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

SNAPSHOT ON SUBGROUPS

BLA#	125522
Drug Name:	Repatha (Evolocumab)
Indication(s):	Hyperlipidemia and mixed dyslipidemia
Applicant:	Amgen

Biometrics Division:	II
Statistical Reviewer:	Shuxian Sinks, PhD
Concurring Statistical Reviewers:	Mark Rothmann, PhD Ruthanna Davi, PhD Thomas Permutt, PhD
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Eileen Craig, MD, Medical Officer James Smith, MD, Deputy Division Director
Project Manager:	Kati Johnson
Professional Affairs and Stakeholder Engagement Team:	Naomi Lowy, MD, Medical Officer

Keywords: subgroup analyses

Table of Contents

1 EXECUTIVE SUMMARY

This review examined existing data to assess the treatment effect of Repatha on percent change in LDL-C at week 12 or week 52 within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Repatha on percent change in LDL-C at week 12 or week 52 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 possible using the available data.

I conclude that there was statistical evidence of beneficial effects of Repatha on percent change in LDL-C at week 12 or week 52 within most subgroups examined (including male patients and female patients and both age groups, less than 65 years and 65 and older), and the point estimates for the effect of Repatha were relatively consistent across all subgroups (range of subgroup-specific effects based on analyses integrating study 1, 2, 3 and combining doses: -52% to -73%; range for study 4: -28% to -30%). Specifically, I conclude that

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 for each sex. Available data did not give a strong indication that the treatment effect for Repatha depends on sex.

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 for both age groups examined (below 65 years and 65 years and above). Available data did not give an indication that the treatment effect for Repatha is larger in one age group than the other.

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 in White patients. The effect of Repatha within each of the other racial categories (Black or African American, Asian, and other) is numerically in favor of Repatha but not definitively so without borrowing information from White patients. Available data in non-white patients is very limited; however, it did not give an indication that the treatment effect for Repatha is different for any race.

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 in patients who are not Hispanic or Latino. The effect of Repatha within the Hispanic or Latino category is numerically in favor of Repatha but not definitively so without borrowing information from patients who are not Hispanic or Latino. Available data in Hispanic or Latino patients is very limited; however, it did not give an indication that the treatment effect for Repatha is different by ethnicity.

2 INTRODUCTION

This document is written as part of a pilot partnership between Division of Biometrics II 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 Repatha 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/2015/125522Orig1s000StatR.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 Repatha submission.

3 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

3.1 Available Data

Repatha is approved[1] as an adjunct to diet and maximally tolerated statin therapy for the treatment of adult patients with heterozygous familial hypercholesterolemia, or clinical atherosclerotic heart disease who require additional lowering of LDL-cholesterol. Repatha is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The applicant submitted results of six randomized, double-blind, parallel-group, and placebo- or active-controlled trials to evaluate Repatha for lipid-lowering in different patient populations and across different levels of background statin intensity. Four of the phase 3 studies (20110114, 20110115, 20110116, and 20110117) were 12 weeks long and included patient populations to support the indication for primary hyperlipidemia or mixed dyslipidemia. One long-term study (20110109) was 52 weeks long and was to demonstrate the persistence of efficacy in Repatha among patients with primary hyperlipidemia or mixed dyslipidemia. The indication of HoFH was supported by one randomized, double-blind, placebo-controlled, 12-week trial (20110233).

Clinical trial data reflected in product labeling is restricted to the patient population with heterozygous familial hypercholesterolemia (HeFH), or clinical atherosclerotic cardiovascular disease (CVD) that requires additional lowering of LDL-cholesterol, or with homozygous familial hypercholesterolemia (HoFH). Consistent with product labeling, this review focuses on the results from the four studies described in Table 1. Findings in the overall group for each of these four studies are provided in Table 2.

