Common Drug Review
Clinical Review Report

July 2016

Drug	Alirocumab (Praluent)
Indication	Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C). The effect of Praluent on cardiovascular morbidity and mortality has not been determined.
Listing request	As an adjunct to diet and maximally tolerated statin (MTS) therapy with or without other lipid-lowering therapies (LLT), Praluent should be reimbursed for adults with HeFH or high-risk patients who have had prior cardiovascular (CV) events and require additional lowering of LDL-C. Prior CV events include myocardial infarction (MI), unstable angina (UA) requiring hospitalization, coronary revascularization, and ischemic stroke.
Dosage form(s)	75 mg/mL and 150 mg/mL pre-filled syringe
NOC date	April 11, 2016
Manufacturer	Sanofi-Aventis Canada Inc.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

TABLE OF CONTENTS

ABBREVIATIONS i
EXECUTIVE SUMMARY ii
1. INTRODUCTION 1
1.1 Disease Prevalence and Incidence 1
1.2 Standards of Therapy 1
1.3 Drug 1
2. OBJECTIVES AND METHODS 3
2.1 Objectives 3
2.2 Methods 3
3. RESULTS 5
3.1 Findings From the Literature 5
3.2 Included Studies 14
3.3 Patient Disposition 25
3.4 Exposure to Study Treatments 29
3.5 Critical Appraisal 29
3.6 Efficacy 30
3.7 Harms 41
4. DISCUSSION 47
4.1 Summary of Available Evidence 47
4.2 Interpretation of Results 47
4.3 Potential Place in Therapy 49
5. CONCLUSIONS 50
APPENDIX 1: PATIENT INPUT SUMMARY 51
APPENDIX 2: LITERATURE SEARCH STRATEGY 55
APPENDIX 3: EXCLUDED STUDIES 57
APPENDIX 4: DETAILED OUTCOME DATA 58
APPENDIX 5: VALIDITY OF OUTCOME MEASURES 66
REFERENCES 67

Tables

Table 1: Summary of Results for Clinical Cardiovascular Disease Studies viii
Table 2: Summary of Results for Familial Hypercholesterolemia–Specific Studies ix
Table 3: Summary of Results for Mixed Population Study xi
Table 4: Summary of Results for OPTIONS 1 xii
Table 5: Summary of Results for OPTIONS 2 xiii
Table 6: Summary of Results for ALTERNATIVE and MONO xiv
Table 7: Key Characteristics of PCSK9 Inhibitors 2
Table 8: Inclusion Criteria for the Systematic Review 3
Table 9: Details of Included Studies for COMBO 1 and COMBO 2 6
Table 10: Details of Included Studies Specific to Heterozygous Familial Hypercholesterolemia 7
Table 11: Details of Included Studies for Mixed Population 9
Table 12: Details of Included Studies for OPTIONS 1 and OPTIONS 2 10
Table 13: Details of Included Studies for MONO and ALTERNATIVE 12

Table 14: Summary of Baseline Characteristics for Clinical Cardiovascular Disease Studies 17
Table 15: Summary of Baseline Characteristics for Studies Specific to Heterozygous Familial Hypercholesterolemia 18
Table 16: Summary of Baseline Characteristics for Mixed Population Study 19
Table 17: Summary of Baseline Characteristics for OPTIONS 1 20
Table 18: Summary of Baseline Characteristics for OPTIONS 2 21
Table 19: Summary of Baseline Characteristics for ALTERNATIVE and MONO 21
Table 20: Patient Disposition for Clinical Cardiovascular Disease Studies 26
Table 21: Patient Disposition for Studies Specific to Heterozygous Familial Hypercholesterolemia 27
Table 22: Patient Disposition for Mixed Population Studies 27
Table 23: Patient Disposition for OPTIONS 1 and OPTIONS 2 28
Table 24: Patient Disposition for ALTERNATIVE and MONO 29
Table 25: Key Efficacy Outcomes for Clinical Cardiovascular Disease studies 34
Table 26: Key Efficacy Outcomes for Studies Specific to Heterozygous Familial Hypercholesterolemia 36
Table 27: Key Efficacy Outcomes for Mixed Population Study 38
Table 28: Key Efficacy Outcomes for OPTIONS 1 39
Table 29: Key Efficacy Outcomes for OPTIONS 2 40
Table 30: Key Efficacy Outcomes for ALTERNATIVE and MONO 41
Table 31: Harms for Clinical Cardiovascular Disease Studies 43
Table 32: Harms for Studies Specific to Heterozygous Familial Hypercholesterolemia 44
Table 33: Harms for Mixed Population Study 45
Table 34: Harms for OPTIONS 1 and OPTIONS 2 45
Table 35: Harms for ALTERNATIVE and MONO 46
Table 36: Subgroup Data for Clinical Cardiovascular Disease Studies 58
Table 37: Subgroup Data for Studies Specific to Heterozygous Familial Hypercholesterolemia 59
Table 38: Subgroup Data for Studies Specific to Heterozygous Familial Hypercholesterolemia (HIGH FH) 60
Table 39: Subgroup Data for Mixed Population Study 61
Table 40: Subgroup Data for OPTIONS 1 62
Table 41: Subgroup Data for OPTIONS 2 63
Table 42: Subgroup Data for ALTERNATIVE and MONO 65

