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: subgroup analyses

Table of Contents

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 approved[1] 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;

[1]Possible 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

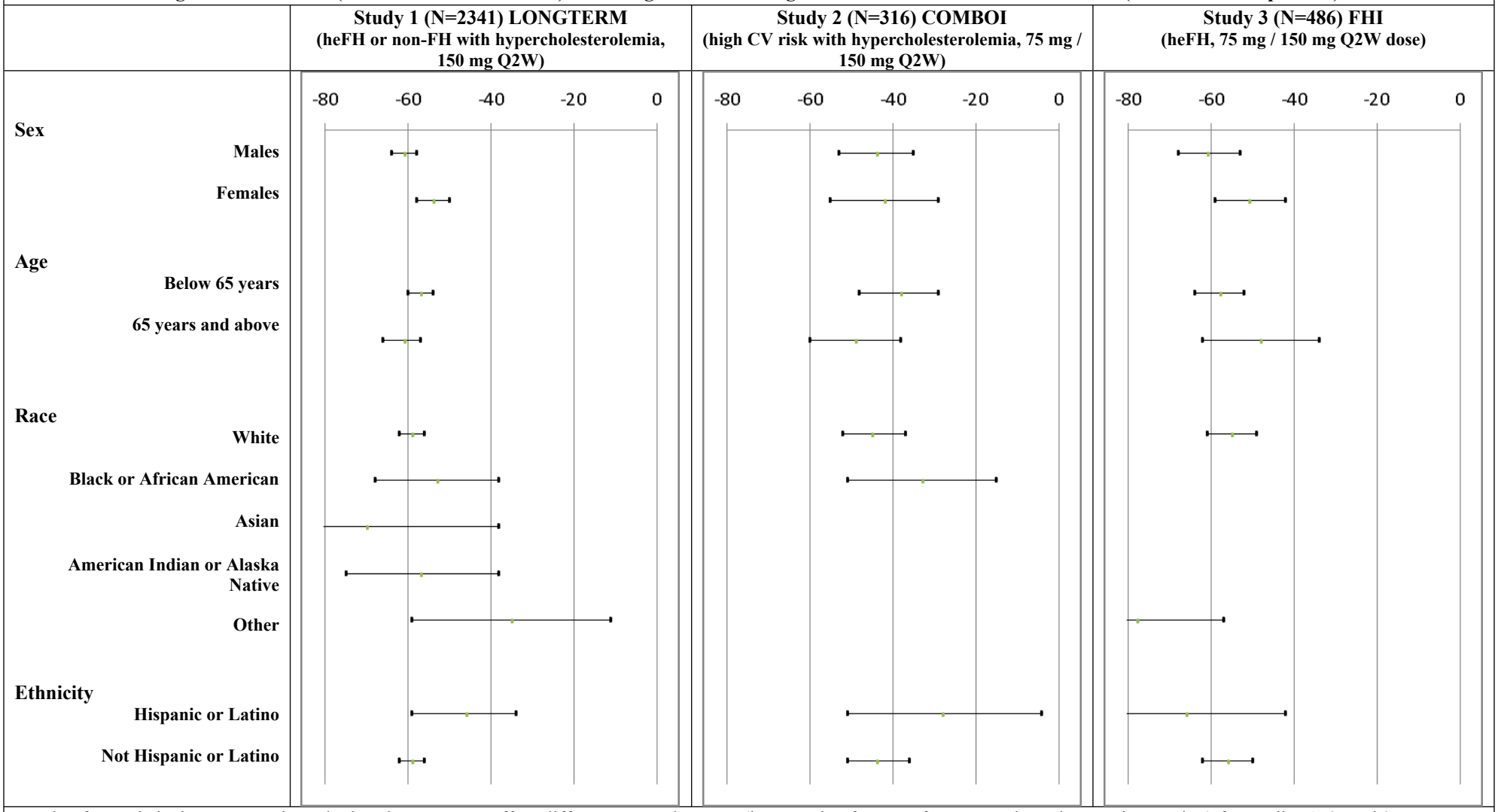
available within each age, sex, race, and ethnicity subset. Despite these possible statistical limitations associated with multiplicity and low power, these investigations are undertaken in the interest of transparency and to provide as much information regarding subgroup differences as is possible using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