[1] http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2015/125522Orig1s000ltr.pdf

Table 1. Summary of study designs

Study	Population	Design	Primary Endpoint/	Treatment arms (N)
Study 1 (20110115)	Patients with atherosclerotic CVD, as add on to atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg	R, DB, PC, PG	Percent Change in LDL-C from baseline at week 12	- REPATHA 140 mg every two weeks (n=105) - REPATHA 420 mg once per month (n=105) - Placebo every two weeks (n=42) - Placebo once monthly (n=44)
Study 2 (20110109)	Patients with atherosclerotic CVD, as add on to atorvastatin 80 mg with or without ezetimibe 10 mg daily	R, DB, PC, PG	Percent change in LDL-C from baseline at week 52	- REPATHA 420 mg once per month (n=95) - Placebo once monthly (n=44)
Study 3 (20110117)	Patients with HeFH on statins with or without other lipid-lowering therapies	R, DB, PC, PG	Percent change in LDL-C from baseline at week 12	- REPATHA 140 mg every two weeks n=110) - REPATHA 420 mg once per month (n=110) - Placebo every two weeks (n=54) - Placebo once per month (n=55)
Study 4 (20110233)	Patients (not on lipid-apheresis therapy) with HoFH, as adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe)	R, DB, PC, PG	Percent change in LDL-C from baseline at week 12	- REPATHA 420 mg once per month (n=33) - Placebo once monthly (n=16)

CVD – cardiovascular disease; HeFH – heterozygous familial hypercholesterolemia; HoFH – homozygous familial hypercholesterolemia; R – randomized; DB – double-blind; PC – placebo-controlled; PG – parallel-group;
Source: FDA Reviewer

Table 2. % LDL-C change at week 12 or 52 by trial (ITT population; preferred FDA analysis)

	LS Mean: % Change	Difference: Repatha - Control (95% CI)
Study 1(20110115)		
Repatha 140mg every 2 weeks (n=105)	-64%	-71% (-81, -61)
Placebo every 2 weeks(n=42)	7%	
Repatha 420 mg once monthly (n=105)	-58%	-63% (-76, -50)
Placebo once monthly (n=44)	5%	
Study 2 (20110109)		
Repatha 420 mg once monthly (n=95)	-52%	-54% (-65, -42)
Placebo once monthly (n=44)	2%	
Study 3 (20110117)		
Repatha 140 mg every 2 weeks (n=110)	-62%	-61% (-67, -55)
Placebo every 2 weeks (n=54)	-1%	
Repatha 420 mg once monthly (n=110)	-56%	-60% (-68, -52)
Placebo once monthly (n=55)	4%	
Study 4 (20110233)		
Repatha 420 mg once monthly (n=33)	-22%	
Placebo once monthly (n=16)	9%	-31% (-44, -18)

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, time points, or doses. While we acknowledge that differences in the treatment effect across differing populations, time points, 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, time points, and doses. For example if the treatment effect for Repatha in male patients is larger than that of female patients in one population, combining this study with a study of patients in another population is more appropriate if the treatment effect for Repatha is also larger for male patients than female patients in that population. We believe that in general this type of assumption is much more likely to be true than the former.

With afore mentioned considerations, all studies, doses, and time points are considered individually. In addition, studies targeting similar patient populations and data from multiple dose levels are combined in adjusted or stratified analyses. An overall treatment effect (compared to placebo) is estimated by combining Repatha doses using patients with Atherosclerotic CVD in study 1. Similarly, an overall treatment effect (compared to placebo) is estimated by combining Repatha doses for HeFH patients in study 3. In addition, due to the similarity in patient populations, patients with Atherosclerotic CVD in studies 1 and 2 are combined and an overall treatment effect combining doses is estimated in an analysis adjusted for or stratified by study and dose. Similarly, patients in studies 1, 2, and 3 are combined and an overall treatment effect combining doses is estimated in an analysis adjusted for or stratified by study and dose. Tests for treatment-by-subgroup interaction are used to quantitatively assess whether there is evidence that the treatment effect differs by subgroup. Study 4 is not combined with any other studies in that the HoFH population is clinically very different than the other populations studied.

