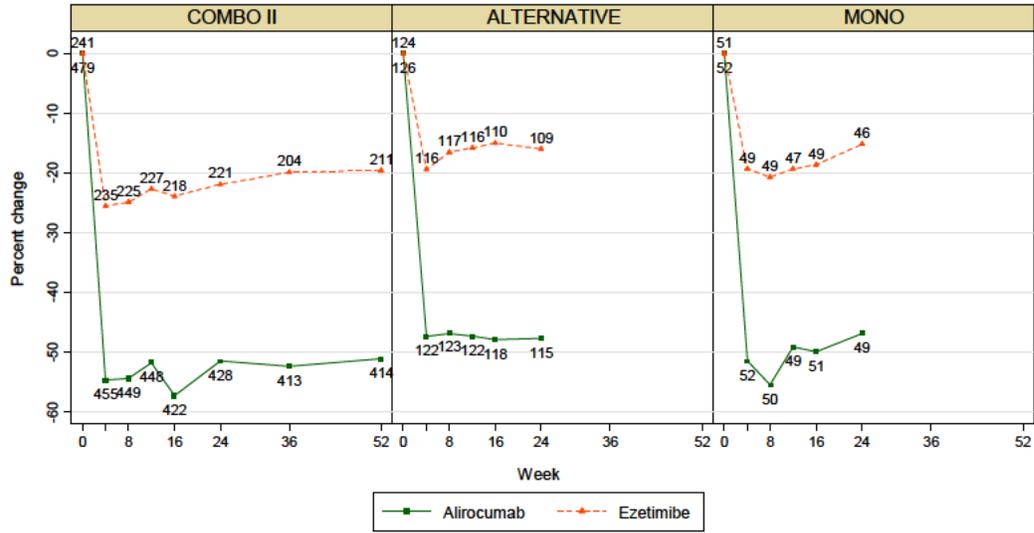


Figure 9. % LDL-C change mean profile plots for OPTIONS I and OPTIONS II along with number of subjects with a response at each visit (ITT population).

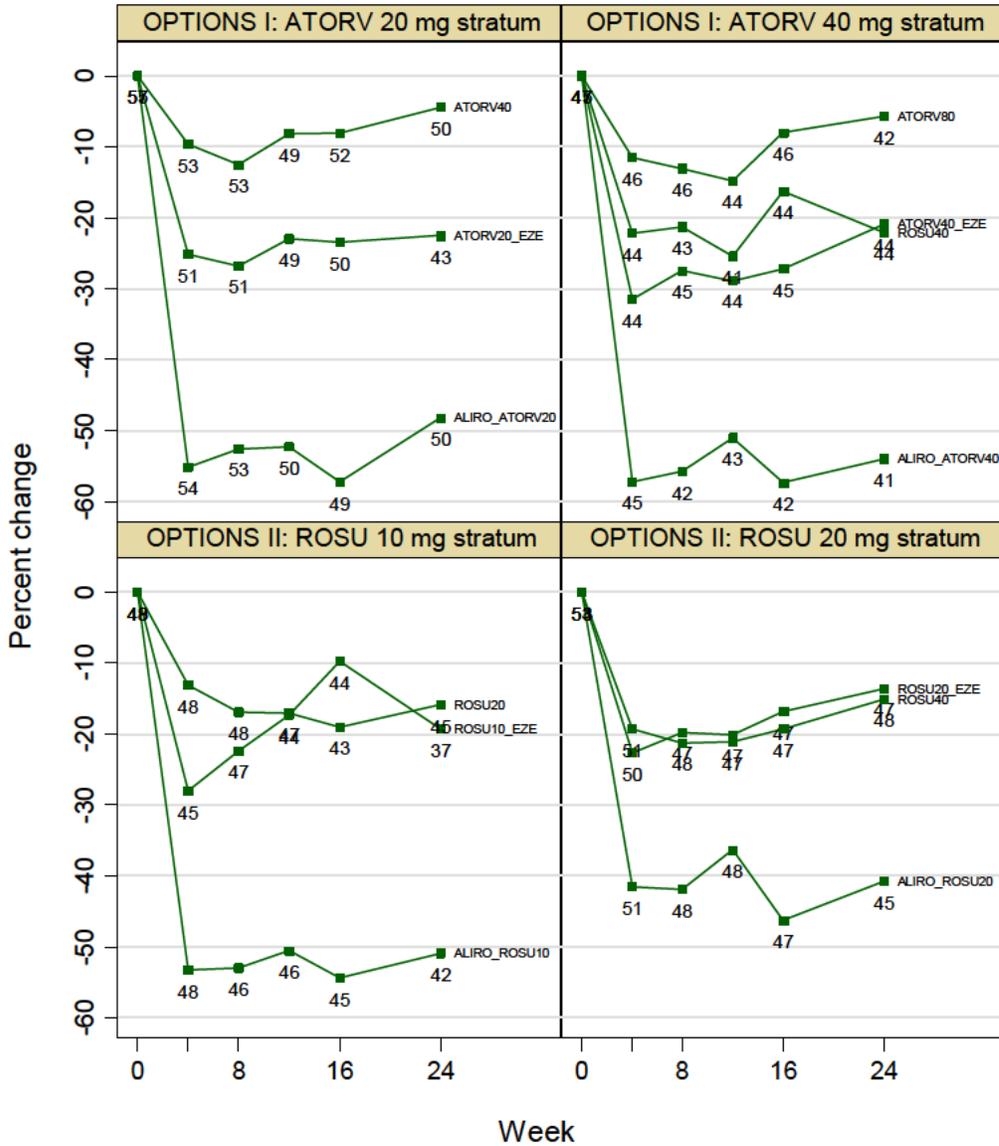


Table 14. % LDL-C change at week 24 by trial (ITT population; preferred FDA analysis)

	Baseline (mg/dL)	LS Mean: % Change	Difference: Alirocumab - Control (95% CI)
FH I (EFC12492)			
Aliro 75mg/150mg (N=323)	145	-47%	
Placebo (N=163)	144	9%	-56% (-62, -51)
FH II (R727-CL-1112)			
Aliro 75mg/150mg (N=167)	135	-47%	
Placebo (N=82)	134	3%	-50% (-57, -43)
HIGH FH (EFC12732)			
Aliro 150mg (N=72)	196	-43%	
Placebo (N=35)	201	-7%	-36% (-49, -24)
COMBO I (EFC11568)			
Aliro 75mg/150 mg (N=209)	100	-44%	
Placebo (N=107)	105	-2%	-43% (-50, -35)
LONG TERM (LTS11717)			
Aliro 150mg (N=1553)	123	-58%	
Placebo (N=788)	122	1%	-58% (-61, -56)
COMBO II (EFC11569)			
Aliro 75mg/150mg (N=479)	108	-48%	
Ezetimibe (N=241)	104	-20%	-28% (-33, -23)
OPTIONS I (R727-CL-1110):			
Atorvastatin 20mg stratum			
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	103	-42%	
Atorvastatin 40mg (N=57)	101	-4%	-37% (-51, -24)
Ezetimibe + Atorvastatin 20mg (N=55)	101	-20%	-21% (-35, -7)
Atorvastatin 40 mg stratum			
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	117	-49%	
Atorvastatin 80mg (N=47)	109	-4%	-45% (-57, -32)
Ezetimibe + Atorvastatin 40mg (N=47)	99	-20%	-29% (-42, -16)
Rosuvastatin 40mg (N=45)	110	-22%	-28% (-40, -15)
OPTIONS II (R727-CL-1118):			
Rosuvastatin 10mg stratum			
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	108	-46%	
Rosuvastatin 20mg (N=48)	106	-16%	-30% (-41, -18)
Ezetimibe + Rosuvastatin 10mg (N=48)	102	-18%	-28% (-40, -16)
Rosuvastatin 20mg stratum			
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	118	-34%	
Rosuvastatin 40mg (N=53)	114	-15%	-18% (-38, 1)
Ezetimibe + Rosuvastatin 20mg (N=53)	119	-11%	-23% (-42, -3)
ALTERNATIVE (R727-CL-1119)			
Aliro 75mg/150mg (N=126)	191	-44%	
Ezetimibe (N=125)	194	-13%	-30% (-37, -24)
MONO (EFC11716)			
Aliro 75mg/150mg (N=52)	141	-45%	
Ezetimibe (N=51)	138	-14%	-31% (-40, -22)

3.2.4.2 Cardiovascular events

In this section data on adjudicated MACE (CHD death, fatal and non-fatal MI, fatal and non-fatal ischemic stroke, or unstable angina requiring hospitalization) are presented to help evaluate whether there is some evidence of cardiovascular benefit. These endpoints are the same ones included in the primary MACE endpoint in the ongoing CVOT trial.

The analysis included CV events occurring during the treatment emergent adverse event (TEAE) period and the post-treatment period. The TEAE period included events 70 days after last double-blind dose of study treatment. The post-treatment period included events after the TEAE period. Importantly, these results differ from the applicant's as they only counted events during the TEAE period. In my opinion, data from both periods are needed to assess cardiovascular benefit, which is consistent with the intention-to-treat principle.

Due to the limited number of CV observed across trials, data from select trials with similar design features were combined. The trial groups explored are

- Placebo-controlled (FH I, FH II, HIGH FH, COMBO I, LONG TERM)
- Placebo-controlled with the 75 mg/150 mg regimen (FH I, FH II, COMBO I)
- Placebo-controlled with the 150 mg regimen (HIGH FH, LONG TERM)
- Ezetimibe-controlled (COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, MONO)

Estimates are study adjusted using inverse probability treatment weights (IPTW) to allow unconfounded descriptive comparisons between treatment arms. This approach has also been referred to as weighting by sample size (Pharmaceutical Statistics. 2011; 10: 3-7). IPTW avoids shortcomings associated with naïve data pooling by estimating what would have happened if everyone in a trial group received a given treatment .

In total, 93 MACE were observed in 10 trials, 58 in the alicumab group and 35 in the control arms (See Table 19 in the Appendix). This is well below the 1613 MACE planned for the placebo-controlled CVOT designed to detect a 15% reduction in MACE. The majority of events came from LONG TERM (52 MACE) and COMBO II (21 MACE). In COMBO II there were more MACE for alicumab compared to ezetimibe (3.3% vs. 2.1%). In LONG TERM there were fewer MACE for alicumab compared to placebo (1.7% vs. 3.2%), with cause-specific hazard ratio (CS-HR) 0.54 (95% CI = 0.32, 0.94) that is larger than the CS-HR 0.46 (95% CI = 0.26, 0.82) estimated by the applicant that used data only from the TEAE period. Treatment effect estimates are referred to as cause-specific since they were estimated from a cause-specific hazard model, done by fitting the traditional Cox regression model with competing events that impede the occurrence of MACE (i.e., non-CHD death) censored. Note that CS-HR pertains to the effect of alicumab on MACE only and does not adjust for how alicumab could impact the competing event.

Study-adjusted results from the different trial groups are displayed in Table 15. In the placebo pool (both alicumab dosing regimens), the frequency of MACE was smaller for alicumab (1.8%) than placebo (2.4%). The estimated CS-HR was 0.74 with 95% CI (0.46, 1.19), which was larger than the CS-HR estimated by the applicant using data from the TEAE period only

(CS-HR = 0.65; 95% CI = 0.40, 1.08). In the ezetimibe controlled pool, the frequency of MACE was greater for alicumab (1.4%) compared to ezetimibe (1.1%). This imbalance is driven by an excess in fatal and non-fatal MI events for alicumab (1.3% vs. 0.7%).

In summary, there were too few MACE to conclude with high statistical confidence that alicumab provides CV benefit. These findings should be interpreted cautiously.

Table 15. Study adjusted MACE frequencies by trial type (TEAE period + post-treatment period)

Trial type Treatment arm	CHD death	Total MI	Total Stroke	Angina	Composite
Placebo controlled (5 trials; N=3499)					
Alirocumab (N=2324)	0.4%	0.9%	0.6%	0.0%	1.8%
Placebo (N=1175)	0.6%	1.6%	0.3%	0.1%	2.4%
Alirocumab 75 mg/150 mg (3 trials; N=1051)					
Alirocumab 75 mg/150 mg (N=699)	0.6%	0.6%	0.4%	0.1%	1.4%
Placebo (N=352)	0.3%	0.6%	0.0%	0.0%	0.9%
Alirocumab 150 mg (2 trials; N=2488)					
Alirocumab 150 mg (N=1625)	0.4%	1.0%	0.6%	0.0%	1.9%
Placebo (N=823)	0.7%	2.1%	0.4%	0.1%	3.0%
Ezetimibe controlled (5 trials; N=1484)					
Alirocumab 75 mg/150 mg (N=864)	0.2%	1.3%	0.1%	0.1%	1.8%
Placebo (N=620)	0.4%	0.7%	0.2%	0.0%	1.1%

3.2.4.3 Low LDL-C values

Subjects' calculated LDL-C values were lowered considerably in the trials. Because the health consequence (safety and efficacy) of achieving and sustaining low LDL-C values are unknown, this section summarizes the occurrence of low LDL-C values at weeks 12 and 24 for the individual trials and trial pools. The trial pools explored are

- Placebo-controlled with the 75 mg/150 mg regimen (FH I, FH II, COMBO I)
- Placebo-controlled with the 150 mg regimen (HIGH FH, LONG TERM)
- Ezetimibe-controlled with background statin (COMBO I, OPTIONS I, OPTIONS II)
- Ezetimibe-controlled not with background statin (ALTERNATIVE, MONO)

Incidence estimates are study adjusted using IPTW to allow unconfounded descriptive comparisons between treatment arms.

Alirocumab had disproportionately more subjects with lower LDL-C at weeks 12 and 24 than either placebo or active-control (Table 16). The greatest percentage of subjects with low values was in LONG TERM; at week 12 the alicumab arm had 11% with LDL-C < 15 mg/dL, 27% < 25 mg/dL and 64% < 50 mg/dL, compared to 1% with LDL-C < 50 mg/dL for placebo. Similar numbers were observed at week 24. The other trial with the 150 mg regimen (HIGH FH) did not have similar numbers of low LDL-C; this difference may have resulted from subjects in HIGH FH having greater LDL-C values at baseline.

Results from the different trial groups are displayed in Table 17. The 150 regimen pool results were largely driven by LONG TERM. For each pool except ezetimibe-controlled not with background statin, at least 5% of the alicumab treated patients had LDL-C < 25 mg/dL. A possible explanation for the different trend for the ezetimibe-controlled not with background statin pool was they tended to have larger LDL-C values at baseline (Table 12).