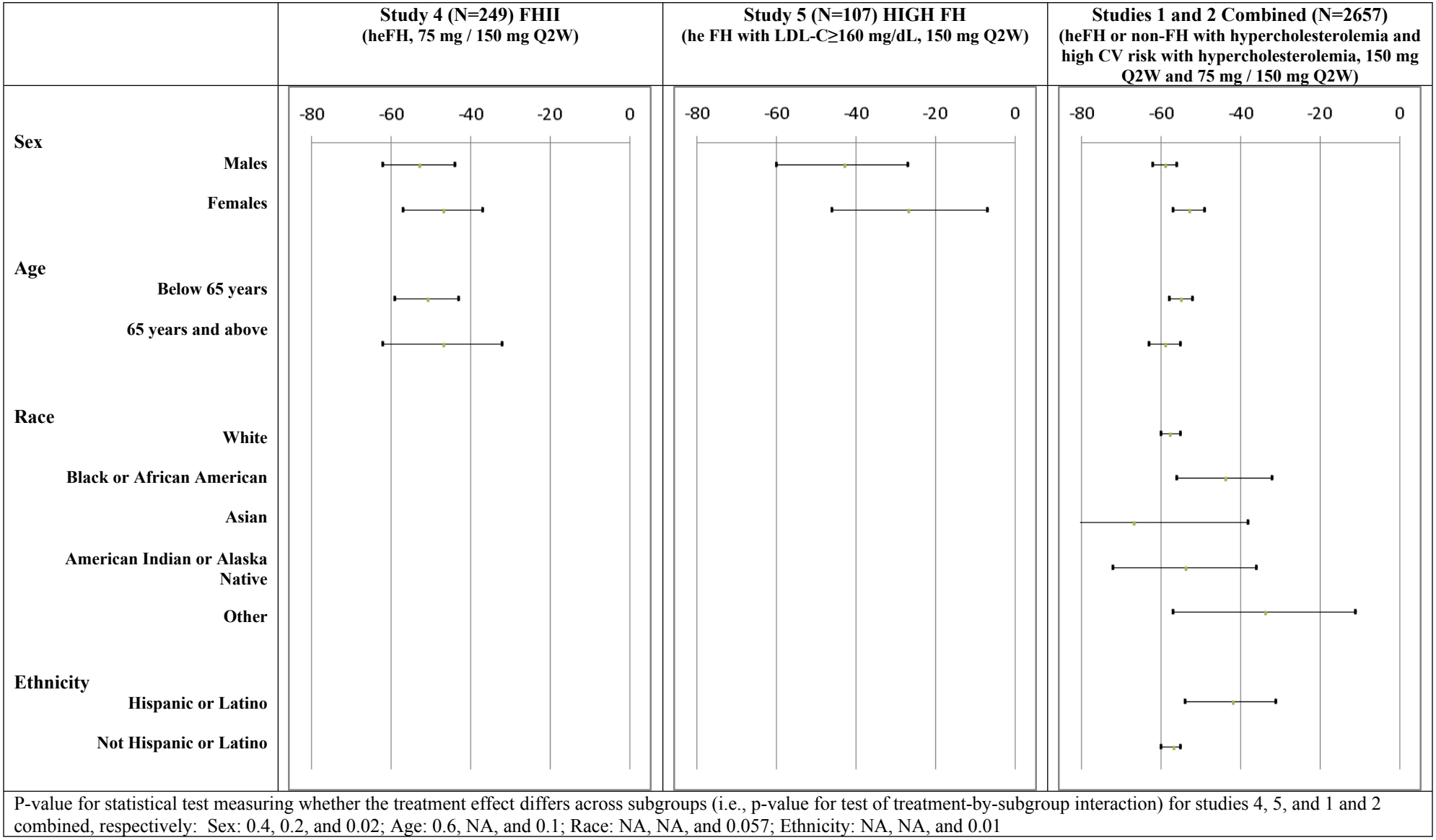
3.3 Results by Sex, Race, Age, and Ethnicity

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.