We acknowledge that these analyses are exploratory and the trials were not designed for such investigations. In general, these comparisons may be limited due to the number of comparisons that are done and by the power for a given comparison. Consistency in the differences in treatment effect across subgroups by study and/or dose is qualitatively examined as a means to minimize (but 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 Repatha on percent change in LDL-C is large and measurement of the endpoint is precise so that differences between Repatha 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 power, these investigations are undertaken in the interest of transparency

and to provide as much information regarding subgroup differences as possible using the available data.

All subgroup analyses presented in this review are adapted from statistical methods utilized to assess the primary efficacy endpoint as part of the original statistical review of this product. (http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000StatR.pdf).

3.3 Results by Sex, Race, Age, and Ethnicity

This section provides estimates of the difference between Repatha and placebo in mean percent change from baseline in LDL-C by sex, age, race, and ethnicity. Tests for treatment-by-subgroup interaction are also provided if available. Figures 1 to 6 display the results by subgroup for each individual study and dose. Figures 7 and 8 provide estimates of an overall treatment effect (with doses combined) for studies 1 and 3, respectively. Figure 9 provides estimates of an overall treatment effect (with doses combined) for studies 1 and 3. Figure 10 provides an overall estimate of the treatment effect (with doses combined) from studies 1, 2, and 3.

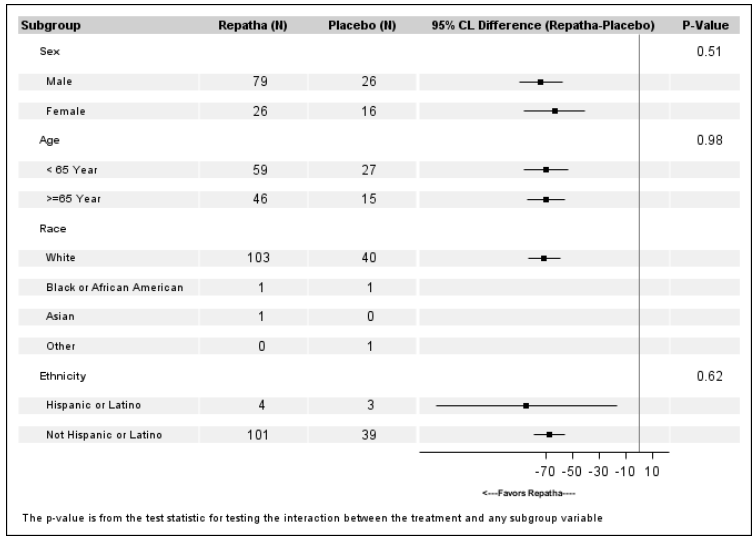


Figure 1 Study 1 (Atherosclerotic CVD A80R40S40)- Effect of Repatha on LDLC-by Subgroup (Q2W) at Week 12