Table 16. Frequency of low calculated LDL-C values at weeks 12 and 24 by trial

Treatment Arm (N=)	Week 12				Week 24			
	< 15	15-25	25-50	Missing	< 15	15-25	25-50	Missing
FH I (EFC12492)								
Aliro 75/150 (N=323)	1%	2%	21%	6%	2%	2%	24%	10%
Placebo (N=163)	0%	0%	0%	7%	0%	0%	0%	9%
FH II (R727-CL-1112)								
Aliro 75/150 (N=167)	1%	1%	21%	9%	2%	3%	30%	6%
Placebo (N=82)	0%	0%	0%	7%	0%	0%	0%	5%
HIGH FH (EFC12732)								
Aliro 150 (N=72)	0%	6%	7%	6%	1%	3%	11%	13%
Placebo (N=35)	0%	0%	0%	6%	0%	0%	0%	6%
COMBO I (EFC11568)								
Aliro 75/150 (N=209)	4%	10%	38%	8%	4%	10%	39%	10%
Placebo (N=107)	0%	0%	1%	7%	0%	0%	2%	9%
LONG TERM (LTS11717)								
Aliro 150 (N=1553)	11%	16%	37%	8%	11%	14%	35%	11%
Placebo (N=788)	0%	0%	1%	5%	0%	0%	1%	10%
COMBO II (EFC11569)								
Aliro 75/150 (N=479)	5%	11%	39%	6%	4%	9%	39%	11%
Eze (N=241)	0%	0%	14%	6%	0%	0%	12%	8%
OPTIONS I (R727-CL-1110):								
Atorvastatin 20mg stratum								
Aliro 75/150 + Ator 20mg (N=57)	5%	11%	35%	12%	4%	9%	40%	12%
Ator 40mg (N=57)	0%	0%	0%	14%	0%	0%	0%	12%
Ator 20mg + Eze (N=55)	0%	0%	11%	11%	0%	0%	9%	22%
Atorvastatin 40 mg stratum								
Aliro 75/150 + Ator 40mg (N=47)	2%	11%	34%	9%	6%	13%	32%	13%
Ator 40mg + Eze (N=47)	0%	0%	28%	6%	0%	0%	15%	6%
Ator 80mg (N=47)	0%	0%	2%	6%	0%	0%	0%	11%
Rosu 40mg (N=45)	0%	2%	9%	9%	0%	2%	9%	2%
OPTIONS II (R727-CL-1118):								
Rosuvastatin 10mg stratum								
Aliro 75/150 + Rosu 10mg (N=49)	4%	10%	33%	6%	4%	8%	39%	14%
Rosu 10mg + Eze (N=48)	0%	2%	13%	8%	0%	0%	10%	23%
Rosu 20mg (N=48)	0%	0%	4%	2%	0%	0%	4%	6%
Rosuvastatin 20mg stratum								
Aliro 75/150 + Rosu 20mg (N=54)	2%	7%	7%	11%	6%	0%	28%	17%
Rosu 20mg + Eze (N=53)	0%	0%	11%	11%	0%	0%	11%	11%
Rosu 40mg (N=53)	0%	0%	6%	11%	0%	0%	6%	9%
ALTERNATIVE (R727-CL-1119)								
Aliro 75/150 (N=126)	0%	0%	12%	3%	0%	0%	12%	9%
Ator (N=63)	0%	0%	5%	6%	0%	0%	2%	8%
Eze (N=125)	0%	0%	0%	6%	0%	0%	0%	13%
MONO (EFC11716)								
Aliro 75/150 (N=52)	0%	2%	15%	6%	0%	0%	29%	6%
Eze (N=51)	0%	0%	0%	8%	0%	0%	0%	10%

Table 17. Study adjusted frequencies of low calculated LDL-C values by trial type

Treatment Arm	Week 12				Week 24			
	< 15	15-25	25-50	Missing	< 15	15-25	25-50	Missing
Placebo controlled								
Alirocumab 75 mg/150 mg								
Aliro 75/150	1.6%	3.9%	25.9%	7.1%	2.4%	4.6%	29.9%	9.0%
Placebo	0.0%	0.0%	0.3%	7.1%	0.0%	0.0%	0.6%	7.9%
Alirocumab 150 mg								
Aliro 150	10.2%	15.9%	35.7%	7.4%	10.4%	13.5%	33.9%	10.8%
Placebo	0.0%	0.0%	0.5%	5.3%	0.0%	0.0%	0.6%	10.0%
Ezetimibe controlled								
With statin								
Aliro 75/150	4.2%	10.7%	34.6%	7.6%	4.4%	8.2%	37.8%	11.9%
Ezetimibe	0.0%	0.2%	14.3%	7.1%	0.3%	0.0%	11.8%	11.0%
Without statin								
Aliro 75/150	0.0%	0.6%	12.9%	3.9%	0.0%	0.0%	16.8%	7.9%
Ezetimibe	0.0%	0.0%	0.0%	6.8%	0.0%	0.0%	0.0%	11.9%

3.2.4.4 Measured vs. Calculated LDL-C

Results of analyses using measured and calculated LDL-C were compared by the applicants to assess sensitivity of the primary analysis that used calculated values. While such a comparison is important to assess the accuracy of the estimated treatment effect, there are important limitations to what the applicant did.

First, the trials were not designed to support a comparison of the two approaches. If they were, calculated values would have been obtained when TG > 400 mg/dL. It is therefore not possible to get a reliable estimate of the differences between approaches since the calculated values were not systematically collected where the measurement error is the greatest. Although the impact may not be too great since the overall percentage with a TG > 400 mg/dL at week 24 was relatively small (~1%), the limitation remains.

Second, there are important differences between the MMRM for calculated values and the MMRM for measured values used by the applicants, which make the comparisons difficult. The issue is that measured values were not captured at the same frequency as calculated values, resulting in the data supporting the analyses not being the same. Consider FH I, which captured measured values at baseline and week 24. For measured LDL-C, only subjects with baseline and week 24 data would contribute to the analysis. This is not the case for calculated LDL-C. Subjects that did not have a week 24 measurement would still influence the week 24 results by impacting the correlation at earlier visits. Thus, the subjects that indirectly contribute data to the separate analysis are different. How this ultimately impacts the comparison is unclear.

The difference between measured and calculated values sampled from the same study day as a function of triglyceride level is shown in Figure 10. There are two important observations about the measurement error. First, for calculated LDL-C < 100 mg/dL, the calculated values are systematically smaller than measured values, and systematically larger for calculated LDL-C > 100 mg/dL. Second, the degree of measurement error increased with increasing TG levels.

To assess the implication of the above findings, information from subjects with paired measured and calculated LDL-C values at week 24 were used to get unadjusted estimates of the treatment effect based on calculated values and using measured values (

Figure 11). In this group of subjects there did not appear to be a systematic difference in results, as evident by the points being distributed about the $y=x$ reference line. This relationship was also explored for patients with and without mixed dyslipidemia at baseline, since the group with mixed dyslipidemia ($TG > 150$ mg/dL) would be highly susceptible to increased measurement error. This relationship is shown in Figure 12. For those without mixed dyslipidemia there is little difference in the estimated treatment effect using either measure or calculated values. Compared to treatment effect estimates using measured values, the subtracted difference in the estimates using calculated values ranged from being 2.7% smaller to 2.7% greater. For the group with mixed dyslipidemia the treatment effect estimates were still distributed about the $y=x$ reference line, but with considerably more variation. Compared to the treatment effect estimates using measured values, the subtracted difference in the estimates using treated values ranged from being 4.6% smaller to 8.9% greater. Overall, the fact that the values were fairly distributed about the reference line provides some assurance that the analysis using calculated LDL-C may be reasonable. However, whether calculated is good for the entire sample is unknown since we don't know what happened to those without paired data (i.e., those missing week 24 data or had high TG).

Figure 10. Relationship between measured and calculated LDL-C (mg/dL) by triglyceride level (mg/dL)

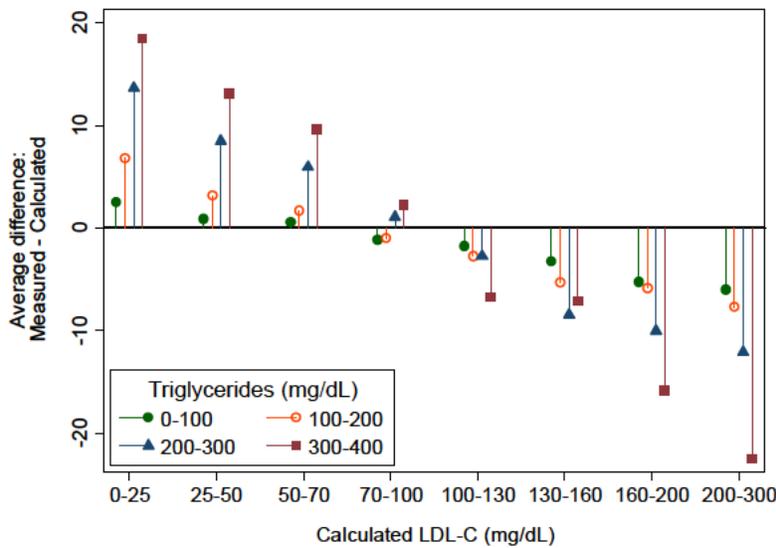


Figure 11. Treatment difference at Week 24 using measured and calculated LDL-C values in subjects with paired data

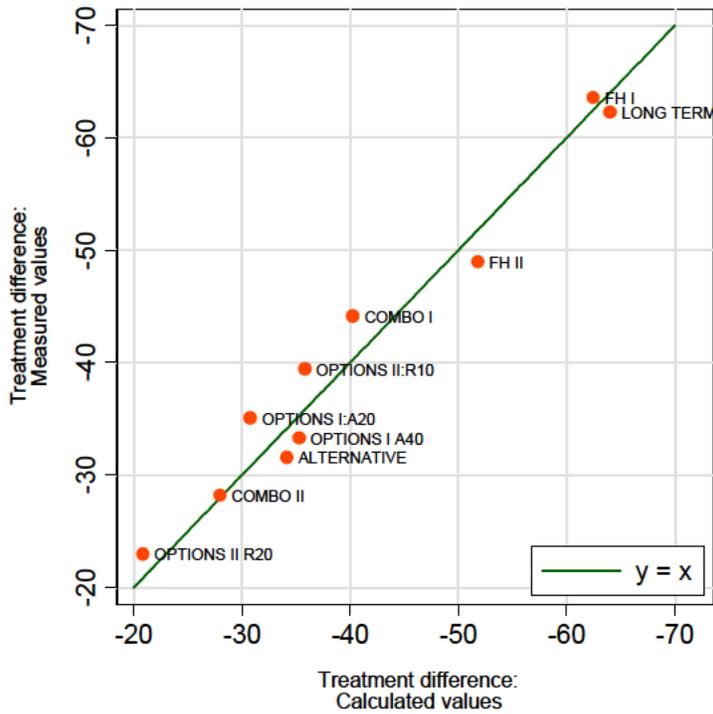
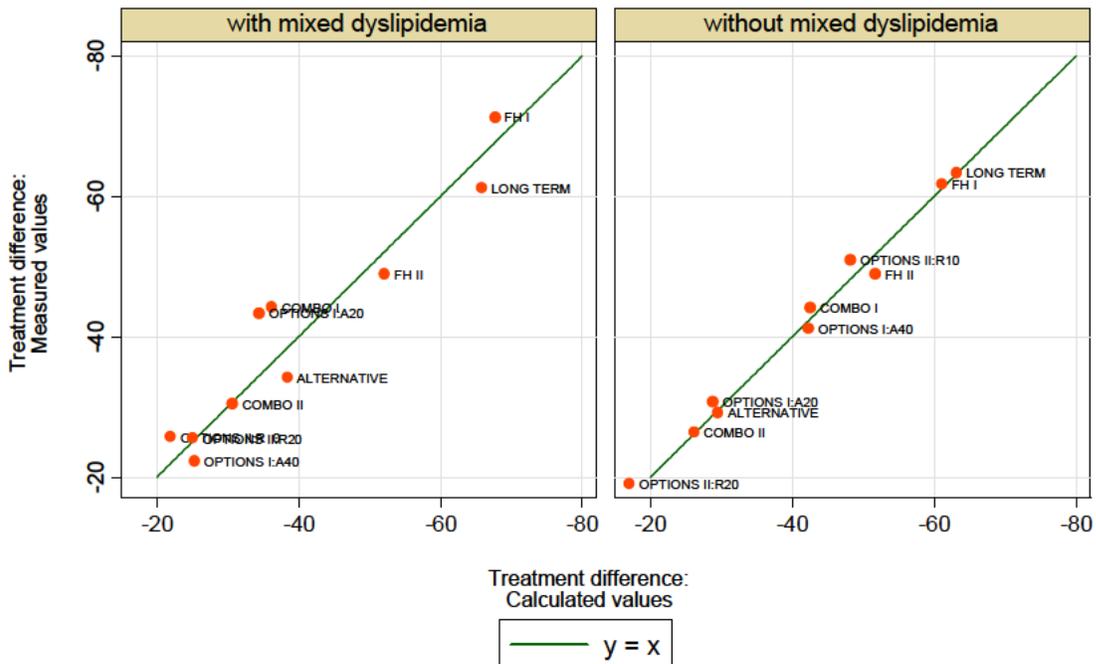


Figure 12. Treatment difference at Week 24 using measured and calculated LDL-C values in subjects with paired data by mixed dyslipidemia status at baseline



3.2.4.5 Secondary endpoints

Across trials there were a very large number of prespecified hypotheses (~ 400). Due to the challenges of providing a cohesive summary of results across trials, I will instead highlight trends in the individual lipids results at weeks 12 and 24. Week 12 data are summarized as it provides an estimate of the effect of alicumab 75 mg in the trials that allowed for up-titration. I do not summarize results from analyses that estimated the on-treatment estimand for considerations stated in Section 3.2.2.

For completeness, results from the hierarchical testing across the trials are summarized in Table 20 to Table 22 in the Appendix. Results from the applicant's prespecified analysis of secondary lipid endpoints at weeks 12 and 24 are summarized in Table 23 to Table 30 in the Appendix. Results from the FDA's analysis of TG and Lp(a) using a Hodges-Lehmann estimate are summarized in Table 31 and Table 32 in the Appendix. In the FDA analysis, missing follow-up data were imputed using baseline observation carried forward (BOCF). BOCF was chosen as it reasonable aligns itself with the imputation approach in our preferred analysis and has an aspect as an imputation under no difference (as these are superiority comparisons) . However, because missing values are treated as known, emphasis should primarily be placed on the estimated treatment difference (and not the CI) as the precision of the estimate is under-stated.

In the summary of results below, statistically significant refers to the CI (99% for OPTIONS I, 98.75% for OPTIONS II, and 95% for the other trials) for the difference in means excluding zero.