Figure

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies 5

ABBREVIATIONS

AE	adverse event
CDR	CADTH Common Drug Review
CI	confidence interval
CV	cardiovascular
CVD	cardiovascular disease
FH	familial hypercholesterolemia
HeFH	heterozygous familial hypercholesterolemia
ITT	intention-to-treat population
LDL-C	low-density lipoprotein cholesterol
LLT	lipid lowering therapies
LS	least squares
MI	myocardial infarction
MTS	maximally tolerated statin
PCSK9	proprotein convertase subtilisin/kexin type 9
SAE	serious adverse event
UA	unstable angina
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Low-density lipoprotein cholesterol (LDL-C) is the key component in total cholesterol and is believed to play a crucial role in the formation of atherosclerotic plaques. Familial hypercholesterolemia (FH) is a common genetic disorder characterized by markedly elevated plasma levels of LDL-C.[1] Hyperlipidemia is typically defined by an elevated LDL-C, and although the cut-off for therapy is also impacted by the patient's risk factors, for patients with established cardiovascular disease (CVD), the recommended target LDL-C is ≤ 2.0 mmol/L. For primary prevention in FH, and for treatment in patients in whom therapy is limited by intolerance and who fail to achieve an LDL-C ≤ 2.0 mmol/L, the Canadian Cardiovascular Society guidelines recommend a reduction in LDL-C of at least 50% from baseline.[2]

Initial interventions for hyperlipidemia include diet and lifestyle modifications. The standard lipid-lowering therapy for the last few decades has been the use of HMG-CoA reductase inhibitors, more commonly known as statins. The next most common drug used in management of hyperlipidemia is ezetimibe, an inhibitor of cholesterol absorption. Ezetimibe is typically used in combination with a statin, most commonly atorvastatin. Monoclonal antibodies that bind and inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) represent a new class of lipid-lowering therapy.

Evolocumab was the first PCSK9 inhibitor to be reviewed by CADTH. In 2016, the CADTH Canadian Drug Expert Committee recommended that evolocumab be reimbursed as an adjunct to diet and maximally tolerated statin therapy in adult patients with HeFH who require additional lowering of LDL-C, if the patient:

- has a confirmed diagnosis of heterozygous familial hypercholesterolemia (HeFH)
- is unable to reach LDL-C target (i.e., LDL-C < 2.0 mmol/L)
- is currently receiving optimally tolerated standard of care (typically statins with or without ezetimibe).

The CADTH Canadian Drug Expert Committee did not recommend that evolocumab be reimbursed for adult patients with a high risk of cardiovascular (CV) events because there was insufficient evidence to evaluate the clinical benefit of evolocumab in such patients, as these patients represented a relatively small proportion (< 35%) of the patients studied in the clinical trials.

Alirocumab is the subject of the current review. Alirocumab is administered by subcutaneous injection at a dose of either 75 mg or 150 mg every two weeks.

Indication under review
As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
Reimbursement criteria requested by sponsor
As an adjunct to diet and maximally tolerated statin therapy with or without other lipid lowering therapies (LLT) for adults with HeFH or high-risk patients who have had prior cardiovascular (CV) events and require additional lowering of LDL-C.