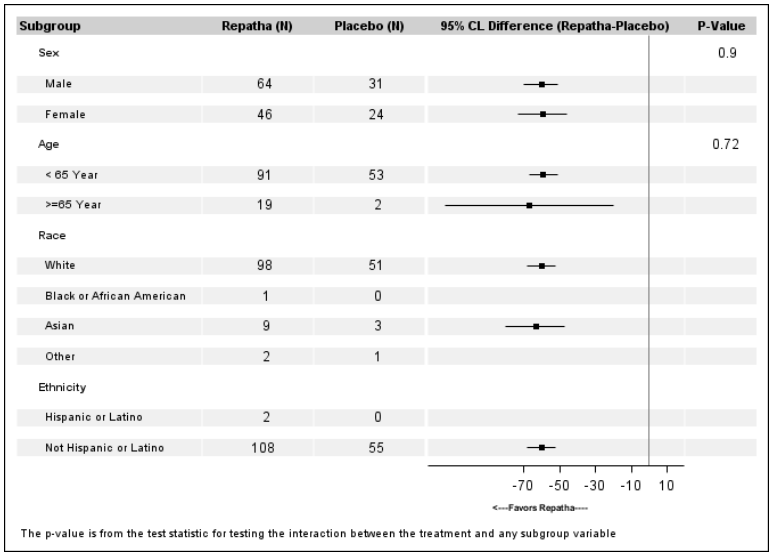


Figure 2 Study 1 (Atherosclerotic CVD A80R40S40)- Effect of Repatha on LDLC-by Subgroup (QM) at Week 12

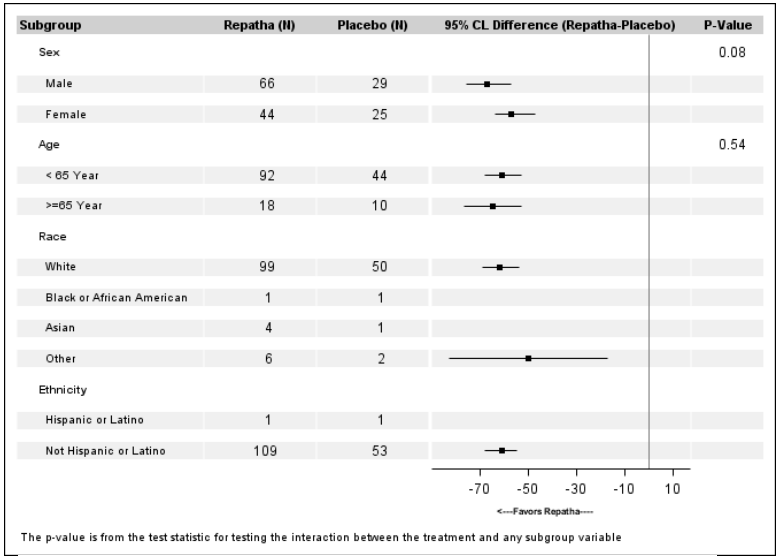


Figure 3 Study 3 (HeFH) Effect of Repatha on LDL-C by Subgroup (Q2W) at Week 12

Figure 4 Study 3 (HeFH) Effect of Repatha on LDL-C by Subgroup (QM) at Week 12

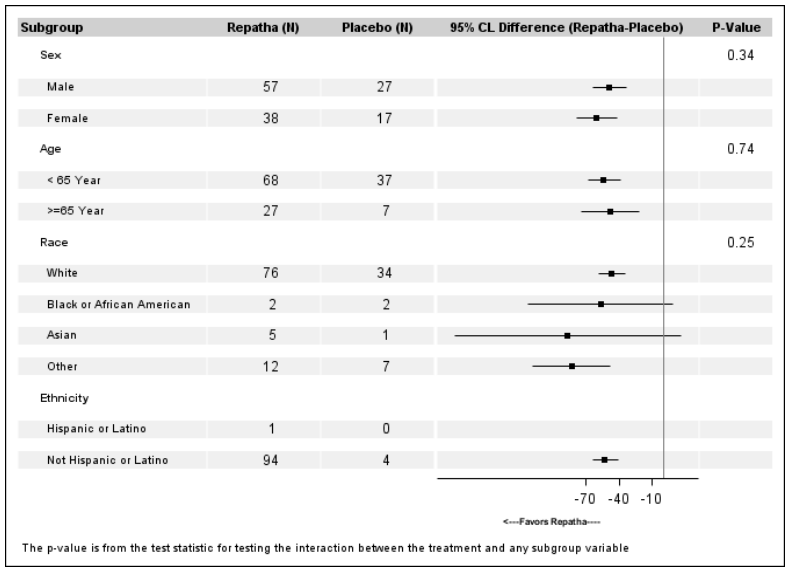


Figure 5 Study 2 (Atherosclerotic CVD A80+/-E)- Effect of Repatha on LDLC-by Subgroup(QM) at Week 52