Apolipoprotein A1: Four out of the five placebo controlled trials had statistically significantly greater average increase in percent ApoA1 change at week 24. The estimated excess increase ranged from 3% to 6%, with the 4% greater increase in HIGH FH not being statistically significant. Compared to active-control at week 24, alicumab consistently had greater increases that were not statistically significantly different from control. Trials where the differences were statistically significant included COMBO II, OPTIONS I (excluding comparisons with atorvastatin 80 mg and rosuvastatin 40 mg), OPTIONS II (only ezetimibe + rosuvastatin 20 mg), and MONO.

Apolipoprotein B: Across all trials, the alicumab group had statistically significantly greater average reductions in percent ApoB at weeks 12 and 24. Compared to placebo at week 24, the estimated excess reduction ranged from 30% to 54% compared to placebo when added to a maximally tolerated statin with or with other LMT. Compared to ezetimibe at week 24, the estimated excess reduction was 22% greater when added to a maximally tolerated statin, between 17% and 27% greater when added to a less than maximal dose of statin, and about 25% greater when given without a statin.

Cholesterol: Alirocumab consistently had statistically significantly greater average reductions in total cholesterol at the nominal 5% level at weeks 12 and 24. Compared to placebo at week 24, the estimated excess reduction in cholesterol ranged from 25% to 39% when added to a

maximally tolerated statin with or without other LMT. Compared to active-control at week 24, the reduction was statistically significant in all trials except for the comparison with ezetimibe + rosuvastatin 20 mg OPTIONS II. Compared to ezetimibe at week 24, the estimated reduction was 15% greater when added to a maximally tolerated statin, between 6% and 14% greater reduction when added to less than maximal statin, and about 20% when given without a statin.

HDL Cholesterol: Four out of the five placebo controlled trials had statistically significantly greater average increase in percent HDL-C change at week 24. Compared to placebo at week 24, the estimated increase in HDL-C ranged from 4% to 8%, with the 4% increase in HIGH FH not being statistically significant. Compared to active-control, alicumab consistently had increased levels that were not statistically significant. Compared to ezetimibe at week 24, the estimated increase was 8% greater when added to a maximally tolerated statin, between 5% and 9% greater when added to less than maximal statin, and between 1% and 4% when given without statin.

LDL Cholesterol: Results from week 24 were discussed above in Section 3.2.4.1. Results at week 12 were aligned with the week 24 results, with the magnitude of the estimated average reduction being slightly larger at week 24.

Lipoprotein A: Alirocumab consistently had statistically significantly greater average reduction in total Lp(a) at weeks 12 and 24. Compared to placebo at week 24, the estimated excess reduction ranged from 15% to 26% when added to a maximally tolerated statin with or without other LMT. These reductions were all statistically significant at the nominal 5% level. Compared to active-control at week 24, the difference in average reduction was not statistically significant in MONO, OPTIONS I (both comparisons in the atorvastatin 20 mg stratum) and OPTIONS II (compared to ezetimibe in the rosuvastatin 20 mg stratum).

Non HDL Cholesterol: Across all trials, the alicumab group had statistically significantly larger reduction in percent non-HDL-C cholesterol at weeks 12 and 24. Compared to placebo at week 24, the estimated excess reduction ranged from 37% to 52% when added to a maximally tolerated statin with or without other LMT. Compared to ezetimibe at week 24, the estimated average decrease was 23% greater when added to a maximally tolerated statin, between 18% and 26% greater when added to a less than maximal statin, and about 25% greater when given without a statin.

Triglycerides: Alirocumab consistently had greater average reduction in TG compared to control at weeks 12 and 24 that were not statistically significant. Compared to placebo at week 24, the estimated average excess reduction ranged from 1% to 19% when added to a maximally tolerated statin with or without other LMT. The difference was statistically significant FH I, FH II, LONG TERM. Compared to ezetimibe at week 24, there was no difference in TG when added to a maximally tolerated statin, an estimated difference in average change ranging from a 2% greater increase to 9% greater decrease when added to a less than maximal statin, and decreases that were 1% and 6% greater when given without a statin.

3.3 Evaluation of Safety

An evaluation of safety of the phase 3 clinical trials is included in the FDA clinical review by Dr. Mary Roberts of the Division of Metabolism and Endocrinology Products.

3.4 Benefit-risk assessment

The consistent excess reduction of LDL-C in patients treated with alicumab demonstrates that alicumab is an effective agent for lowering LDL-C. This was shown in different patient populations and across different background levels of statin intensity (maximally tolerated dose of statin, less than maximally tolerated dose of statin, and without statin). However, too few CV events were observed to assess whether the excess LDL-C lowering translates into CV benefit in the studied populations. This presents a challenge in characterizing the benefit-risk for alicumab in the absence of a dedicated CVOT. In my opinion, the risk-benefit profile for alicumab is different for those on a maximally tolerated dose of statin compared to those not receiving a maximally tolerated dose of statin. This distinction is based on my understanding (based on discussions with clinical colleagues and literature review) that statins provide cardio-protective benefits, with the benefits exhibiting a dose-response relationship.

For those not receiving a maximally tolerated dose of a statin, additional lowering of LDL-C can be achieved by either increasing the statin dose or possibly adding alicumab to the less than maximal dose. If the statin dose is increased, LDL-C would lower, but, more importantly, there would be a clinical benefit associated with increasing the dose. If alicumab was instead added to the less than maximal dose of statin, LDL-C would decrease. However, whether there would be an additional clinical benefit of including alicumab to the treatment regimen is unknown. Given available treatment options for this patient population, I consider there to be too much uncertainty regarding the benefit of alicumab to conclude with a high degree of confidence that alicumab's benefit out-weighs the risk.

For those on a maximally tolerated dose of a statin that require additional lowering of LDL-C, no cholesterol lowering agent has been shown to provide additional CV benefit when added to a statin²³. Therefore, the uncertainty with the CV benefit from the limited outcomes data included in this submission could, in my opinion, support the use of alicumab on top of a maximally tolerated dose of a statin.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In this section, results from the analysis of the primary efficacy endpoint within subgroup levels are summarized. The subgroups explored are summarized in the table below. The analysis was performed within a study rather than pooling data across trials to allow for an evaluation of

² The 2013 ACC/AHA Guidelines states on page 45 "The panel could find no data supporting the routine use of nonstatin drugs combined with statin therapy to reduce further ASCVD events"

³ This statement does not consider the CVOT IMPROVE-IT which studied adding ezetimibe to simvastatin since the data from the study has not yet been reviewed by FDA

trends across independent data sources. In some cases a given trial could not support a subgroup analysis. One reason is the trial did not enroll enough subjects with that characteristic to support an analysis. As an example, in HIGH FH a subgroup analysis was not done for race since there were only 13 randomized subjects that were not White. The other reason a subgroup analysis was not done is related the trial design. For example, a subgroup analysis by region (i.e., US site vs. non-US site) could not be done for FH II since it was conducted outside the US.

Table 18. Listing of factors, levels and trials for the subgroup analysis

Factor	Levels	Trials
Sex	Females; Males	All
Age	< 65 years; ≥ 65 years	All
Race	White; Other	FH I, COMBO I, COMBO II, LONG TERM
Region	US; non-US	All except FH I and COMBO I
BMI	< 30 kg/m ² ; ≥ 30 kg/m ²	All
Diabetes	No; Yes	All except FH II, HIGH FH, MONO
HefH	No; Yes	LONG TERM
Statin intensity	Not high; High	FH I, FH II, HIGH FH, COMBO I, COMBO II, LONG TERM
LDL-C	< 130 mg/dL; ≥ 130 mg/dL	All except HIGH FH
LDL-C	< 190 mg/dL; ≥ 190 mg/dL	HIGH FH

Subgroup analysis on the primary efficacy endpoints was performed using a MMRM in the ITT population with treatment, visit, baseline LDL-C and treatment by visit interaction as covariates in the model. The analysis was performed within the individual level that defined the subgroup. Formal tests for interaction were not performed.

Results from the subgroup analysis are summarized in Table 33 to Table 41 in the Appendix. Findings were found to be consistent across levels of the subgroups. A noteworthy finding was observed for sex. It was the only factor found that consistently had the treatment effect greater in one level of the subgroup versus the other, with the estimated effect being larger in all 10 trials for males than for females. No systematic difference in average baseline LDL-C values between males and females were observed across trials, which could have possibly explained the difference. Compared to the females, males had greater levels in one trial (HIGH FH), similar levels in two trials (FH I, MONO) and lower levels in the other seven trials.

5 SUMMARY AND CONCLUSIONS

5.1 Summary and Conclusions

In total, there were 5296 subjects randomized in the 10 trials reviewed in this submission, with 3188 assigned to receive alicumab. The primary endpoint in all 10 trials was percent change in calculated LDL-C from baseline to week 24. Two trials investigated the 150 mg dose throughout the study; the other trials allowed for up-titration from the 75 mg dose to the 150 mg dose if LDL-C at week 8 was not below a particular threshold. Alicumab had greater LDL-C reduction than control (active or placebo) in all trials. The excess reduction at week 24 for alicumab was statistically significant at the prespecified alpha level in nine trials and in a tenth trial significant for two of the four primary comparisons. The comparisons in OPTIONS II that were not significant for superior % LDL-C change were alicumab + rosuvastatin 20 mg vs. rosuvastatin 40 mg, and alicumab + rosuvastatin 20 mg vs. ezetimibe + rosuvastatin 20 mg. The overall findings were found to be consistent across the applicant's primary efficacy analysis and our preferred analysis that more appropriately represented missing data for subjects that stopped treatment early.

I have concern the applicant's analysis exaggerates the magnitude of the ITT effect at week 24. The issue is how missing data were represented in the analysis for subjects that stopped treatment prior to the week 24 visit. After stopping study drug, data from phase 2 and 3 trials show that LDL-C levels tended to return to baseline levels. However, the applicant's primary analysis effectively assumed the LDL-C lowering would be sustained after stopping drug early.

The amount of missing data ranged between 6% and 13% at week 24 across trials. Given the amount of missing data and the magnitude of the treatment effect, it is unlikely missing data could be such that it altered the study conclusions.

Based on our preferred analysis, the estimated excess reduction in LDL-C ranged between 36% and 58% compared to placebo when added to a maximally tolerated statin with or without other LMTs. Compared to ezetimibe, the estimated excess reduction was 28% when added to a maximally tolerated statin alone, between 21% and 23% when added to a less than maximal statin dose, and about 30% when given without a statin.

An interaction appears to exist for sex, with the estimated effect being larger in all 10 trials for males than the estimated effect for females. It is unclear whether this difference could be explained by systematic differences in baseline LDL-C between males and females.

A total of 93 MACE were observed in 10 trials, 58 in the alicumab group and 35 in the control arms. The majority of events came from LONG TERM (52 MACE), with fewer MACE for alicumab compared to placebo (1.7% vs. 3.2%). In an integrated analysis of placebo-controlled trials, the frequency of MACE was smaller for alicumab (1.8% vs. 2.4%). There were too few MACE in the trials reviewed to conclude with high statistical confidence that alicumab provides CV benefit.

The main statistical issues in this submission are:

- LDL-C is a surrogate endpoint. There were too few CV events observed in the phase 3 trials to allow for a robust evaluation of whether alicumab provides CV benefit or not.
- Each trial only investigated one alicumab dosing regimen. The trials therefore do not support unconfounded inferences of the additional LDL lowering (if any) of either up-titrating or initiating treatment at 150 mg instead of 75 mg.

5.2 Labeling Recommendations

Below are high-level recommendations for the label included with the BLA submission.

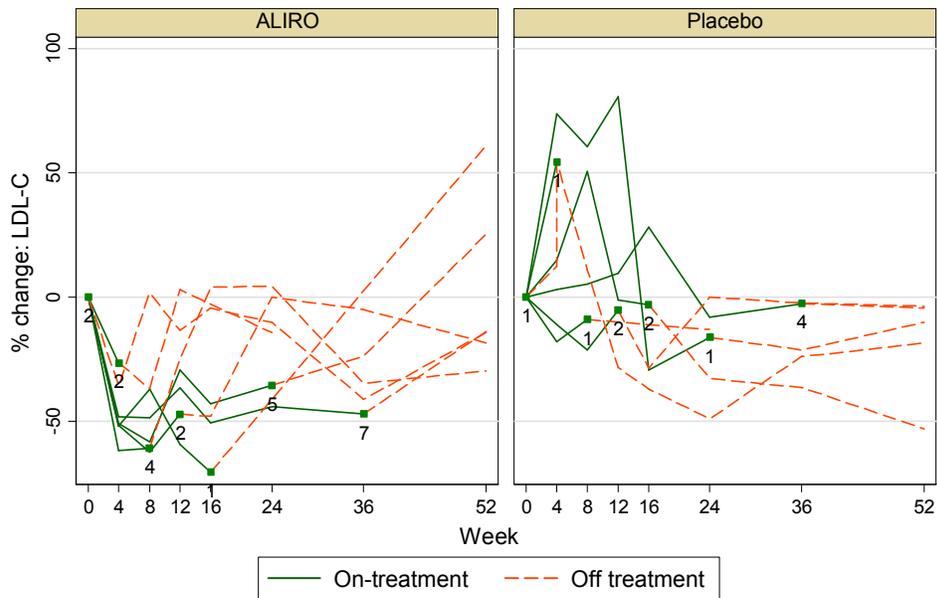
- I support previous FDA recommendations (See Section 2.1.2) that data from active-controlled trials not be included in the label until data from the CVOT have been reviewed and demonstrates that alicumab provides cardiovascular benefit.
- In the absence of a CVOT, the indication should be narrowed to include patients on a background of maximally tolerated statin dose.