Results and Interpretation

Included Studies

Ten multi-centre, manufacturer-sponsored, phase 3 double-blind randomized controlled trials were included in this review. The primary outcome of all 10 studies was the per cent change from baseline in LDL-C after 24 weeks. Six of the included studies were directly aligned with the manufacturer's proposed reimbursement criteria, as they included patients who were at high risk of CV events (COMBO 1 and COMBO 2), or who had HeFH (FH 1, FH 2, and HIGH FH), or who were a mixed population of both types of patient (LONG TERM). The remaining four studies (OPTIONS 1, OPTIONS 2, MONO, and ALTERNATIVE) included broader populations of patients, notably patients without FH and with a lower proportion of patients with clinical CVD.

Studies Specific to Familial Hypercholesterolemia or Clinical Cardiovascular Disease

In COMBO 1, 316 primarily clinical CVD patients were randomized 2:1 to either alirocumab 75 mg every two weeks or matched placebo for 52 weeks. In COMBO 2, 720 primarily clinical CVD patients were randomized 2:1 to either alirocumab 75 mg daily or ezetimibe for 104 weeks. In the FH-specific studies, (FH 1: N = 486; FH 2: N = 249) patients with HeFH were randomized 2:1 to either alirocumab or placebo for 78 weeks, and in HIGH FH, 107 patients were randomized to alirocumab 150 mg every two weeks or matched placebo for 78 weeks. In LONG TERM, a mixed population of 2,341 patients with FH, or clinical CVD or both was randomized 2:1 to either alirocumab 150 mg every two weeks or matched placebo for 78 weeks. In HIGH FH and LONG TERM, patients were initiated on the higher dose of alirocumab 150 mg every two weeks; in the other studies, patients started on alirocumab 75 mg every two weeks and could be up-titrated based on response after 12 weeks.

Other Studies

In OPTIONS 1, 355 patients on a background of atorvastatin 20 mg or 40 mg daily were randomized to seven groups, three on each of those background doses of atorvastatin plus either alirocumab 75 mg every two weeks, ezetimibe daily, or placebo daily, and an additional seventh group on rosuvastatin 40 mg daily. OPTIONS 2 had a similar design, with 305 patients randomized to six groups, on a background of either rosuvastatin 10 mg or 20 mg daily, to either alirocumab 75 mg every two weeks, ezetimibe daily, or placebo daily. In MONO, 103 patients whose risk level warranted that they be considered for lipid-lowering therapy were randomized 1:1 to either alirocumab or ezetimibe as monotherapy (no concomitant lipid-lowering therapy). In ALTERNATIVE, 314 patients with moderate or high CV risk and statin intolerance were randomized 2:2:1 to alirocumab 75 mg every two weeks or ezetimibe 10 mg daily or atorvastatin 20 mg daily for 24 weeks. In all four studies, alirocumab-treated patients could be up-titrated at week 12 from 75 mg to 150 mg every two weeks.

A limitation common to all included studies, which affected internal validity, was the high proportion (> 20%) of patients who withdrew, although this limitation was mitigated by the use of the mixed-effect model with repeated measures method to account for missing data, and several sensitivity analyses of the primary outcome were performed in an effort to mitigate the risk of bias. Limitations related to external validity included the fact that the studies were not designed to assess important clinical outcomes such as mortality and CV morbidity, but instead assessed the surrogate outcome of changes in LDL-C levels, although changes in LDL-C levels is a widely accepted surrogate for these clinically relevant outcomes. Finally, none of the included studies directly compared alirocumab with evolocumab, the other PCSK9 inhibitor approved for use in Canada, nor was there evidence available in the literature to compare these two drugs indirectly. Therefore, the relative efficacy and safety of alirocumab versus evolocumab is unknown.

Efficacy

The per cent reduction in LDL-C after 24 weeks was the primary outcome of all studies.