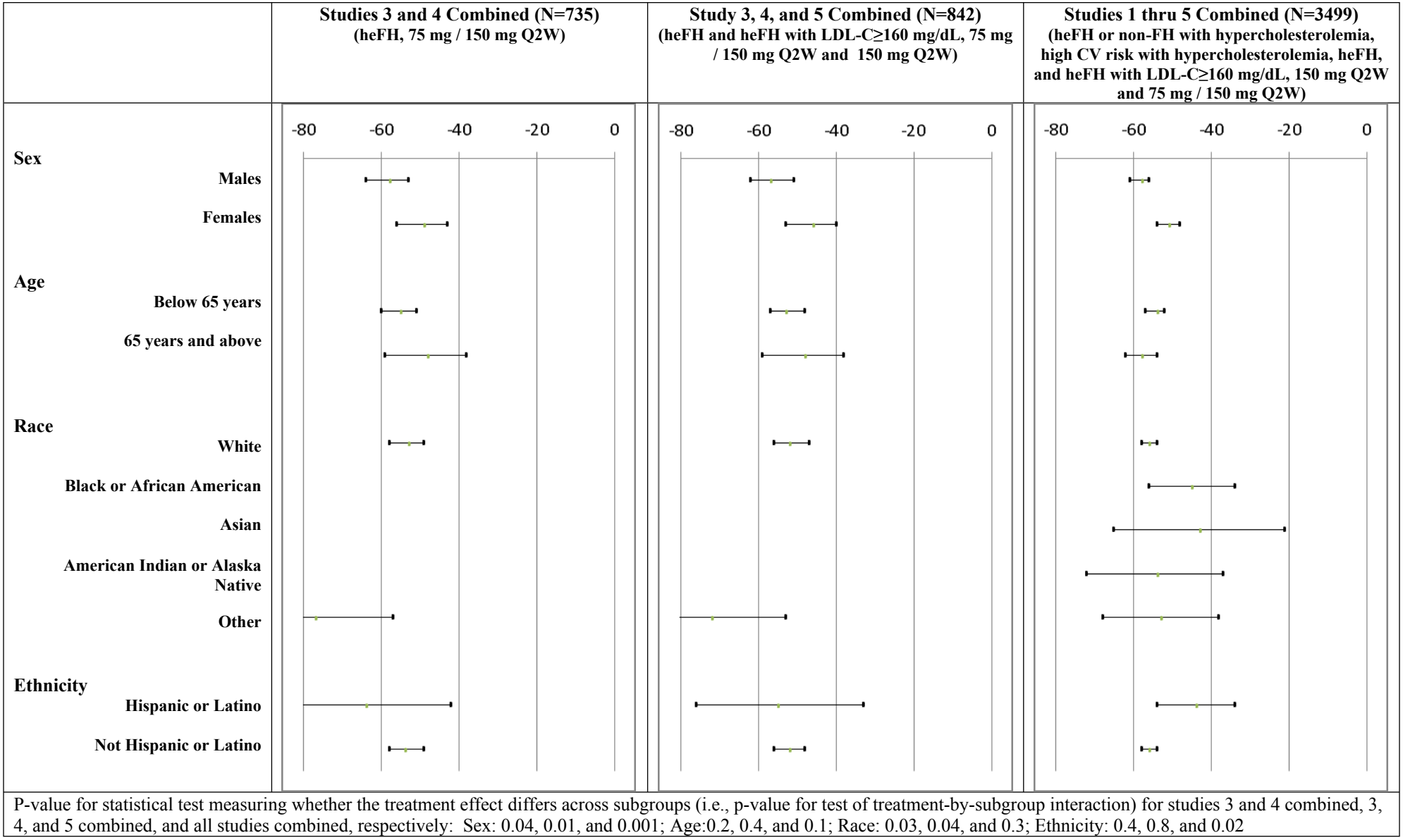
Figure 1: Difference (95% Confidence Interval) in Average Percent Change from Baseline in LDL-C at Week 24 (Praluent minus placebo)



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.

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I concur.