-  (b) (4)

APPENDICES

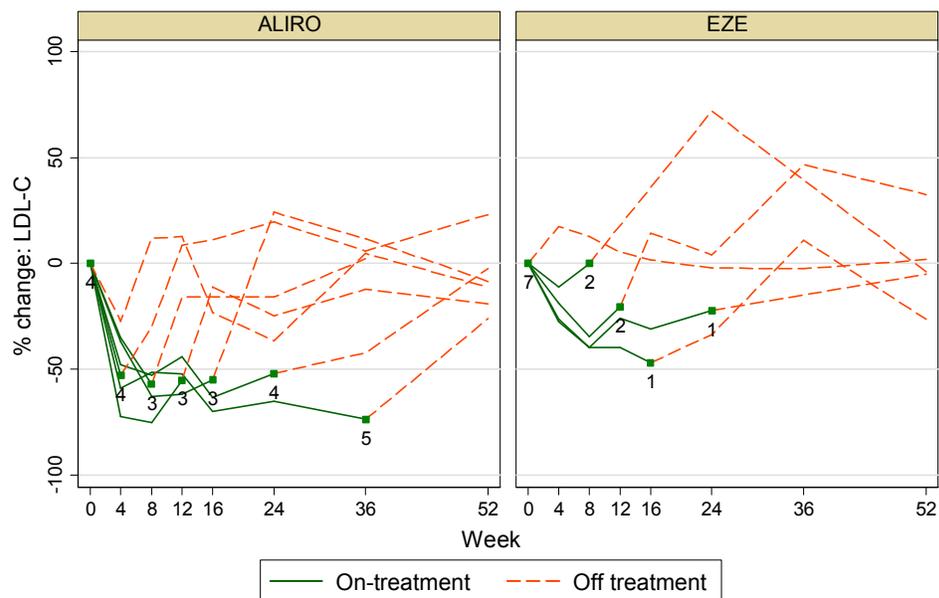
Additional Plots

Figure 13. Mean profile (% change: LDL-C) in subset with data after prematurely discontinuing treatment by treatment arm and timing of last on-treatment measurement (COMBO I)



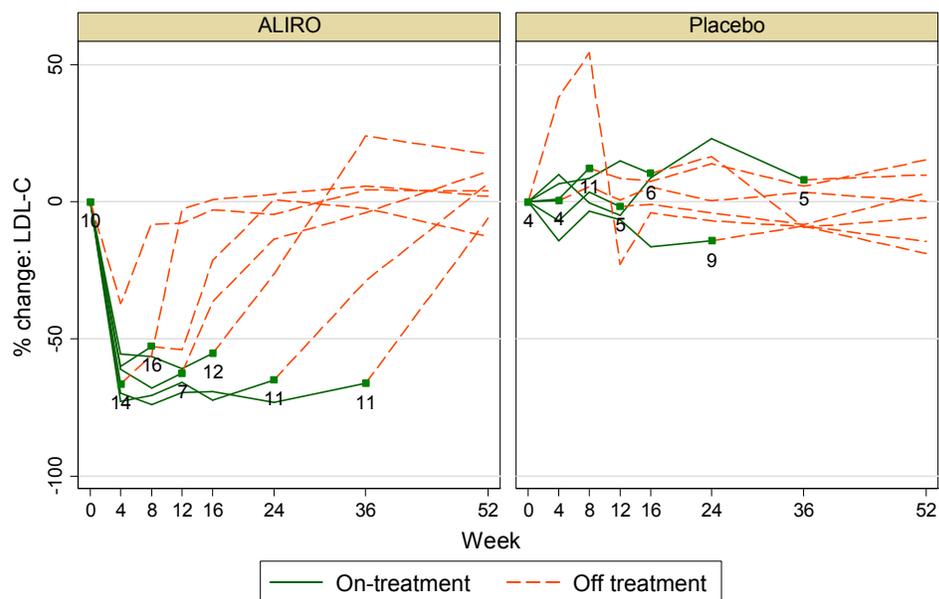
Note: The number below the marker represents the number of subjects that had their last on-treatment assessment at that visit. The number of subjects that provided data for the other visits could be different.

Figure 14. Mean profile (% change: LDL-C) in subset with data after prematurely discontinuing treatment by treatment arm and timing of last on-treatment measurement (COMBO II)



Note: The number below the marker represents the number of subjects that had their last on-treatment assessment at that visit. The number of subjects that provided data for the other visits could be different.

Figure 15. Mean profile (% change: LDL-C) in subset with data after prematurely discontinuing treatment by treatment arm and timing of last on-treatment measurement (LONG TERM)



Note: The number below the marker represents the number of subjects that had their last on-treatment assessment at that visit. The number of subjects that provided data for the other visits could be different.

Figure 16. Boxplot of baseline LDL-C (mg/dL) values by alicrocumab titration status

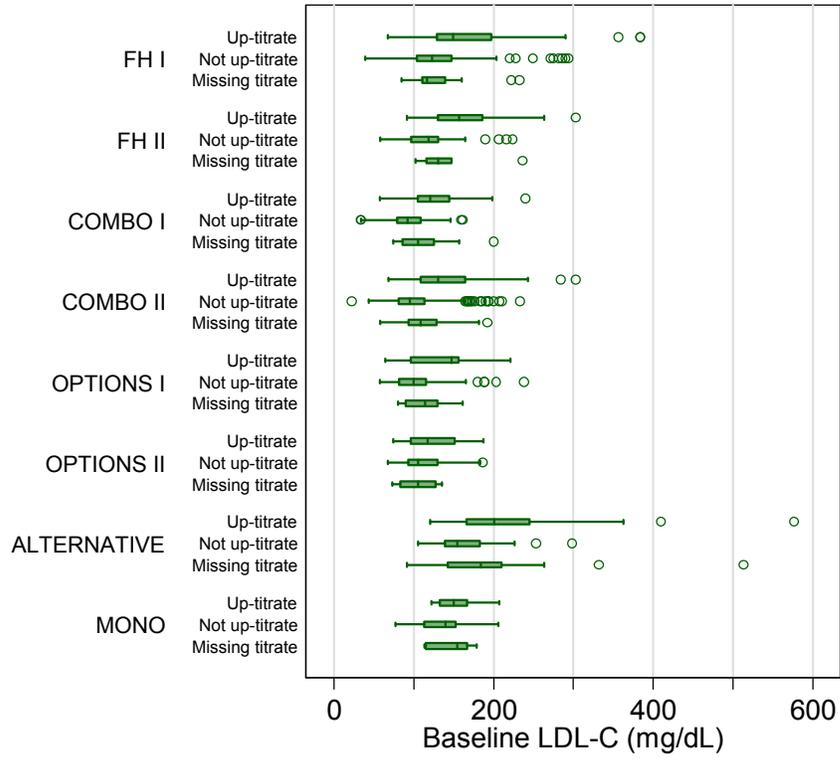


Figure 17. Mean profiles of % LDL-C change (left panel) and LDL-C (mg/dL; right panel) while on-treatment for those that up-titrated (dashed line) and did not up-titrate (solid line) for trials with a less than maximal dose of statin as background therapy (OPTIONS I and OPTIONS II).

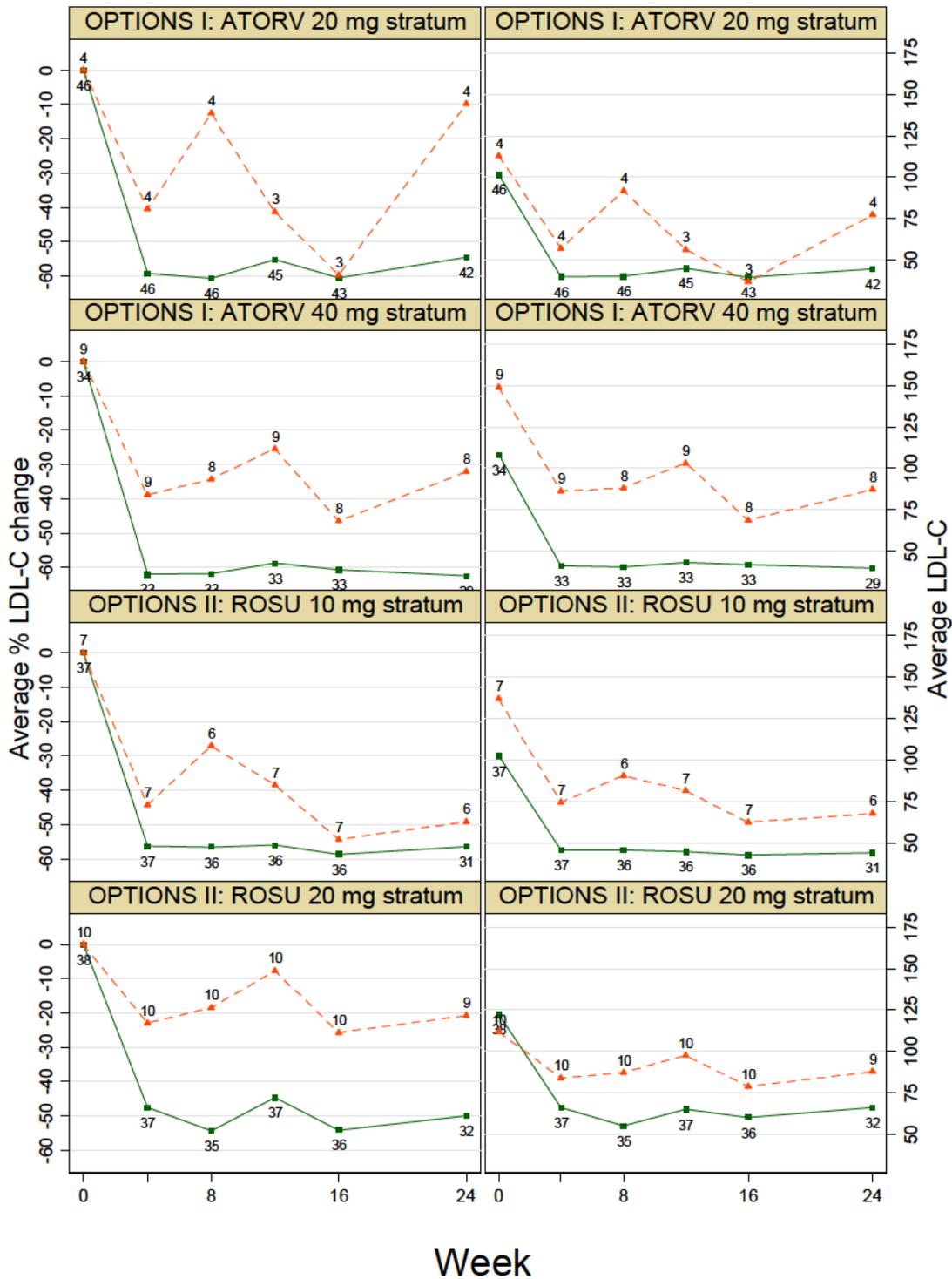
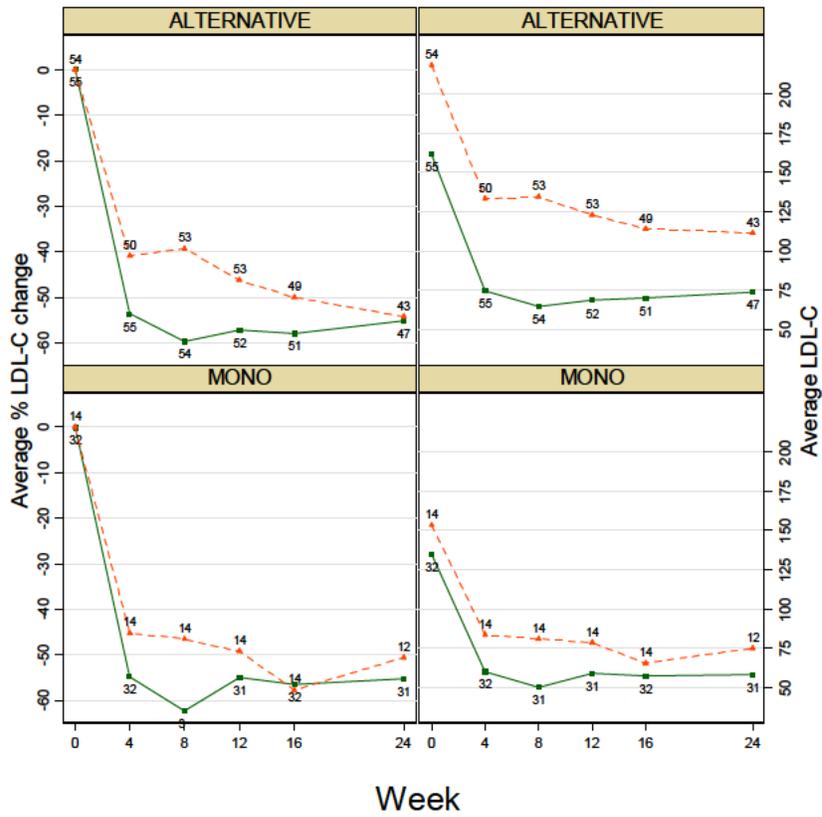


Figure 18. Mean profiles of % LDL-C change (left panel) and LDL-C (mg/dL; right panel) while on-treatment for those that up-titrated (dashed line) and did not up-titrate (solid line) for trials without statin background (ALTERNATIVE and MONO)



Additional Tables

Table 19. Overall adjudicated MACE and components by trial (TEAE period + post-treatment period)

Treatment Arm (N=)	CHD death	Total MI	Total Stroke	Angina	Composite
FH I (EFC12492)					
Aliro 75mg/150mg (N=323)	2	2	1	1	5
Placebo (N=163)	0	0	0	0	0
FH II (R727-CL-1112)					
Aliro 75mg/150mg (N=167)	0	0	0	0	0
Placebo (N=82)	0	1	0	0	1
HIGH FH (EFC12732)					
Aliro 150mg (N=72)	0	4	0	0	4
Placebo (N=35)	0	0	0	0	0
COMBO I (EFC11568)					
Aliro 75mg/150 mg (N=209)	2	2	2	0	5
Placebo (N=107)	1	1	0	0	2
LONG TERM (LTS11717)					
Aliro 150mg (N=1553)	6	13	10	0	27
Placebo (N=788)	6	17	3	1	25
COMBO II (EFC11569)					
Aliro 75mg/150mg (N=479)	2	12	1	1	16
Ezetimibe (N=241)	2	3	1	0	5
OPTIONS I (R727-CL-1110):					
Atorvastatin 20mg stratum					
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	0	0	0	0	0
Atorvastatin 40mg (N=57)	0	0	0	0	0
Atorvastatin 20mg + Ezetimibe (N=55)	0	0	0	0	0
Atorvastatin 40 mg stratum					
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	0	0	0	0	0
Atorvastatin 40mg + Ezetimibe (N=47)	0	0	0	0	0
Atorvastatin 80mg (N=47)	0	0	0	0	0
Rosuvastatin 40mg (N=45)	0	0	0	0	0
OPTIONS II (R727-CL-1118):					
Rosuvastatin 10mg stratum					
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	0	0	0	0	0
Rosuvastatin 10mg + Ezetimibe (N=48)	0	0	0	0	0
Rosuvastatin 20mg (N=48)	0	0	1	0	1
Rosuvastatin 20mg stratum					
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	0	0	0	0	0
Rosuvastatin 20mg + Ezetimibe (N=53)	0	1	0	0	1
Rosuvastatin 40mg (N=53)	0	0	0	0	0
ALTERNATIVE (R727-CL-1119)					
Aliro 75mg/150mg (N=126)	0	1	0	0	1
Atorvastatin 20mg (N=63)	0	0	0	0	0
Ezetimibe (N=125)	0	0	0	0	0
MONO (EFC11716)					
Aliro 75mg/150mg (N=52)	0	0	0	0	0
Ezetimibe (N=51)	0	0	0	0	0