Clinical Cardiovascular Disease Studies

The per cent reductions from baseline in LDL-C after 24 weeks in alirocumab-treated patients were very similar and consistent in COMBO 1 (48%) and COMBO 2 (51%). In COMBO 1, the difference after 24 weeks between the alirocumab and placebo groups was statistically significant (least squares [LS] mean difference between groups −45.9%; 95% confidence interval [CI], −52.5 to −39.3; $P < 0.0001$). In COMBO 2, the difference between alirocumab and ezetimibe was also statistically significant (LS mean difference between groups −29.8%; 95% CI, −34.4 to −25.3; $P < 0.0001$). When compared with placebo in COMBO 1, 75% of alirocumab versus 9% of placebo patients achieved a target of < 1.8 mmol/L (combined estimate for odds ratio 38.5; 95% CI, 16.5 to 89.8; $P < 0.0001$), while in COMBO 2, 77% versus 46% of patients reached this target (odds ratio 5.4; 95% CI, 3.7 to 7.9; $P < 0.0001$). These results suggest that treatment of patients with primarily clinical CVD with alirocumab for 24 weeks is associated with a significant reduction in LDL-C levels of between 30% and 46% versus ezetimibe or placebo and allows significantly more patients to achieve a target LDL-C level of < 1.8 mmol/L.

There were no consistent differences in the number of deaths between treatments within each study. The proportion of patients with a CV event was similar for the alirocumab and placebo groups in COMBO 1 (6 [2.9%] versus 3 [2.8%]) and for the alirocumab and ezetimibe groups in COMBO 2 (23 [4.8%] versus 9 [3.7%]). In both studies, the most common CV event was ischemia-driven coronary revascularization. Quality of life was assessed using the EQ-5D; however, this was a safety outcome, and no statistically significant differences were noted between groups.

Familial Hypercholesterolemia Studies

The per cent reductions from baseline in LDL-C across studies ranged from a low of 46% in HIGH FH to 49% in each of the FH 1 and FH 2 studies. In HIGH FH, the difference after 24 weeks between the alirocumab and placebo groups was statistically significant (LS mean difference between groups −39.1%; 95% CI, −51.1 to −27.1; $P < 0.0001$). This was also the case in FH 1 (LS mean difference between groups −57.9%; 95% CI, −63.3 to −52.6; $P < 0.0001$) and FH 2 (LS mean difference between groups −51.4%; 95% CI, −58.1 to −44.8; $P < 0.0001$). The FH 1 and FH 2 studies also reported the proportion of patients reaching target LDL as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of 1.8 mmol/L for those with prior CV events and < 2.6 mmol/L for those without) or not taking it into account (target of < 1.8 mmol/L for everyone), and these differences between alirocumab and comparators were statistically significant, where reported, in all cases. Taking into account baseline CV risk, in the alirocumab versus placebo groups, 72% versus 2% of patients reached the target LDL-C level in FH 1 (odds ratio 156.0; 95% CI, 48.9 to 498.1; $P < 0.0001$) and 81% versus 11% reached target in FH 2 (odds ratio 52.2; 95% CI, 20.9 to 130.0; $P < 0.0001$). In HIGH FH, targets were also adjusted for baseline risk (very-high CV risk: < 1.8 mmol/L; high CV risk: < 2.6 mmol/L), and the difference between the alirocumab and placebo groups was statistically significant, with 41% of alirocumab-treated patients and 6% of placebo patients reaching target (odds ratio 11.7; 95% CI, 2.5 to 53.5; $P = 0.0016$). These results suggest that treatment of HeFH patients with alirocumab for 24 weeks is associated with a significant reduction in LDL-C levels of between 39% and 58% versus placebo and allows significantly more patients to achieve a target LDL-C level of < 1.8 mmol/L, even in FH patients who had not experienced a prior CV event.

In FH 1, 2% (6 patients) of alirocumab-treated patients died versus none in the placebo group, and two of these deaths were CV related. There were no numerical differences in deaths between groups in the

other studies. There was a numerically higher proportion of alirocumab-treated versus placebo-treated patients experiencing a CV event in the HIGH FH study (6 patients [8%] versus 0), although this was a small study and was clearly not powered to assess this outcome in a formal manner. Non-fatal myocardial infarction was the most common CV event, occurring in 4 (6%) alirocumab-treated patients and none in placebo. There were also numerically more CV events with alirocumab than placebo in FH 1 (8 [2.5%] versus 3 [1.8%] patients), but similar proportions of patients with CV events between the alirocumab and placebo groups in FH 2 (2 [1%] versus 1 [1%]). Quality of life was assessed using the EQ-5D; however, this was a safety outcome and therefore not part of the hierarchy for statistical testing, and no statistically significant differences were noted between groups.