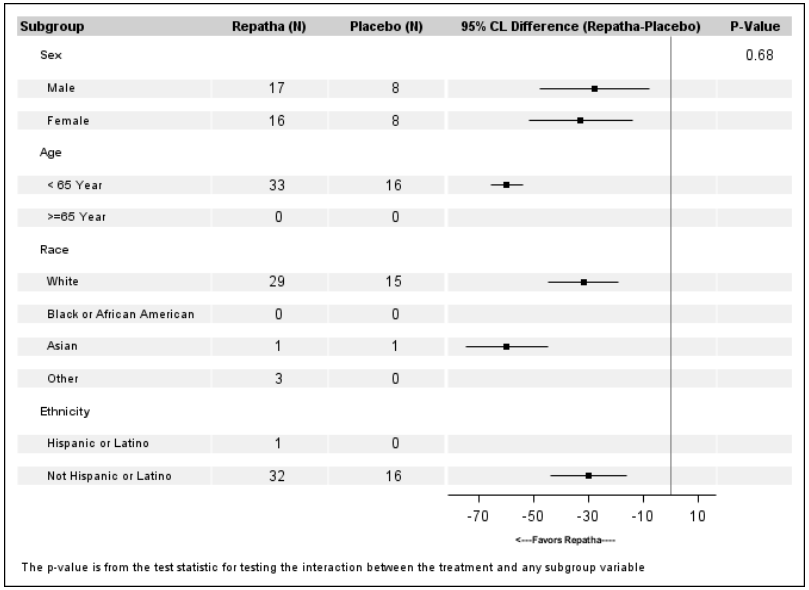
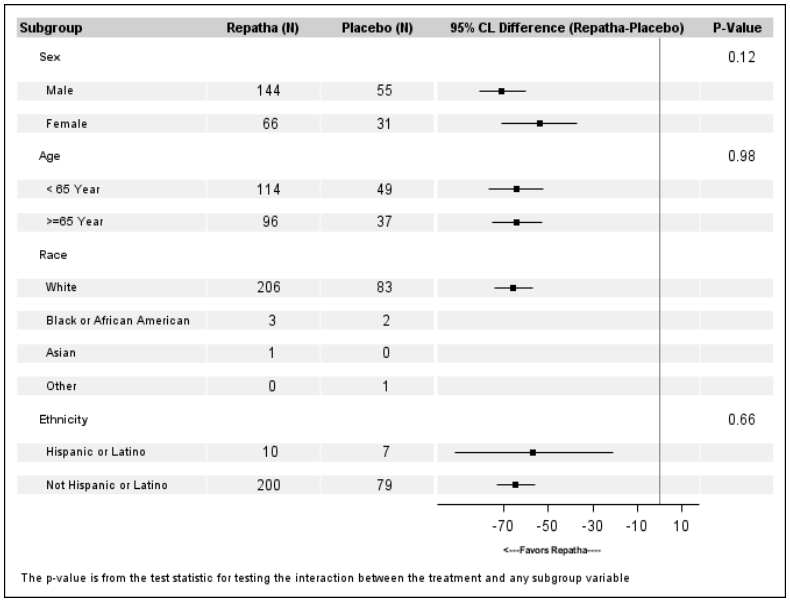