Table 20. Results of hierarchical testing: comparison with placebo

Study Order	FH I	FH II	HIGH FH	COMBO I	LONG TERM
1	LDL-C (24, ITT, ITT)*				
2	LDL-C (24, MITT, OT)*				
3	LDL-C (12, ITT, ITT)*				
4	LDL-C (12, MITT, OT)*				
5	APO-B (24, ITT, ITT)*	APO-B (24, ITT, ITT)*	APO-B (24, ITT, ITT)*	APO-B (24, ITT, ITT)*	LDLMMGDL (24, ITT, ITT)*
6	APO-B (24, MITT, OT)*	APO-B (24, MITT, OT)*	APO-B (24, MITT, OT)*	APO-B (24, MITT, OT)*	APO-B (24, ITT, ITT)*
7	NON HDL-C (24, ITT, ITT)*	APO-B (24, MITT, OT)*			
8	NON HDL-C (24, MITT, OT)*	NON HDL-C (24, ITT, ITT)*			
9	TOTAL-C (24, ITT, ITT)*	TOTAL-C (24, ITT, ITT)*	TOTAL-C (24, ITT, ITT)*	TOTAL-C (24, ITT, ITT)*	NON HDL-C (24, MITT, OT)*
10	APO-B (12, ITT, ITT)*	APO-B (12, ITT, ITT)*	APO-B (12, ITT, ITT)*	APO-B (12, ITT, ITT)*	TOTAL-C (24, ITT, ITT)*
11	NON HDL-C (12, ITT, ITT)*	APO-B (12, ITT, ITT)*			
12	TOTAL-C (12, ITT, ITT)*	TOTAL-C (12, ITT, ITT)*	TOTAL-C (12, ITT, ITT)*	TOTAL-C (12, ITT, ITT)*	NON HDL-C (12, ITT, ITT)*
13	LDL-C (52, ITT, ITT)*	LDL-C (52, ITT, ITT)*	LDL-C (52, ITT, ITT)*	LDL-C (52, ITT, ITT)*	TOTAL-C (12, ITT, ITT)*
14	LDL-C (24, ITT, ITT)*				
15	LDL-C (24, MITT, OT)*				
16	LDL-C (24, ITT, ITT)*				
17	LDL-C (24, MITT, OT)*	LDL-C (24, MITT, OT)*	HDL-C (24, ITT, ITT)	HDL-C (24, ITT, ITT)*	HDL-C (24, MITT, OT)*
18	LP(A) (24, ITT, ITT)*	LP(A) (24, ITT, ITT)*	TG (24, ITT, ITT)	TG (24, ITT, ITT)	LP(A) (24, ITT, ITT)*
19	HDL-C (24, ITT, ITT)*	HDL-C (24, ITT, ITT)*	APO A-1 (24, ITT, ITT)	APO A-1 (24, ITT, ITT)*	HDL-C (24, ITT, ITT)*
20	TG (24, ITT, ITT)*	TG (24, ITT, ITT)*	LP(A) (12, ITT, ITT)*	LP(A) (12, ITT, ITT)*	TG (24, ITT, ITT)*
21	APO A-1 (24, ITT, ITT)*	APO A-1 (24, ITT, ITT)*	HDL-C (12, ITT, ITT)	HDL-C (12, ITT, ITT)*	APO A-1 (24, ITT, ITT)*
22	LP(A) (12, ITT, ITT)*	LP(A) (12, ITT, ITT)*	TG (12, ITT, ITT)	TG (12, ITT, ITT)*	LP(A) (12, ITT, ITT)*
23	HDL-C (12, ITT, ITT)*	HDL-C (12, ITT, ITT)*	APO A-1 (12, ITT, ITT)	APO A-1 (12, ITT, ITT)*	HDL-C (12, ITT, ITT)*
24	TG (12, ITT, ITT)*	TG (12, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	TG (12, ITT, ITT)*
25	APO A-1 (12, ITT, ITT)*	APO A-1 (12, ITT, ITT)	LDL-C (24, MITT, OT)*	LDL-C (24, MITT, OT)*	APO A-1 (12, ITT, ITT)*
26			LDL-C (24, ITT, ITT)*		

* *p*-value below the nominal alpha level to control study-wise type-I error.
 Note: Shaded boxes correspond to statistically significant differences from the hierarchical testing approach to control study-wise type-I error at 5%.

Table 21. Results of hierarchical testing: comparison with ezetimibe

Study Order	COMBO II	OPTIONS I – Atorva 20 mg stratrum	OPTIONS I – Atorva 40 mg stratrum	OPTIONS II – Rosuva 10 mg stratrum	OPTIONS II – Rosuva 20 mg stratrum	ALTER-NATIVE	MONO
1	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*
2	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (12, ITT, ITT)*
3	LDL-C (12, ITT, ITT)*	LDL-C (12, ITT, ITT)*	LDL-C (12, ITT, ITT)*	LDL-C (12, ITT, ITT)*	LDL-C (12, ITT, ITT)	LDL-C (12, ITT, ITT)*	Apo B (24, ITT, ITT)*
4	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)	LDL-C (12, mITT, OT)*	non HDL-C (24, ITT, ITT)*
5	Apo B (24, ITT, ITT)*	Apo B (24, ITT, ITT)*	Apo B (24, ITT, ITT)*	Apo B (24, ITT, ITT)*	Apo B (24, ITT, ITT)*	Apo B (24, ITT, ITT)*	total-C (24, ITT, ITT)*
6	Apo B (24, mITT, OT)*	Apo B (24, mITT, OT)*	Apo B (24, mITT, OT)*	Apo B (24, mITT, OT)*	Apo B (24, mITT, OT)*	Apo B (24, mITT, OT)*	Apo B (12, ITT, ITT)*
7	non HDL-C (24, ITT, ITT)*	non HDL-C (24, ITT, ITT)*	non HDL-C (24, ITT, ITT)*	non HDL-C (24, ITT, ITT)*	non HDL-C (24, ITT, ITT)	non HDL-C (24, ITT, ITT)*	non HDL-C (12, ITT, ITT)*
8	non HDL-C (24, mITT, OT)*	non HDL-C (24, mITT, OT)*	non HDL-C (24, mITT, OT)*	non HDL-C (24, mITT, OT)*	non HDL-C (24, mITT, OT)*	non HDL-C (24, mITT, OT)*	total-C (12, ITT, ITT)*
9	total-C (24, ITT, ITT)*	total-C (24, ITT, ITT)*	total-C (24, ITT, ITT)*	total-C (24, ITT, ITT)*	total-C (24, ITT, ITT)	total-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*
10	Apo B (12, ITT, ITT)*	Apo B (12, ITT, ITT)*	Apo B (12, ITT, ITT)*	Apo B (12, ITT, ITT)*	Apo B (12, ITT, ITT)*	Apo B (12, ITT, ITT)*	LDL-C (24, ITT, ITT)*
11	non HDL-C (12, ITT, ITT)*	non HDL-C (12, ITT, ITT)*	non HDL-C (12, ITT, ITT)*	non HDL-C (12, ITT, ITT)*	non HDL-C (12, ITT, ITT)	non HDL-C (12, ITT, ITT)*	Lp(a) (24, ITT, ITT)
12	total-C (12, ITT, ITT)*	total-C (12, ITT, ITT)*	total-C (12, ITT, ITT)*	total-C (12, ITT, ITT)*	total-C (12, ITT, ITT)	total-C (12, ITT, ITT)*	HDL-C (24, ITT, ITT)
13	LDL-C (52, ITT, ITT)*	LDL-C (24, ITT, ITT)	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)	LDL-C (24, ITT, ITT)*	LDL-C (12, ITT, ITT)*
14	LDL-C (24, ITT, ITT)*	LDL-C (24, mITT, OT)	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)	LDL-C (24, mITT, OT)*	Lp(a) (12, ITT, ITT)
15	LDL-C (24, mITT, OT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)*	LDL-C (24, ITT, ITT)	LDL-C (24, ITT, ITT)*	TG (24, ITT, ITT)
16	Lp(a) (24, ITT, ITT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)	LDL-C (24, mITT, OT)*	TG (12, ITT, ITT)*
17	HDL-C (24, ITT, ITT)*	HDL-C (24, ITT, ITT)	HDL-C (24, ITT, ITT)	HDL-C (24, ITT, ITT)	HDL-C (24, ITT, ITT)*	HDL-C (24, ITT, ITT)*	Apo A-1 (24, ITT, ITT)*
18	TG (24, ITT, ITT)	TG (24, ITT, ITT)	TG (24, ITT, ITT)	TG (24, ITT, ITT)	TG (24, ITT, ITT)	HDL-C (24, ITT, ITT)	Apo A-1 (12, ITT, ITT)*
19	Apo A-1 (24, ITT, ITT)*	Apo A-1 (24, ITT, ITT)*	Apo A-1 (24, ITT, ITT)*	Apo A-1 (24, ITT, ITT)	Apo A-1 (24, ITT, ITT)*	TG (24, ITT, ITT)	
20	Lp(a) (12, ITT, ITT)*	HDL-C (12, ITT, ITT)	HDL-C (12, ITT, ITT)	HDL-C (12, ITT, ITT)	HDL-C (12, ITT, ITT)	Apo A-1 (24, ITT, ITT)	
21	HDL-C (12, ITT, ITT)*	TG (12, ITT, ITT)	TG (12, ITT, ITT)	TG (12, ITT, ITT)	TG (12, ITT, ITT)	Lp(a) (12, ITT, ITT)*	
22	TG (12, ITT, ITT)	Apo A-1 (12, ITT, ITT)	Apo A-1 (12, ITT, ITT)*	Apo A-1 (12, ITT, ITT)	Apo A-1 (12, ITT, ITT)*	HDL-C (12, ITT, ITT)	
23	Apo A-1 (12, ITT, ITT)*					TG (12, ITT, ITT)	
24						Apo A-1 (12, ITT, ITT)	

*p-value below the nominal alpha level to control study-wise type-I error.

Note: Shaded boxes correspond to statistically significant differences from the hierarchical testing approach to control study-wise type-I error at 5%.

Table 22. Results of hierarchical testing: comparison with non-ezetimibe active controls

Study	OPTIONS I			OPTIONS II	
	Atorva 20 mg	Atorva 40 mg		Rosuva 10 mg	Rosuva 20 mg
Control Order	Atorva 40 mg	Atorva 80 mg	Rosuva 40 mg	Rosuva 20 mg	Rosuva 40 mg
1	LDL-C (24, IIT, IIT)*	LDL-C (24, IIT, IIT)*	LDL-C (24, IIT, IIT)*	LDL-C (24, IIT, IIT)*	LDL-C (24, IIT, IIT)
2	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)*	LDL-C (24, mITT, OT)
3	LDL-C (12, IIT, IIT)*	LDL-C (12, IIT, IIT)*	LDL-C (12, IIT, IIT)*	LDL-C (12, IIT, IIT)*	LDL-C (12, IIT, IIT)
4	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)*	LDL-C (12, mITT, OT)
5	Apo B (24, IIT, IIT)*				
6	Apo B (24, mITT, OT)*				
7	non HDL-C (24, IIT, IIT)*				
8	non HDL-C (24, mITT, OT)*				
9	total-C (24, IIT, IIT)*	total-C (24, IIT, IIT)*	total-C (24, IIT, IIT)*	total-C (24, IIT, IIT)*	total-C (24, IIT, IIT)
10	Apo B (12, IIT, IIT)*				
11	non HDL-C (12, IIT, IIT)*	non HDL-C (12, IIT, IIT)			
12	total-C (12, IIT, IIT)*	total-C (12, IIT, IIT)*	total-C (12, IIT, IIT)*	total-C (12, IIT, IIT)*	total-C (12, IIT, IIT)
13	LDL-C (24, IIT, IIT)*				
14	LDL-C (24, mITT, OT)*				
15	LDL-C (24, IIT, IIT)*				
16	LDL-C (24, mITT, OT)*				
17	HDL-C (24, IIT, IIT)				
18	TG (24, IIT, IIT)	TG (24, IIT, IIT)	TG (24, IIT, IIT)*	TG (24, IIT, IIT)	TG (24, IIT, IIT)
19	Apo A-1 (24, IIT, IIT)*	Apo A-1 (24, IIT, IIT)			
20					
21	HDL-C (12, IIT, IIT)*	HDL-C (12, IIT, IIT)	HDL-C (12, IIT, IIT)	HDL-C (12, IIT, IIT)	HDL-C (12, IIT, IIT)
22	TG (12, IIT, IIT)	TG (12, IIT, IIT)	TG (12, IIT, IIT)	TG (12, IIT, IIT)*	TG (12, IIT, IIT)
23	Apo A-1 (12, IIT, IIT)*	Apo A-1 (12, IIT, IIT)*	Apo A-1 (12, IIT, IIT)	Apo A-1 (12, IIT, IIT)	Apo A-1 (12, IIT, IIT)*

* *p*-value below the nominal alpha level to control study-wise type-I error.

Note: Shaded boxes correspond to statistically significant differences from the hierarchical testing approach to control study-wise type-I error at 5%.