Mixed Population Study

In LONG TERM, there was a statistically significantly greater per cent reduction in LDL-C for alirocumab versus placebo after 24 weeks (LS mean difference between groups −61.9%; 95% CI, −64.3, −59.4; $P < 0.001$). The LONG TERM study also reported the proportion of patients reaching target LDL as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of < 1.8 mmol/L for those with prior CV events and < 2.6 mmol/L for those without) or not taking it into account (target of < 1.8 mmol/L for everyone), and these differences between the alirocumab and placebo groups were statistically significant, where reported, in both cases. Taking into account baseline CV risk, in the alirocumab versus placebo groups, 81% versus 9% of patients reached target (odds ratio 71.5; 95% CI, 51.6 to 99.1; $P < 0.0001$) while 79% versus 8% reached target when baseline CV risk was not taken into account (odds ratio 74.6; 95% CI, 53.3 to 104.4; $P < 0.0001$). These results suggest that treatment of patients with FH, clinical CVD, or both FH and CVD with alirocumab for 24 weeks is associated with a significant reduction in LDL-C levels of up to 62% versus placebo and allows significantly more such patients to achieve a target LDL-C level of < 1.8 mmol/L.

In LONG TERM, 8 (0.5%) alirocumab-treated and 10 (1.3%) placebo-treated patients died, respectively, while CV deaths occurred in 4 (0.3%) alirocumab-treated and 7 (0.9%), placebo-treated patients, respectively. Cardiovascular events in LONG TERM occurred in 72 (4.6%) alirocumab-treated patients and 40 (5.1%) placebo patients.

Other Studies

In the remaining four studies, differences between alirocumab and various comparators were consistently statistically significantly in favour of alirocumab, regardless of background therapy, with one exception: in OPTIONS 2, there was no statistically significant difference in per cent change from baseline to 24 weeks in LDL-C in patients on a background of rosuvastatin 20 mg between treatment with alirocumab compared with ezetimibe (LS mean difference between groups −25.3%; 95% CI, −50.9 to 0.3; $P = 0.0136$) or rosuvastatin 40 mg (LS mean difference between groups −20.3%; 95% CI, −45.8 to 5.1; $P = 0.0453$). These comparisons did not reach the threshold for statistical significance of $P = 0.0125$, which had been adjusted for multiple comparisons between groups. These results suggest that treatment of patients who are not necessarily at high risk of a CV event with alirocumab for 24 weeks can significantly reduce LDL-C levels compared with ezetimibe or a doubling of background statin therapy, but it is uncertain whether this applies to patients treated with rosuvastatin.

Harms

Clinical Cardiovascular Disease Studies

The proportion of patients experiencing any adverse event (AE) was similar between the alirocumab and placebo groups in COMBO 1 (76% in each group after 52 weeks) and COMBO 2 (71% versus 67% after 104 weeks). Upper respiratory tract infection and dizziness were common AEs across studies, but these

events were infrequent (5% to 7% of patients). The most common notable harm in both studies was an allergic event, which occurred in 5% to 9% of patients across studies. The proportion of patients experiencing a serious adverse event (SAE) was similar between the alirocumab and placebo groups in COMBO 1 (13% in each group after 52 weeks) and the alirocumab versus ezetimibe groups in COMBO 2 (19% versus 18% after 104 weeks). In COMBO 1, withdrawal due to adverse event (WDAEs) occurred in 6% of alirocumab-treated patients and 8% of placebo patients, and in COMBO 2, WDAEs occurred in 8% of alirocumab-treated patients and 5% of ezetimibe patients. Therefore, alirocumab treatment did not appear to be associated with a substantial risk of potential harm in patients with clinical CVD.

Familial Hypercholesterolemia Studies

The proportion of patients with an AE after 78 weeks was numerically lower in the alirocumab treatment group versus the placebo groups in FH 2 (75% versus 82%) and HIGH FH (61% versus 71%), and similar between the groups in FH 2 (82% versus 79% for alirocumab and placebo, respectively). The most common AE across studies was nasopharyngitis. The most common notable harm across the FH studies was injection site reaction, and there was a larger proportion of alirocumab-treated versus placebo-treated patients in HIGH FH (8% versus 3%) with this AE. The proportion of patients experiencing an SAE was similar between alirocumab patients and placebo patients in FH 1 (14% in each after 78 weeks), FH 2 (9% in alirocumab, 10% in placebo after 78 weeks) and HIGH FH (11% in each after 78 weeks). In FH 1, WDAEs occurred in 3% of alirocumab patients versus 6% of placebo patients, in FH 2 WDAEs occurred in 4% of alirocumab patients versus 1% of placebo patients, and in HIGH FH WDAEs occurred in 4% of alirocumab patients versus 3% of placebo patients. Thus, alirocumab treatment did not appear to associated with a substantial risk of potential harm in HeFH patients.