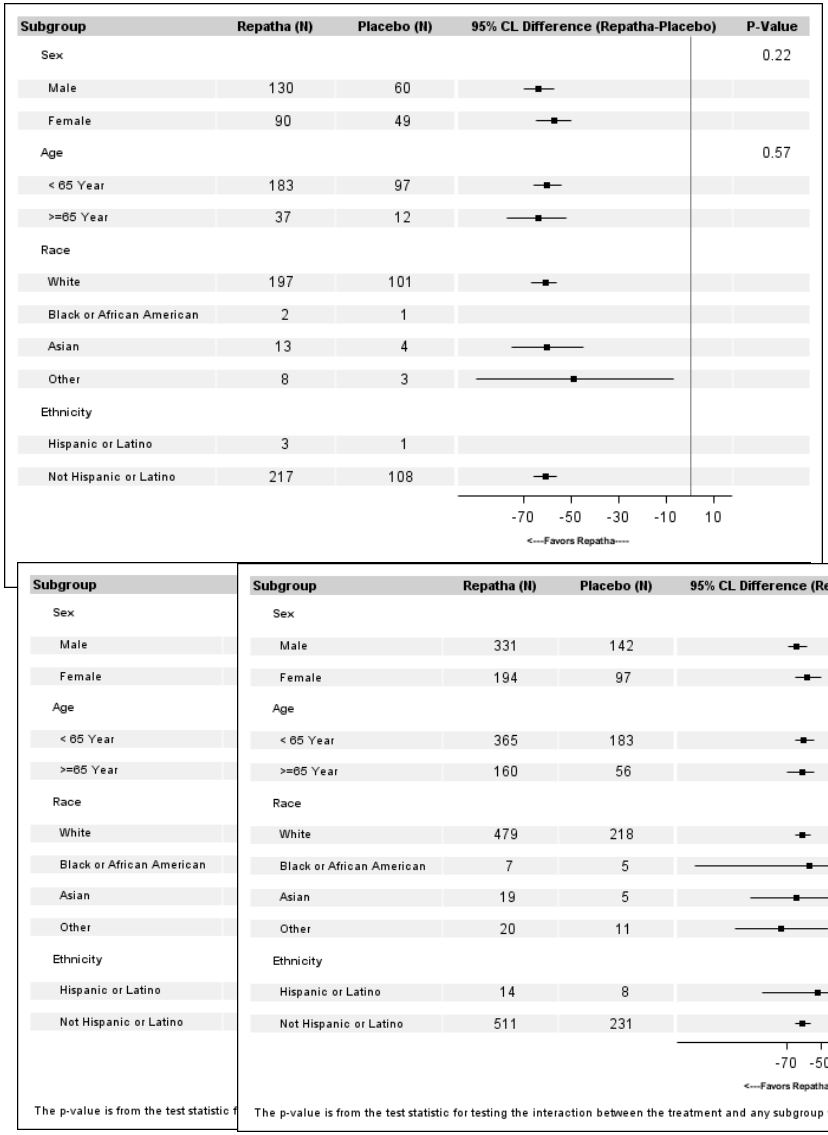
Figure 6 Study 4 (HoFH)- Effect of Repatha on LDL-C by Subgroup (QM) at Week 12



Subgroup	Repatha (N)	Placebo (N)	95% CL Difference (Repatha-Placebo)	P-Value
Sex				0.12
Male	144	55		
Female	66	31		
Age				0.98
< 65 Year	114	49		
>=65 Year	96	37		
Race				
White	206	83		
Black or African American	3	2		
Asian	1	0		
Other	0	1		
Ethnicity				0.66
Hispanic or Latino	10	7		
Not Hispanic or Latino	200	79		

The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

Figure 7 Study 1 (Atherosclerotic CVD A80R40S40) Effect of Repatha on LDL-C by Subgroup (Q2W and QM Combined) at week 12



Subgroup	Repatha (N)	Placebo (N)	95% CL Difference (Repatha-Placebo)	P-Value
Sex				0.22
Male	130	60		
Female	90	49		
Age				0.57
< 65 Year	183	97		
>=65 Year	37	12		
Race				
White	197	101		
Black or African American	2	1		
Asian	13	4		
Other	8	3		
Ethnicity				
Hispanic or Latino	3	1		
Not Hispanic or Latino	217	108		