Table 23. % ApoA1 change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	3%		5%	
Placebo (N=163)	0%	3% (0, 5)	0%	5% (2, 7)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	0%		3%	
Placebo (N=82)	-2%	2% (-1, 6)	-2%	4% (1, 7)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	5%		6%	
Placebo (N=35)	1%	4% (-2, 9)	2%	4% (-2, 9)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	4%		3%	
Placebo (N=107)	-2%	6% (2, 9)	-3%	6% (3, 9)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	5%		4%	
Placebo (N=788)	1%	4% (3, 5)	1%	3% (2, 4)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	2%		5%	
Ezetimibe (N=241)	-3%	4% (3, 6)	-1%	6% (4, 8)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	6%		9%	
Atorvastatin 40mg (N=57)	-1%	6% (1, 12)	0%	7% (1, 13)
Ezetimibe + Atorvastatin 20mg (N=55)	2%	4% (-2, 9)	1%	7% (0, 13)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	10%		6%	
Atorvastatin 80mg (N=47)	1%	8% (2, 14)	2%	4% (-3, 10)
Rosuvastatin 40mg (N=45)	5%	4% (-2, 10)	4%	1% (-6, 8)
Ezetimibe + Atorvastatin 40mg (N=47)	2%	8% (2, 14)	-1%	8% (1, 14)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	4%		7%	
Rosuvastatin 20mg (N=48)	4%	0% (-6, 7)	6%	1% (-5, 8)
Ezetimibe + Rosuvastatin 10mg (N=48)	2%	2% (-5, 8)	5%	2% (-6, 9)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	8%		6%	
Rosuvastatin 40mg (N=53)	2%	8% (2, 14)	4%	4% (-3, 10)
Ezetimibe + Rosuvastatin 20mg (N=53)	1%	7% (1, 13)	-1%	8% (1, 14)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	6%		5%	
Ezetimibe (N=125)	4%	2% (-1, 4)	3%	2% (-1, 6)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	2%		5%	
Ezetimibe (N=51)	-2%	4% (0, 8)	-1%	5% (1, 10)

[†]99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 24. % ApoB change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-34%		-41%	
Placebo (N=163)	3%	-38% (-41, -34)	5%	-46% (-50, -42)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-35%		-43%	
Placebo (N=82)	-1%	-35% (-39, -30)	-3%	-39% (-44, -35)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-39%		-39%	
Placebo (N=35)	-9%	-30% (-39, -21)	-9%	-30% (-40, -21)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-35%		-37%	
Placebo (N=107)	3%	-38% (-44, -33)	-1%	-36% (-41, -30)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-56%		-53%	
Placebo (N=788)	0%	-56% (-58, -54)	1%	-54% (-56, -52)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-40%		-41%	
Ezetimibe (N=241)	-17%	-22% (-26, -19)	-18%	-22% (-26, -19)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-38%		-34%	
Atorvastatin 40mg (N=57)	-7%	-31% (-41, -22)	-5%	-29% (-41, -18)
Ezetimibe + Atorvastatin 20mg (N=55)	-13%	-25% (-34, -16)	-10%	-24% (-36, -12)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-37%		-42%	
Atorvastatin 80mg (N=47)	-10%	-27% (-36, -17)	-4%	-38% (-51, -25)
Rosuvastatin 40mg (N=45)	-14%	-22% (-32, -12)	-11%	-31% (-44, -18)
Ezetimibe + Atorvastatin 40mg (N=47)	-19%	-16% (-25, -6)	-14%	-27% (-40, -14)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-36%		-37%	
Rosuvastatin 20mg (N=48)	-8%	-28% (-40, -16)	-7%	-29% (-43, -15)
Ezetimibe + Rosuvastatin 10mg (N=48)	-12%	-24% (-36, -12)	-9%	-26% (-40, -12)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-29%		-28%	
Rosuvastatin 40mg (N=53)	-13%	-15% (-26, -4)	-9%	-19% (-32, -6)
Ezetimibe + Rosuvastatin 20mg (N=53)	-15%	-14% (-26, -3)	-12%	-17% (-30, -4)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-36%		-36%	
Ezetimibe (N=125)	-12%	-25% (-29, -20)	-11%	-25% (-30, -20)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-37%		-37%	
Ezetimibe (N=51)	-12%	-26% (-31, -20)	-11%	-26% (-32, -19)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 25. % Cholesterol change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-28%		-31%	
Placebo (N=163)	4%	-32% (-36, -29)	7%	-39% (-42, -35)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-27%		-31%	
Placebo (N=82)	3%	-30% (-34, -25)	2%	-33% (-37, -28)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-33%		-33%	
Placebo (N=35)	-5%	-28% (-36, -19)	-5%	-28% (-37, -20)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-25%		-28%	
Placebo (N=107)	1%	-26% (-31, -22)	-3%	-25% (-29, -21)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-38%		-35%	
Placebo (N=788)	1%	-39% (-43, -35)	4%	-39% (-43, -35)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-29%		-29%	
Ezetimibe (N=241)	-15%	-14% (-17, -12)	-15%	-15% (-18, -12)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-29%		-27%	
Atorvastatin 40mg (N=57)	-7%	-23% (-30, -15)	-4%	-23% (-33, -13)
Ezetimibe + Atorvastatin 20mg (N=55)	-13%	-16% (-24, -8)	-11%	-16% (-26, -6)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-30%		-34%	
Atorvastatin 80mg (N=47)	-10%	-19% (-28, -11)	-5%	-29% (-39, -18)
Rosuvastatin 40mg (N=45)	-14%	-15% (-24, -7)	-12%	-22% (-32, -11)
Ezetimibe + Atorvastatin 40mg (N=47)	-18%	-10% (-18, -1)	-14%	-18% (-29, -8)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-29%		-29%	
Rosuvastatin 20mg (N=48)	-9%	-20% (-30, -11)	-8%	-20% (-32, -9)
Ezetimibe + Rosuvastatin 10mg (N=48)	-11%	-17% (-27, -8)	-6%	-22% (-33, -10)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-20%		-21%	
Rosuvastatin 40mg (N=53)	-13%	-6% (-15, 3)	-8%	-12% (-23, -1)
Ezetimibe + Rosuvastatin 20mg (N=53)	-14%	-6% (-15, 4)	-13%	-8% (-19, 3)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-33%		-32%	
Ezetimibe (N=125)	-12%	-21% (-24, -18)	-11%	-21% (-24, -17)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-30%		-30%	
Ezetimibe (N=51)	-12%	-18% (-23, -14)	-11%	-19% (-25, -13)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 26. % HDL change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	6%		9%	
Placebo (N=163)	2%	4% (1, 7)	1%	8% (5, 11)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	6%		6%	
Placebo (N=82)	2%	4% (1, 8)	-1%	7% (3, 11)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	8%		8%	
Placebo (N=35)	8%	-0% (-8, 8)	4%	4% (-3, 10)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	7%		4%	
Placebo (N=107)	-2%	9% (6, 13)	-4%	7% (4, 11)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	7%		5%	
Placebo (N=788)	2%	5% (1, 8)	1%	4% (1, 7)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	9%		9%	
Ezetimibe (N=241)	3%	6% (3, 8)	1%	8% (5, 11)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	5%		5%	
Atorvastatin 40mg (N=57)	-4%	7% (-1, 15)	1%	3% (-5, 11)
Ezetimibe + Atorvastatin 20mg (N=55)	-2%	6% (-2, 14)	0%	5% (-4, 13)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	8%		7%	
Atorvastatin 80mg (N=47)	3%	6% (-3, 14)	5%	3% (-6, 12)
Rosuvastatin 40mg (N=45)	4%	4% (-5, 13)	5%	2% (-7, 11)
Ezetimibe + Atorvastatin 40mg (N=47)	5%	4% (-5, 12)	3%	6% (-3, 15)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	6%		9%	
Rosuvastatin 20mg (N=48)	1%	5% (-3, 13)	2%	8% (-1, 16)
Ezetimibe + Rosuvastatin 10mg (N=48)	0%	6% (-3, 14)	4%	5% (-3, 14)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	8%		7%	
Rosuvastatin 40mg (N=53)	2%	7% (-1, 15)	3%	5% (-3, 14)
Ezetimibe + Rosuvastatin 20mg (N=53)	3%	5% (-3, 13)	-2%	9% (1, 17)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	9%		8%	
Ezetimibe (N=125)	8%	1% (-2, 5)	7%	1% (-3, 6)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	9%		6%	
Ezetimibe (N=51)	2%	7% (2, 13)	2%	4% (-1, 10)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 27. % LDL-C change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-44%		-49%	
Placebo (N=163)	6%	-49% (-54, -44)	9%	-58% (-63, -53)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-44%		-49%	
Placebo (N=82)	5%	-48% (-55, -42)	3%	-51% (-58, -45)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-47%		-46%	
Placebo (N=35)	-7%	-40% (-51, -29)	-7%	-39% (-51, -27)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-46%		-48%	
Placebo (N=107)	1%	-47% (-54, -41)	-2%	-46% (-52, -39)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-63%		-61%	
Placebo (N=788)	1%	-65% (-67, -62)	1%	-62% (-64, -59)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-51%		-51%	
Ezetimibe (N=241)	-22%	-29% (-34, -25)	-21%	-30% (-34, -25)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-48%		-44%	
Atorvastatin 40mg (N=57)	-9%	-40% (-54, -26)	-5%	-39% (-56, -22)
Ezetimibe + Atorvastatin 20mg (N=55)	-23%	-26% (-40, -12)	-20%	-24% (-40, -7)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-51%		-55%	
Atorvastatin 80mg (N=47)	-15%	-36% (-48, -24)	-5%	-49% (-65, -34)
Rosuvastatin 40mg (N=45)	-23%	-27% (-39, -16)	-21%	-33% (-48, -17)
Ezetimibe + Atorvastatin 40mg (N=47)	-29%	-21% (-33, -9)	-22%	-31% (-47, -16)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-50%		-50%	
Rosuvastatin 20mg (N=48)	-17%	-32% (-50, -15)	-16%	-33% (-55, -11)
Ezetimibe + Rosuvastatin 10mg (N=48)	-17%	-31% (-49, -14)	-11%	-38% (-60, -16)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-33%		-37%	
Rosuvastatin 40mg (N=53)	-21%	-11% (-28, 6)	-15%	-21% (-42, 0)
Ezetimibe + Rosuvastatin 20mg (N=53)	-19%	-14% (-31, 3)	-12%	-25% (-46, -3)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-47%		-45%	
Ezetimibe (N=125)	-16%	-31% (-37, -26)	-15%	-30% (-36, -24)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-48%		-47%	
Ezetimibe (N=51)	-20%	-28% (-36, -21)	-16%	-32% (-40, -23)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 28. % Lp(a) change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-21%		-25%	
Placebo (N=163)	-4%	-17% (-22, -13)	-7%	-18% (-23, -13)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-25%		-30%	
Placebo (N=82)	-6%	-19% (-25, -13)	-10%	-20% (-26, -14)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-23%		-24%	
Placebo (N=35)	-2%	-22% (-34, -9)	-9%	-15% (-27, -3)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-20%		-21%	
Placebo (N=107)	0%	-20% (-26, -13)	-6%	-15% (-21, -8)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-28%		-29%	
Placebo (N=788)	-3%	-25% (-27, -23)	-4%	-26% (-28, -23)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-22%		-28%	
Ezetimibe (N=241)	1%	-23% (-27, -19)	-6%	-22% (-26, -17)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-24%		-24%	
Atorvastatin 40mg (N=57)	-12%	-12% (-27, 2)	-20%	-3% (-18, 11)
Ezetimibe + Atorvastatin 20mg (N=55)	-5%	-19% (-33, -4)	-11%	-13% (-28, 2)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-28%		-31%	
Atorvastatin 80mg (N=47)	-2%	-26% (-43, -10)	-10%	-21% (-36, -6)
Rosuvastatin 40mg (N=45)	12%	-39% (-56, -23)	-5%	-26% (-40, -12)
Ezetimibe + Atorvastatin 40mg (N=47)	8%	-36% (-52, -20)	0%	-31% (-46, -16)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-21%		-28%	
Rosuvastatin 20mg (N=48)	-1%	-20% (-32, -8)	-4%	-24% (-39, -9)
Ezetimibe + Rosuvastatin 10mg (N=48)	-4%	-17% (-29, -4)	-4%	-24% (-39, -8)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-16%		-23%	
Rosuvastatin 40mg (N=53)	4%	-20% (-35, -5)	-5%	-17% (-35, -0)
Ezetimibe + Rosuvastatin 20mg (N=53)	8%	-24% (-39, -9)	-6%	-17% (-34, 0)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-22%		-26%	
Ezetimibe (N=125)	-5%	-17% (-23, -11)	-7%	-19% (-26, -12)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-17%		-17%	
Ezetimibe (N=51)	-14%	-3% (-13, 7)	-12%	-4% (-15, 6)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 29. % Non-HDL-C at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-38%		-43%	
Placebo (N=163)	5%	-44% (-48, -39)	10%	-52% (-57, -48)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-38%		-43%	
Placebo (N=82)	4%	-42% (-48, -36)	3%	-46% (-52, -40)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-41%		-42%	
Placebo (N=35)	-7%	-34% (-45, -24)	-6%	-36% (-46, -25)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-37%		-39%	
Placebo (N=107)	3%	-40% (-46, -34)	-2%	-37% (-43, -31)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-54%		-52%	
Placebo (N=788)	1%	-55% (-57, -53)	1%	-52% (-54, -50)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-43%		-42%	
Ezetimibe (N=241)	-21%	-22% (-26, -18)	-19%	-23% (-27, -19)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-41%		-37%	
Atorvastatin 40mg (N=57)	-7%	-34% (-44, -23)	-6%	-30% (-44, -17)
Ezetimibe + Atorvastatin 20mg (N=55)	-17%	-23% (-34, -13)	-15%	-22% (-35, -8)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-43%		-48%	
Atorvastatin 80mg (N=47)	-13%	-29% (-40, -18)	-7%	-41% (-55, -27)
Rosuvastatin 40mg (N=45)	-20%	-23% (-34, -11)	-18%	-30% (-44, -16)
Ezetimibe + Atorvastatin 40mg (N=47)	-27%	-15% (-26, -4)	-20%	-26% (-41, -12)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-42%		-43%	
Rosuvastatin 20mg (N=48)	-12%	-30% (-43, -17)	-11%	-31% (-47, -15)
Ezetimibe + Rosuvastatin 10mg (N=48)	-16%	-25% (-38, -12)	-10%	-32% (-49, -15)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-30%		-31%	
Rosuvastatin 40mg (N=53)	-18%	-12% (-25, 1)	-11%	-20% (-36, -5)
Ezetimibe + Rosuvastatin 20mg (N=53)	-19%	-12% (-24, 1)	-14%	-18% (-34, -2)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-42%		-40%	
Ezetimibe (N=125)	-16%	-26% (-30, -21)	-15%	-25% (-30, -21)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-43%		-41%	
Ezetimibe (N=51)	-17%	-26% (-32, -19)	-15%	-25% (-33, -18)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 30. % TG change at weeks 12 and 24 (ITT population; the applicants MMRM)