Mixed Population Study

In LONG TERM, 81% of alirocumab patients versus 83% of placebo patients experienced an AE after 78 weeks. The most common AE was nasopharyngitis. The most common notable harm was allergic reaction, occurring in 10% of alirocumab and placebo patients. There were similar proportions of alirocumab-treated versus placebo-treated patients experiencing an SAE in LONG TERM (19% versus 20% after 78 weeks). WDAEs occurred in 7% of alirocumab patients versus 6% of placebo patients in LONG TERM. Thus, alirocumab treatment did not appear to associated with a substantial risk of potential harm in patients with HeFH, clinical CVD, or both.

Other Studies

The proportion of patients experiencing an AE ranged between 64% and 86% across the remaining four studies. Numerical differences in AEs between groups were noted in OPTIONS 2, where AEs occurred in 56% of alirocumab patients and 54% of ezetimibe patients versus 67% of atorvastatin 40 mg patients, and in MONO, where AEs occurred in 69% of alirocumab patients and 78% of ezetimibe patients. There were no clear and consistent differences between groups in the risk of notable harms. Across studies, SAEs were reported in between 2% and 11% of patients, with no more than a 3% difference between groups within any study. The ALTERNATIVE study had a notably higher rate of WDAEs (~25%) compared with the other studies, where WDAEs ranged between 4% and 10%. These results are consistent with the results of the studies in other populations that suggest that alirocumab treatment is not associated with a substantial risk of potentially serious harm.

Conclusions

Ten multi-centre, manufacturer-sponsored, phase 3 double-blind randomized controlled trials included in this review assessed the effects of treatment with alirocumab compared with placebo or ezetimibe on LDL-C levels over 24 weeks. Six studies included patients who were at high risk of CV events (COMBO 1 and COMBO 2), or who had HeFH (FH 1, FH 2, and HIGH FH), or who were a mixed population of both types of patient (LONG TERM), while the remaining four studies (OPTIONS 1, OPTIONS 2, MONO, and ALTERNATIVE) included broader populations of patients, including patients without FH or with clinical CVD. The results of COMBO 1 and COMBO 2 suggested that treatment of patients with clinical CVD with alirocumab for 24 weeks is associated with a statistically significant reduction in LDL-C levels of between 30% and 46% versus ezetimibe or placebo and allows statistically significantly more patients to achieve a target LDL-C level of < 1.8 mmol/L. The results of FH 1, FH 2, and HIGH FH suggested that treatment of HeFH patients with alirocumab for 24 weeks is associated with a statistically significant reduction in LDL-C levels of between 51% and 58% versus placebo and allows statistically significantly more patients to achieve a target LDL-C level of < 1.8 mmol/L, even in FH patients who had not experienced a prior CV event. The results of LONG TERM suggested that treatment of patients with HeFH or clinical CVD or both FH and CVD with alirocumab for 24 weeks is associated with a statistically significant reduction in LDL-C levels of up to 62% versus placebo and allows statistically significantly more such patients to achieve a target LDL-C level of < 1.8 mmol/L. The results of the other studies suggested that treatment of patients who are not necessarily at high risk of a CV event with alirocumab for 24 weeks statistically significantly reduces LDL-C levels compared with ezetimibe or a doubling of background statin therapy, although it is uncertain whether this applies to patients treated with rosuvastatin. There were no important or consistent differences among treatment groups across all of the included studies with respect to harms such as mortality, AEs, SAEs, or WDAEs, except for harms related to administration (such as injection site reactions). Therefore, alirocumab treatment did not appear to be associated with a substantial risk of serious harm, but there is still limited evidence regarding the long-term safety of alirocumab. Despite the availability of post-hoc analyses from the LONG TERM study, the effect of alirocumab on CV morbidity and mortality has not been determined. In addition, none of the included studies directly compared alirocumab with evolocumab, the other PCSK9 inhibitor approved for use in Canada, nor was there evidence available in the literature to compare these two drugs indirectly. Therefore, the relative efficacy and safety of alirocumab versus evolocumab is unknown.