Subgroup	Repatha (N)	Placebo (N)	95% CL Difference (Repatha-Placebo)	P-Value
Sex				0.22
Male	331	142		
Female	194	97		
Age				0.65
< 65 Year	365	183		
>=65 Year	160	56		
Race				0.84
White	479	218		
Black or African American	7	5		
Asian	19	5		
Other	20	11		
Ethnicity				0.58
Hispanic or Latino	14	8		
Not Hispanic or Latino	511	231		

The p-value is from the test statistic for testing the interaction between the treatment and any subgroup variable

Figure 10 Study 1, Study 2, and Study 3- Effect of Repatha on LDL-C by Subgroup (Q2W and QM Combined)

Figure 9 Study 1 and Study 2- Effect of Repatha on LDL-C by Subgroup (Q2W and QM Combined)

Examination of treatment effect by sex: Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 week or week 52 within each sex. None of the studies give a strong indication that the treatment effect for Repatha is different between female patients and male patients, as evidenced by the p-values for treatment-by-sex interaction. In addition, point estimates for the treatment effect for male patients and female patients are consistent within studies and combinations of studies and doses and appear to be suggestive of normal variation in point estimates with no underlying difference in the treatment effect for the two sexes.

Description of the effect of Repatha in male patients versus female patients on percent change in LDL-C could reliably be achieved by displaying results from the combined analysis of all doses from studies 1 through 3 and the analysis of study 4 alone. Combining doses and studies 1 through 3 is motivated by the fact that each of the analyses for individual and combined doses and/or studies provides a consistent conclusion regarding sex, that is the analyses do not suggest a difference in treatment effect by sex. The recommendation to represent study 4 alone is made because the patient population in study 4 (HoFH) is very different from the other studies.

Examination of treatment effect by age: Repatha is statically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 for both age groups examined (< 65 years and ≥ 65 years) in Atherosclerotic CVD and HeFH patients. None of the studies give a strong indication that the treatment effect for Repatha is larger in one age group than the other as evidenced by the p-values associated with the treatment-by-sex interaction. The numerical differences in point estimates for percent change in LDL-C are consistent within studies 1, 2, and 3 and combination of studies and doses from studies 1, 2, and 3 and appear to be suggestive of normal variation in point estimates with no underlying difference in the treatment effect for the two age groups. Study 4 targets HoFH patients, a patient population that is very different from that of studies 1, 2, and 3, and consistent with the nature of the disease includes only patients younger than 65 years old so that no assessment regarding the difference in treatment effect by age in this patient population is possible with existing data.

Description of the effect of Repatha in those younger than 65 years old and those at least 65 years old, on percent change in LDL-C could reliably be achieved by displaying results from the combined analysis of all doses from studies 1 through 3. Analyses by age for the HoFH patient population are not possible as consistent with the nature of the disease; study 4 included only patients younger than 65 years old. Combining doses and studies 1 through 3 is motivated by the fact that each of the analyses for individual and combined doses and/or studies provides a consistent conclusion regarding age; which is there is no suggestion of a difference in treatment effect by age. The recommendation not to combine study 4 with studies 1 through 3 is made because the patient population in study 4 (HoFH) is very different from the other studies.

Examination of treatment effect by race: Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 within White patients. White patients represent 100%, 79%, and 91% of subjects analyzed in studies 1, 2, and 3, respectively, making it difficult to draw any meaningful conclusions regarding the effect of

Repatha within Non-white races (without borrowing information from White patients). The effect for Repatha in comparison to placebo within each of the other racial categories is numerically in favor of Repatha but not definitively so with 95% confidence intervals for the difference overlapping zero in some cases. With available data (which is quite limited in non-white patients), there is no indication of a differing treatment effect by race suggesting that data from White patients might be applicable to the estimation of the treatment effect in Non-white patients. Study 4 targets HoFH patients, a patient population that is very different from that of studies 1, 2, and 3, and includes almost exclusively White patients so that no assessment regarding the difference in treatment effect by race in this patient population is possible with existing data.