	Week 12		Week 24	
	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-8%		-10%	
Placebo (N=163)	2%	-10% (-15, -4)	6%	-16% (-21, -11)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-8%		-10%	
Placebo (N=82)	1%	-9% (-16, -1)	0%	-11% (-17, -4)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-9%		-11%	
Placebo (N=35)	-4%	-5% (-17, 7)	-2%	-9% (-20, 3)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-11%		-6%	
Placebo (N=107)	3%	-14% (-21, -7)	-5%	-1% (-8, 7)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-17%		-16%	
Placebo (N=788)	1%	-18% (-20, -15)	2%	-17% (-20, -15)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-14%		-13%	
Ezetimibe (N=241)	-15%	2% (-2, 6)	-13%	-0% (-5, 5)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-12%		-12%	
Atorvastatin 40mg (N=57)	-5%	-8% (-23, 8)	-7%	-5% (-19, 8)
Ezetimibe + Atorvastatin 20mg (N=55)	1%	-13% (-28, 2)	-3%	-9% (-23, 5)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-12%		-19%	
Atorvastatin 80mg (N=47)	-5%	-7% (-22, 7)	-7%	-12% (-27, 3)
Rosuvastatin 40mg (N=45)	-4%	-8% (-23, 6)	0%	-19% (-33, -4)
Ezetimibe + Atorvastatin 40mg (N=47)	-17%	5% (-10, 19)	-14%	-5% (-20, 10)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-14%		-11%	
Rosuvastatin 20mg (N=48)	8%	-22% (-37, -8)	-2%	-9% (-25, 7)
Ezetimibe + Rosuvastatin 10mg (N=48)	-8%	-6% (-21, 9)	-8%	-3% (-19, 14)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-10%		-9%	
Rosuvastatin 40mg (N=53)	-3%	-7% (-21, 7)	-10%	1% (-14, 16)
Ezetimibe + Rosuvastatin 20mg (N=53)	-12%	2% (-12, 17)	-11%	2% (-13, 18)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-8%		-9%	
Ezetimibe (N=125)	-9%	1% (-6, 9)	-4%	-6% (-13, 2)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-12%		-12%	
Ezetimibe (N=51)	-2%	-10% (-19, -0)	-11%	-1% (-13, 10)

[†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 31. % Lp(a) change at weeks 12 and 24 (ITT population; FDA HL analysis)

	Week 12		Week 24	
	Median: % Δ	Difference: Alirocumab - Control (95% CI)	Median: % Δ	Difference: Alirocumab - Control (95% CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-20%		-21%	
Placebo (N=163)	0%	-17% (-21, -12)	-2%	-15% (-20, -11)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-21%		-28%	
Placebo (N=82)	0%	-18% (-24, -12)	-9%	-20% (-26, -13)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-19%		-18%	
Placebo (N=35)	0%	-20% (-31, -7)	-5%	-10% (-20, 0)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-13%		-15%	
Placebo (N=107)	0%	-15% (-21, -10)	0%	-11% (-17, -4)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-25%		-25%	
Placebo (N=788)	0%	-24% (-26, -21)	0%	-23% (-25, -20)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-18%		-23%	
Ezetimibe (N=241)	0%	-21% (-25, -18)	0%	-20% (-25, -16)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-21%		-17%	
Atorvastatin 40mg (N=57)	0%	-12% (-23, 0)	-11%	-1% (-13, 3)
Ezetimibe + Atorvastatin 20mg (N=55)	0%	-18% (-29, -7)	0%	-10% (-21, 0)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-17%		-20%	
Atorvastatin 80mg (N=47)	0%	-20% (-33, -7)	-9%	-11% (-24, 0)
Ezetimibe + Atorvastatin 40mg (N=47)	9%	-30% (-41, -19)	0%	-22% (-33, -11)
Rosuvastatin 40mg (N=45)	3%	-32% (-46, -18)	-4%	-16% (-29, -4)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-14%		-20%	
Rosuvastatin 20mg (N=48)	0%	-17% (-26, -9)	0%	-19% (-29, -8)
Ezetimibe + Rosuvastatin 10mg (N=48)	0%	-14% (-25, -5)	0%	-20% (-31, -8)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-7%		-10%	
Rosuvastatin 40mg (N=53)	0%	-18% (-29, -7)	-1%	-11% (-22, 0)
Ezetimibe + Rosuvastatin 20mg (N=53)	0%	-19% (-31, -7)	0%	-11% (-23, 0)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-20%		-18%	
Ezetimibe (N=125)	0%	-16% (-23, -10)	0%	-16% (-21, -11)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-5%		0%	
Ezetimibe (N=51)	-8%	0% (-9, 6)	0%	0% (-10, 3)

Table 32. % TG change at weeks 12 and 24 (ITT population; FDA HL analysis)

	Week 12		Week 24	
	Median: % Δ	Difference: Alirocumab - Control (95% CI)	Median: % Δ	Difference: Alirocumab - Control (95% CI)
FH I (EFC12492)				
Aliro 75mg/150mg (N=323)	-6%		-11%	
Placebo (N=163)	0%	-10% (-15, -4)	0%	-16% (-22, -11)
FH II (R727-CL-1112)				
Aliro 75mg/150mg (N=167)	-6%		-7%	
Placebo (N=82)	-1%	-7% (-14, 0)	0%	-10% (-17, -3)
HIGH FH (EFC12732)				
Aliro 150mg (N=72)	-7%		-8%	
Placebo (N=35)	-10%	1% (-13, 14)	4%	-9% (-23, 5)
COMBO I (EFC11568)				
Aliro 75mg/150 mg (N=209)	-12%		-7%	
Placebo (N=107)	1%	-15% (-22, -8)	0%	-3% (-11, 4)
LONG TERM (LTS11717)				
Aliro 150mg (N=1553)	-16%		-14%	
Placebo (N=788)	0%	-17% (-20, -14)	0%	-16% (-19, -13)
COMBO II (EFC11569)				
Aliro 75mg/150mg (N=479)	-13%		-12%	
Ezetimibe (N=241)	-14%	1% (-3, 5)	-12%	1% (-3, 6)
OPTIONS I (R727-CL-1110):				
Atorvastatin 20mg stratum				
Aliro 75mg/150mg + Atorvastatin 20mg (N=57)	-14%		-14%	
Atorvastatin 40mg (N=57)	-3%	-7% (-18, 3)	-2%	-2% (-13, 6)
Ezetimibe + Atorvastatin 20mg (N=55)	0%	-12% (-22, -1)	0%	-8% (-18, 1)
Atorvastatin 40 mg stratum				
Aliro 75mg/150mg + Atorvastatin 40mg (N=47)	-14%		-18%	
Atorvastatin 80mg (N=47)	-3%	-8% (-19, 4)	0%	-12% (-25, 0)
Ezetimibe + Atorvastatin 40mg (N=47)	-18%	3% (-7, 13)	-13%	-6% (-17, 5)
Rosuvastatin 40mg (N=45)	-3%	-9% (-20, 3)	-4%	-15% (-27, -3)
OPTIONS II (R727-CL-1118):				
Rosuvastatin 10mg stratum				
Aliro 75mg/150mg + Rosuvastatin 10mg (N=49)	-14%		-2%	
Rosuvastatin 20mg (N=48)	5%	-20% (-32, -9)	-4%	-8% (-20, 5)
Ezetimibe + Rosuvastatin 10mg (N=48)	-5%	-7% (-18, 5)	-2%	-1% (-16, 6)
Rosuvastatin 20mg stratum				
Aliro 75mg/150mg + Rosuvastatin 20mg (N=54)	-6%		-6%	
Rosuvastatin 40mg (N=53)	0%	-4% (-14, 6)	-10%	3% (-6, 13)
Ezetimibe + Rosuvastatin 20mg (N=53)	-13%	6% (-4, 16)	-10%	6% (-4, 18)
ALTERNATIVE (R727-CL-1119)				
Aliro 75mg/150mg (N=126)	-10%		-5%	
Ezetimibe (N=125)	-6%	-2% (-9, 6)	0%	-5% (-12, 2)
MONO (EFC11716)				
Aliro 75mg/150mg (N=52)	-12%		-8%	
Ezetimibe (N=51)	0%	-12% (-21, -3)	-8%	-2% (-12, 10)

Table 33. Subgroup analysis results by sex (females; males)

	Females			Males		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	127	-43%		163	-53%	
Placebo	63	8%	-51% (-59, -43)	86	10%	-63% (-70, -56)
FH II (R727-CL-1112)						
Aliro 75mg/150mg	76	-46%		81	-52%	
Placebo	36	4%	-50% (-59, -40)	42	2%	-54% (-63, -45)
HIGH FH (EFC12732)						
Aliro 150mg	34	-39%		29	-54%	
Placebo	13	-14%	-24% (-45, -3)	20	-2%	-52% (-66, -37)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	68	-44%		121	-51%	
Placebo	29	2%	-46% (-59, -33)	68	-3%	-47% (-55, -40)
LONG TERM (LTS11717)						
Aliro 150mg	506	-53%		880	-66%	
Placebo	280	3%	-56% (-61, -52)	428	-1%	-65% (-68, -62)
COMBO II (EFC11569)						
Aliro 75mg/150mg	105	-46%		323	-52%	
Ezetimibe	62	-20%	-26% (-35, -16)	159	-21%	-31% (-36, -26)
OPTIONS I (R727-CL-1110):						
Atorvastatin 20mg stratum						
Aliro 75mg/150mg + Atorva 20mg	21	-31%		29	-54%	
Atorva 40mg	17	-4%	-27% (-60, 7)	33	-5%	-49% (-66, -33)
Ezetimibe + Atorva 20mg	20	-14%	-18% (-50, 14)	23	-25%	-29% (-46, -11)
Atorvastatin 40 mg stratum						
Aliro 75mg/150mg + Atorva 40mg	13	-29%		28	-65%	
Atorva 80mg	13	-14%	-16% (-53, 22)	29	-2%	-64% (-77, -50)
Ezetimibe + Atorva 40mg	10	-12%	-18% (-60, 24)	34	-26%	-40% (-53, -26)
Rosuva 40mg	13	-13%	-16% (-55, 22)	31	-26%	-40% (-53, -27)
OPTIONS II (R727-CL-1118):						
Rosuvastatin 10mg stratum						
Aliro 75mg/150mg + Rosuva 10mg	15	-44%		27	-55%	
Rosuva 20mg	15	-18%	-26% (-58, 6)	30	-15%	-39% (-54, -24)
Ezetimibe + Rosuva 10mg	17	-12%	-31% (-62, -1)	20	-18%	-37% (-54, -21)
Rosuvastatin 20mg stratum						
Aliro 75mg/150mg + Rosuva 20mg	21	-29%		24	-43%	
Rosuva 40mg	13	-20%	-9% (-37, 19)	35	-14%	-29% (-67, 9)
Ezetimibe + Rosuva 20mg	20	-26%	-3% (-29, 22)	27	-1%	-42% (-82, -2)
ALTERNATIVE (R727-CL-1119)						
Aliro 75mg/150mg	51	-41%		64	-48%	
Ezetimibe	47	-14%	-27% (-37, -16)	61	-16%	-32% (-39, -25)
MONO (EFC11716)						
Aliro 75mg/150mg	22	-41%		27	-52%	
Ezetimibe	20	-19%	-23% (-35, -10)	26	-13%	-39% (-50, -28)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 34. Subgroup analysis results by age (< 65 years; ≥ 65 years)

	< 65 years			≥ 65 years		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	238	-49%		52	-48%	
Placebo	127	10%	-59% (-65, -53)	22	1%	-49% (-59, -39)
FH II (R727-CL-1112)						
Aliro 75mg/150mg	127	-48%		30	-50%	
Placebo	60	3%	-52% (-59, -44)	18	1%	-51% (-61, -41)
HIGH FH (EFC12732)						
Aliro 150mg	54	-45%		9	-49%	
Placebo	30	-8%	-37% (-50, -24)	3	4%	-54% (-89, -18)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	112	-45%		77	-53%	
Placebo	56	-3%	-41% (-50, -32)	41	0%	-53% (-62, -44)
LONG TERM (LTS11717)						
Aliro 150mg	872	-61%		514	-62%	
Placebo	446	0%	-61% (-64, -57)	262	2%	-64% (-68, -60)
COMBO II (EFC11569)						
Aliro 75mg/150mg	252	-48%		176	-55%	
Ezetimibe	139	-20%	-28% (-34, -21)	82	-22%	-33% (-40, -26)
OPTIONS I (R727-CL-1110):						
Atorvastatin 20mg stratum						
Aliro 75mg/150mg + Atorva 20mg	25	-41%		25	-49%	
Atorva 40mg	27	-1%	-40% (-57, -23)	23	-10%	-39% (-68, -9)
Ezetimibe + Atorva 20mg	22	-25%	-16% (-34, 2)	21	-15%	-34% (-62, -5)
Atorvastatin 40 mg stratum						
Aliro 75mg/150mg + Atorva 40mg	20	-54%		21	-54%	
Atorva 80mg	22	-2%	-51% (-71, -31)	20	-9%	-45% (-69, -20)
Ezetimibe + Atorva 40mg	25	-24%	-30% (-50, -9)	19	-21%	-33% (-58, -7)
Rosuva 40mg	31	-21%	-32% (-51, -13)	13	-18%	-36% (-64, -8)
OPTIONS II (R727-CL-1118):						
Rosuvastatin 10mg stratum						
Aliro 75mg/150mg + Rosuva 10mg	23	-49%		19	-54%	
Rosuva 20mg	22	-16%	-33% (-54, -12)	23	-17%	-37% (-57, -18)
Ezetimibe + Rosuva 10mg	27	-13%	-36% (-56, -16)	10	-22%	-32% (-56, -9)
Rosuvastatin 20mg stratum						
Aliro 75mg/150mg + Rosuva 20mg	36	-36%		9	-39%	
Rosuva 40mg	31	-14%	-22% (-46, 2)	17	-19%	-21% (-88, 47)
Ezetimibe + Rosuva 20mg	23	-16%	-21% (-46, 5)	24	-4%	-35% (-99, 29)
ALTERNATIVE (R727-CL-1119)						
Aliro 75mg/150mg	54	-45%		61	-46%	
Ezetimibe	63	-16%	-29% (-37, -20)	45	-15%	-31% (-39, -22)
MONO (EFC11716)						
Aliro 75mg/150mg	38	-47%		11	-49%	
Ezetimibe	38	-16%	-31% (-41, -22)	8	-14%	-35% (-56, -14)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 35. Subgroup analysis results by race (White; Other)

	White			Other		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	267	-48%		23	-53%	
Placebo	131	8%	-57% (-62, -51)	18	13%	-65% (-84, -47)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	154	-51%		35	-38%	
Placebo	81	-3%	-48% (-55, -41)	16	-1%	-37% (-55, -18)
LONG TERM (LTS11717)						
Aliro 150mg	1289	-62%		97	-53%	
Placebo	656	1%	-62% (-65, -60)	52	1%	-55% (-65, -44)
COMBO II (EFC11569)						
Aliro 75mg/150mg	362	-51%		66	-46%	
Ezetimibe	190	-21%	-31% (-36, -26)	31	-23%	-23% (-35, -12)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 36. Subgroup analysis results by US site (No; Yes)