TABLE 1: SUMMARY OF RESULTS FOR CLINICAL CARDIOVASCULAR DISEASE STUDIES

	COMBO 1		COMBO 2	
Result	**Alirocumab N = 209**	**Placebo N = 107**	**Alirocumab N = 467**	**Ezetimibe N = 240**
Mean (SD) calculated LDL baseline, mmol/L	2.597 (0.770)	2.709 (0.836)	2.805 (0.946)	2.706 (0.884)
Estimated LS mean (SE) from baseline at week 24 (%)[a]	−48.2 (1.9)	−2.3 (2.7)	−50.6 (1.4)	−20.7 (1.9)
Estimated mean difference % (95% CI)	−45.9 (−52.5 to −39.3), *P* < 0.0001		−29.8 (−34.4 to −25.3), *P* < 0.0001	
Proportion of patients reaching calculated LDL-C < 1.8 mmol/L	75.0	9.0	77.0	45.6
Combined estimate for odds ratio (95% CI)[b]	38.5 (16.5 to 89.8), *P* < 0.0001		5.4 (3.7 to 7.9), *P* < 0.0001	
Deaths, n (%)	2 (1.0)	3 (2.8)	2 (0.4)	4 (1.7)
CHD deaths (including undetermined cause), n (%)	1 (0.5)	1 (0.9)	2 (0.4)	2 (0.8)
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	6 (2.9)	3 (2.8)	23 (4.8)	9 (3.7)
• CHD death (including undetermined cause)	1 (0.5)	1 (0.9)	2 (< 1)	2 (1)
• Non-fatal MI	1 (0.5)	1 (0.9)	12 (3)	3 (1)
• Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (1.0)	0	1 (< 1)	1 (< 1)
• Unstable angina requiring hospitalization	0	0	1 (< 1)	0
• CHF requiring hospitalization	0	1 (0.9)	1 (< 1)	1 (< 1)
• Ischemia-driven coronary revascularization procedure	3 (1.4)	1 (0.9)	16 (3)	4 (2)
EQ-5D utility score mean (SD) baseline	0.826 (0.208)	0.847 (0.204)	0.84 (0.19)	0.83 (0.19)
EQ-5D utility score week 52 LS mean (SE) change from baseline (%)	−0.021 (0.014)	0.039 (0.021)	−0.004 (0.008)	0.002 (0.011)
LS mean difference (95% CI) vs. placebo	−0.060 (−0.110 to −0.010), *P* = 0.0183		−0.006 (−0.032 to 0.021), *P* = 0.6747	
Harms				
AE, patients, n (%)	157 (76)	81 (76)	341 (71)	162 (67)
SAE, patients, n (%)	26 (13)	14 (13)	90 (19)	43 (18)
WDAE, patients, n (%)	13 (6)	8 (8)	36 (8)	13 (5)

AE = adverse event; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL–5 Dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes et al. 2015,[5] Cannon et al. 2015.[6]