Description of the effect of Repatha in the racial subgroups could be achieved by displaying results from studies 2 and 3 as study 1 did not include any Non-white patients or for the sake of consistency with other subgrouping factors examined in this review, by display of the analysis of the combined studies 1 through 3. The recommendation not to combine study 4 with studies 1 through 3 is made because the patient population in study 4 (HoFH) is very different from the other studies

Examination of treatment effect by ethnicity: Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 within patients who are not Hispanic or Latino. Patients who are not Hispanic or Latino represent 94%, 99%, and 99% of subjects analyzed in studies 1, 2, and 3, respectively, making it difficult to draw any meaningful conclusions regarding the effect of Repatha within Hispanic or Latino patients (without borrowing information from patients who are not Hispanic or Latino). The effect for Repatha in comparison to placebo within the Hispanic or Latino subgroup is numerically in favor of Repatha but not definitively so with 95% confidence intervals for the difference overlapping zero in most cases. With available data (which is quite limited in Hispanic or Latino patients), there is no indication of a differing treatment effect by ethnicity suggesting that data from patients who are not Hispanic or Latino might be applicable to the estimation of the treatment effect in Hispanic or Latino patients. Study 4 targets HoFH patients, a patient population that is very different from that of studies 1, 2, and 3, and includes patients who are not Hispanic or Latino only so that no assessment regarding the difference in treatment effect by ethnicity in this patient population is possible with existing data.

Description of the effect of Repatha in the ethnicity subgroups could be achieved by displaying results from study 1 alone as studies 2 and 3 included very few Hispanic or Latino patients, or for the sake of consistency with other subgrouping factors examined in this review, by display of the analysis of the combined studies 1 through 3. The recommendation not to combine study 4 with studies 1 through 3 is made because the patient population in study 4 (HoFH) is very different from the other studies.

4 SUMMARY AND CONCLUSIONS

This review examined existing data to assess the treatment effect of Repatha on percent change in LDL-C at week 12 or week 52 within each sex, age, race, and ethnicity subgroup and whether the treatment effect of Repatha on percent change in LDL-C at week 12 or week 52 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 possible using the available data.

I conclude that there was statistical evidence of beneficial effects of Repatha on percent change in LDL-C at week 12 or week 52 within most subgroups examined (including male patients and female patients and both age groups, less than 65 years and 65 and older), and the point estimates for the effect of Repatha were relatively consistent across all subgroups (range of subgroup-specific effects based on analyses integrating study 1, 2, 3 and combining doses: -52% to -73%; range for study 4: -28% to -30%). Specifically, I conclude that

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 for each sex. Available data did not give a strong indication that the treatment effect for Repatha depends on sex.

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 for both age groups examined (below 65 years and 65 years and above). Available data did not give an indication that the treatment effect for Repatha is larger in one age group than the other.

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 in White patients. The effect of Repatha within each of the other racial categories (Black or African American, Asian, and other) is numerically in favor of Repatha but not definitively so without borrowing information from White patients. Available data in non-white patients is very limited; however, it did not give an indication that the treatment effect for Repatha is different for any race.

- Repatha is statistically significantly better than placebo with respect to the percent change in LDL-C at week 12 or week 52 in patients who are not Hispanic or Latino. The effect of Repatha within the Hispanic or Latino category is numerically in favor of Repatha but not definitively so without borrowing information from patients who are not Hispanic or Latino. Available data in Hispanic or Latino patients is very limited; however, it did not give an indication that the treatment effect for Repatha is different by ethnicity.

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

/s/

SHUXIAN Z SINKS
10/26/2015

MARK D ROTHMANN
10/26/2015
I concur

RUTHANNA C DAVI
10/26/2015

THOMAS J PERMUTT
10/26/2015
I concur.