	US Site: No			US Site: Yes		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	225	-49%		65	-50%	
Placebo	113	10%	-58% (-65, -52)	36	8%	-57% (-67, -47)
HIGH FH (EFC12732)						
Aliro 150mg	47	-46%		16	-46%	
Placebo	24	-2%	-44% (-57, -30)	9	-14%	-32% (-57, -6)
LONG TERM (LTS11717)						
Aliro 150mg	1092	-61%		294	-61%	
Placebo	571	0%	-61% (-63, -58)	137	6%	-66% (-73, -60)
COMBO II (EFC11569)						
Aliro 75mg/150mg Ezetimibe	305	-53%		123	-46%	
	163	-23%	-30% (-35, -25)	58	-15%	-31% (-41, -21)
OPTIONS I (R727-CL-1110):						
Atorvastatin 20mg stratum						
Aliro 75mg/150mg + Atorva 20mg	17	-47%		33	-42%	
Atorva 40mg	10	-8%	-38% (-62, -15)	40	-5%	-37% (-58, -16)
Ezetimibe + Atorva 20mg	6	-37%	-9% (-36, 18)	37	-17%	-25% (-46, -4)
Atorvastatin 40 mg stratum						
Aliro 75mg/150mg + Atorva 40mg	15	-68%		26	-44%	
Atorva 80mg	10	-1%	-67% (-85, -49)	32	-5%	-39% (-60, -19)
Ezetimibe + Atorva 40mg	13	-18%	-51% (-67, -34)	31	-25%	-19% (-41, 2)
Rosuva 40mg	17	-27%	-41% (-57, -26)	27	-20%	-24% (-46, -2)
OPTIONS II (R727-CL-1118):						
Rosuvastatin 10mg stratum						
Aliro 75mg/150mg + Rosuva 10mg	17	-52%		25	-50%	
Rosuva 20mg	16	-21%	-31% (-52, -11)	29	-14%	-36% (-55, -18)
Ezetimibe + Rosuva 10mg	17	-24%	-28% (-48, -9)	20	-12%	-38% (-58, -18)
Rosuvastatin 20mg stratum						
Aliro 75mg/150mg + Rosuva 20mg	16	-37%		29	-33%	
Rosuva 40mg	23	-16%	-21% (-50, 8)	25	-13%	-20% (-59, 18)
Ezetimibe + Rosuva 20mg	22	-25%	-12% (-42, 18)	25	-4%	-30% (-69, 9)
ALTERNATIVE (R727-CL-1119)						
Aliro 75mg/150mg	34	-40%		81	-47%	
Ezetimibe	36	-14%	-26% (-40, -12)	72	-16%	-31% (-38, -24)
MONO (EFC11716)						
Aliro 75mg/150mg	34	-40%		81	-47%	
Ezetimibe	36	-14%	-26% (-40, -12)	72	-16%	-31% (-38, -24)

* with baseline and week 24 data; [†]99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 37. Subgroup analysis results by BMI (< 30 kg/m²; ≥ 30 kg/m²)

	< 30 kg/m ²			≥ 30 kg/m ²		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	185	-47%		105	-52%	
Placebo	84	9%	-56% (-64, -48)	65	9%	-61% (-68, -53)
FH II (R727-CL-1112)						
Aliro 75mg/150mg	102	-49%		55	-49%	
Placebo	64	3%	-52% (-60, -44)	14	5%	-54% (-68, -41)
HIGH FH (EFC12732)						
Aliro 150mg	42	-43%		21	-52%	
Placebo	23	-8%	-35% (-50, -20)	10	-1%	-51% (-72, -30)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	71	-52%		117	-46%	
Placebo	43	-2%	-49% (-59, -40)	54	-2%	-44% (-53, -35)
LONG TERM (LTS11717)						
Aliro 150mg	777	-62%		605	-60%	
Placebo	365	1%	-63% (-66, -60)	341	0%	-60% (-64, -56)
COMBO II (EFC11569)						
Aliro 75mg/150mg	246	-53%		182	-48%	
Ezetimibe	117	-19%	-33% (-40, -27)	104	-22%	-26% (-32, -19)
OPTIONS I (R727-CL-1110):						
Atorvastatin 20mg stratum						
Aliro 75mg/150mg + Atorva 20mg	21	-51%		29	-42%	
Atorva 40mg	24	-11%	-39% (-66, -12)	26	1%	-43% (-63, -23)
Ezetimibe + Atorva 20mg	17	-23%	-27% (-55, 0)	26	-23%	-19% (-38, 1)
Atorvastatin 40 mg stratum						
Aliro 75mg/150mg + Atorva 40mg	22	-56%		19	-51%	
Atorva 80mg	21	2%	-57% (-82, -33)	21	-11%	-40% (-58, -22)
Ezetimibe + Atorva 40mg	21	-18%	-37% (-63, -12)	23	-27%	-24% (-42, -6)
Rosuva 40mg	25	-15%	-41% (-65, -17)	19	-28%	-23% (-42, -4)
OPTIONS II (R727-CL-1118):						
Rosuvastatin 10mg stratum						
Aliro 75mg/150mg + Rosuva 10mg	21	-59%		21	-43%	
Rosuva 20mg	21	-15%	-43% (-56, -31)	24	-16%	-26% (-52, -1)
Ezetimibe + Rosuva 10mg	14	-25%	-33% (-47, -20)	23	-7%	-36% (-61, -11)
Rosuvastatin 20mg stratum						
Aliro 75mg/150mg + Rosuva 20mg	27	-44%		18	-28%	
Rosuva 40mg	23	-12%	-32% (-52, -11)	25	-17%	-11% (-58, 37)
Ezetimibe + Rosuva 20mg	21	-27%	-17% (-38, 4)	26	1%	-29% (-77, 18)
ALTERNATIVE (R727-CL-1119)						
Aliro 75mg/150mg	73	-46%		42	-44%	
Ezetimibe	69	-16%	-30% (-38, -23)	39	-15%	-29% (-39, -19)
MONO (EFC11716)						
Aliro 75mg/150mg	28	-45%		21	-50%	
Ezetimibe	32	-13%	-32% (-43, -21)	14	-22%	-28% (-42, -14)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 38. Subgroup analysis results by diabetes status (non-diabetic; diabetic)

	Non-diabetic			Diabetic		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	261	-48%		29	-54%	
Placebo	131	10%	-59% (-64, -53)	18	3%	-57% (-69, -45)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	102	-53%		87	-43%	
Placebo	59	-2%	-50% (-58, -42)	38	-3%	-40% (-51, -29)
LONG TERM (LTS11717)						
Aliro 150mg	900	-62%		486	-60%	
Placebo	462	2%	-64% (-67, -61)	246	-1%	-59% (-63, -54)
COMBO II (EFC11569)						
Aliro 75mg/150mg	300	-52%		128	-47%	
Ezetimibe	153	-22%	-30% (-35, -25)	68	-18%	-29% (-39, -20)
OPTIONS I (R727-CL-1110):						
Atorvastatin 20mg stratum						
Aliro 75mg/150mg + Atorva 20mg	20	-37%		30	-49%	
Atorva 40mg	23	-9%	-28% (-57, 1)	27	-2%	-48% (-67, -29)
Ezetimibe + Atorva 20mg	21	-11%	-26% (-55, 3)	22	-29%	-20% (-40, -0)
Atorvastatin 40 mg stratum						
Aliro 75mg/150mg + Atorva 40mg	19	-60%		22	-46%	
Atorva 80mg	19	-2%	-59% (-80, -37)	23	-6%	-40% (-62, -18)
Ezetimibe + Atorva 40mg	30	-18%	-42% (-62, -22)	14	-33%	-13% (-39, 13)
Rosuva 40mg	26	-17%	-43% (-63, -23)	18	-29%	-17% (-42, 7)
OPTIONS II (R727-CL-1118):						
Rosuvastatin 10mg stratum						
Aliro 75mg/150mg + Rosuva 10mg	23	-51%		19	-51%	
Rosuva 20mg	20	-16%	-36% (-53, -18)	25	-17%	-34% (-59, -9)
Ezetimibe + Rosuva 10mg	19	-23%	-28% (-46, -11)	18	-5%	-46% (-72, -19)
Rosuvastatin 20mg stratum						
Aliro 75mg/150mg + Rosuva 20mg	32	-42%		13	-25%	
Rosuva 40mg	32	-18%	-24% (-56, 7)	16	-9%	-17% (-59, 26)
Ezetimibe + Rosuva 20mg	29	-2%	-40% (-73, -7)	18	-25%	-0% (-40, 40)
ALTERNATIVE (R727-CL-1119)						
Aliro 75mg/150mg	83	-44%		32	-48%	
Ezetimibe	87	-16%	-28% (-35, -22)	21	-12%	-36% (-51, -20)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 39. Subgroup analysis results by HeFH status (No; Yes)

	No			Yes		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
LONG TERM (LTS11717)						
Aliro 150mg	1136	-62%		250	-58%	
Placebo	576	0%	-62% (-65, -59)	132	4%	-61% (-66, -56)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 40. Subgroup analysis results by baseline statin intensity (Not high; High)

	Not High			High		
	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)	N*	LS Mean: % Δ	Difference: Alirocumab - Control (95% [†] CI)
FH I (EFC12492)						
Aliro 75mg/150mg	55	-47%		235	-49%	
Placebo	27	6%	-53% (-66, -40)	122	10%	-59% (-65, -53)
FH II (R727-CL-1112)						
Aliro 75mg/150mg	26	-50%		131	-48%	
Placebo	13	6%	-57% (-74, -39)	65	2%	-51% (-58, -44)
HIGH FH (EFC12732)						
Aliro 150mg	18	-36%		45	-49%	
Placebo	8	3%	-40% (-62, -18)	25	-10%	-40% (-54, -25)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	73	-50%		116	-47%	
Placebo	42	-6%	-44% (-54, -35)	55	0%	-47% (-56, -38)
LONG TERM (LTS11717)						
Aliro 150mg	778	-61%		608	-61%	
Placebo	404	1%	-62% (-65, -58)	304	1%	-62% (-66, -58)
COMBO II (EFC11569)						
Aliro 75mg/150mg	146	-51%		282	-50%	
Ezetimibe	80	-18%	-33% (-41, -26)	141	-22%	-28% (-34, -22)

* with baseline and week 24 data; [†] 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

Table 41. Subgroup analysis results by baseline LDL-C (< 130 mg/dL; ≥ 130 mg/dL)

	< 130 mg/dL*			≥ 130 mg/dL		
	N [†]	LS Mean: % Δ	Difference: Alirocumab - Control (95% ^{††} CI)	N [†]	LS Mean: % Δ	Difference: Alirocumab - Control (95% ^{††} CI)
FH I (EFC12492)						
Aliro 75mg/150mg	121	-41%		169	-54%	
Placebo	62	16%	-57% (-67, -48)	87	4%	-59% (-65, -53)
FH II (R727-CL-1112)						
Aliro 75mg/150mg	86	-44%		71	-54%	
Placebo	46	6%	-50% (-59, -41)	32	-2%	-52% (-62, -43)
HIGH FH (EFC12732)						
Aliro 150mg	39	-43%		24	-49%	
Placebo	17	-4%	-39% (-58, -21)	16	-9%	-40% (-55, -26)
COMBO I (EFC11568)						
Aliro 75mg/150 mg	165	-46%		24	-59%	
Placebo	80	1%	-47% (-54, -40)	17	-19%	-40% (-54, -25)
LONG TERM (LTS11717)						
Aliro 150mg	936	-62%		450	-58%	
Placebo	487	6%	-68% (-71, -65)	221	-10%	-49% (-52, -45)
COMBO II (EFC11569)						
Aliro 75mg/150mg	335	-49%		93	-56%	
Ezetimibe	175	-19%	-31% (-36, -25)	46	-28%	-28% (-36, -20)
OPTIONS I (R727-CL-1110):						
Atorvastatin 20mg stratum						
Aliro 75mg/150mg + Atorva 20mg	42	-42%		8	-55%	
Atorva 40mg	39	-3%	-38% (-57, -19)	11	-13%	-42% (-76, -9)
Ezetimibe + Atorva 20mg	36	-20%	-21% (-40, -2)	7	-19%	-36% (-71, -2)
Atorvastatin 40 mg stratum						
Aliro 75mg/150mg + Atorva 40mg	29	-52%		12	-58%	
Atorva 80mg	33	0%	-52% (-71, -34)	9	-27%	-31% (-54, -8)
Ezetimibe + Atorva 40mg	38	-24%	-28% (-47, -10)	6	-11%	-46% (-73, -20)
Rosuva 40mg	35	-21%	-31% (-50, -12)	9	-24%	-34% (-56, -11)
OPTIONS II (R727-CL-1118):						
Rosuvastatin 10mg stratum						
Aliro 75mg/150mg + Rosuva 10mg	34	-53%		8	-39%	
Rosuva 20mg	34	-14%	-39% (-55, -23)	11	-28%	-11% (-47, 25)
Ezetimibe + Rosuva 10mg	34	-16%	-37% (-53, -22)	3	-9%	-30% (-79, 20)
Rosuvastatin 20mg stratum						
Aliro 75mg/150mg + Rosuva 20mg	28	-30%		17	-40%	
Rosuva 40mg	33	-12%	-18% (-53, 18)	15	-25%	-15% (-39, 9)
Ezetimibe + Rosuva 20mg	31	-7%	-23% (-59, 13)	16	-24%	-16% (-40, 8)
ALTERNATIVE (R727-CL-1119)						
Aliro 75mg/150mg	12	-30%		103	-47%	
Ezetimibe	15	-4%	-27% (-50, -4)	93	-17%	-29% (-35, -24)
MONO (EFC11716)						
Aliro 75mg/150mg	15	-43%		34	-49%	
Ezetimibe	13	-8%	-35% (-52, -18)	33	-19%	-31% (-40, -21)

*Levels defined by 190 mg/dL for HIGH FH; [†] with baseline and week 24 data; ^{††} 99% CI for OPTIONS I and 98.75% CI for OPTIONS II

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/s/

BRADLEY W MCEVOY
04/17/2015

MARK D ROTHMANN
04/17/2015
I concur

THOMAS J PERMUTT
04/17/2015
I concur.

STATISTICS FILING CHECKLIST FOR NDA/BLA

BLA Number: 122259

**Applicants: Sanofi-aventis &
Regeneron**

Stamp Date: 11/24/2014

**Drug Name:
Praluent (alirocumab)**

BLA Type: Priority

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___ YES ___

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.			X	Review issue
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.			X	Review issue

Comments: None

File name: 5_Statistics Filing Checklist for a New NDA_BLA

STATISTICS FILING CHECKLIST FOR NDA/BLA

Bradley W. McEvoy	January 5, 2015
Reviewing Statistician	Date
Mark Rothmann	January 7, 2015
Supervisor/Team Leader	Date

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/s/

BRADLEY W MCEVOY
01/12/2015

MARK D ROTHMANN
01/13/2015
Concur