TABLE 2: SUMMARY OF RESULTS FOR FAMILIAL HYPERCHOLESTEROLEMIA–SPECIFIC STUDIES

	FH 1		FH 2		HIGH FH	
Result	**Alirocumab N = 322**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**	**Alirocumab N = 71**	**Placebo N = 35**
Calculated LDL-C, LS mean (SD) baseline, mmol/L	3.748 (1.326)	3.739 (1.213)	3.486 (1.069)	3.470 (1.078)	5.083 (1.499)	5.205 (1.125)
Estimated LS mean (SE) change from baseline at week 24 (%)[a]	−48.8 (1.6)	9.1 (2.2)	−48.7 (1.9)	2.8 (2.8)	−45.7 (3.5)	−6.6 (4.9)
Estimated mean difference % (95% CI)	−57.9 (−63.3 to −52.6), *P* < 0.0001		−51.4 (−58.1 to −44.8), *P* < 0.0001		−39.1 (−51.1 to −27.1), *P* < 0.0001	
Patients (%) with or without prior CV events achieving LDL-C < 1.8 mmol/L or < 2.6 mmol/L, respectively, at week 24	72.2%	2.4%	81.4%	11.3%	NR	NR
Combined estimate for odds ratio (95% CI)[b]	156.0 (48.9 to 498.1), *P* < 0.0001		52.2 (20.9 to 130.0), *P* < 0.0001			
Patients (%) achieving LDL-C < 1.8 mmol/L at week 24 (regardless of prior CV events)	59.8%	0.8%	68.2%	1.2%	NR	NR
Combined estimate for odds ratio (95% CI)[b]	244.9 (34.4 to 1,744.4), *P* < 0.0001		239.7 (31.6 to 1,820.3), *P* < 0.0001			
Very-high CV risk patients (%) reaching calculated LDL-C < 1.8 mmol/L or high CV risk patients reaching calculated LDL-C < 2.6 mmol/L at week 24	NR	NR	NR	NR	41.0%	5.7%
Combined estimate for odds ratio (95% CI)[b]					11.7 (2.5 to 53.5), *P* = 0.0016	
Deaths, n (%)	6 (1.9)	0	0	0	0	0
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	8 (2.5)	3 (1.8)	2 (1)	1 (1)	6 (8.3)	0
– CHD death (including undetermined cause)	2 (1)	0	0	0	0	0
– Non-fatal MI	1 (< 1)	0	0	1	4 (6)	0
– Fatal and non-fatal ischemic stroke (including stroke NOS)	1 (< 1)	0	0	0	0	0
– Unstable angina requiring hospitalization	1 (< 1)	0	0	0	0	0
– CHF requiring hospitalization	1 (< 1)	0	0	1	1 (1)	0
– Ischemia-driven coronary revascularization procedure	2 (1)	2 (1)	2 (1)	1	5 (7)	0

	FH 1		FH 2		HIGH FH	
Result	**Alirocumab N = 322**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**	**Alirocumab N = 71**	**Placebo N = 35**
EQ-5D utility score mean (SD) baseline	0.908 (0.139)	0.912 (0.127)	0.917 (0.151)	0.907 (0.154)	0.926 (0.122)	0.883 (0.208)
EQ-5D utility score week 52 LS mean (SE) change from baseline	−0.002 (0.007)	0.007 (0.010)	−0.027 (0.011)	0.000 (0.015)	−0.030 (0.022)	−0.013 (0.030)
LS mean difference (95% CI) vs. placebo	−0.010 (−0.034 to 0.014), *P* = 0.4287		0.027 (−0.010 to 0.064), *P* = 0.1481		−0.017 (−0.092 to 0.057), *P* = 0.6424	
Harms						
AE, patients, n (%)	263 (82)	129 (79)	125 (75)	66 (82)	44 (61)	25 (71)
SAE, patients, n (%)	44 (14)	22 (14)	15 (9)	8 (10)	8 (11)	4 (11)
WDAE, patients, n (%)	11 (3)	10 (6)	6 (4)	1 (1)	3 (4)	1 (3)

AE = adverse event; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; NOS = not otherwise specified; NR = not reported; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time-point interaction.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein et al. 2015,[9] Clinical Study Report for HIGH FH.[10]

TABLE 3: SUMMARY OF RESULTS FOR MIXED POPULATION STUDY

	LONG TERM	
Result	**Alirocumab N = 1530**	**Placebo N = 780**
Mean (SD) baseline LDL-C (mmol/L)	3.18 (1.10)	3.15 (1.08)
Estimated LS mean (SE) change from baseline at week 24 (%)[a]	−61.0 (0.7)	0.8 (1.0)
Estimated mean difference % (95% CI)	−61.9 (−64.3 to −59.4), *P* < 0.001	
Proportion of patients achieving LDL-C < 1.8mmol/L in patients at very-high risk or < 2.6mmol/L in patients at high risk	80.7	8.5
Combined estimate for odds ratio (95% CI)[b]	71.5 (51.6 to 99.1), *P* < 0.0001	
Proportion of patients achieving LDL-C < 1.8mmol/L regardless of risk	79.3	8.0
Combined estimate for odds ratio (95% CI)[b]	74.6 (53.3 to 104.4), *P* < 0.0001	
Deaths, n (%)	8 (0.5)	10 (1.3)
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	72 (4.6)	40 (5.1)
CHD death (including undetermined cause), n (%)	4 (0.3)	7 (0.9)
• Non-fatal MI	14 (1)	18 (2)
• Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	9 (1)	2 (< 1)
• Unstable angina requiring hospitalization	0	1 (< 1)
• CHF requiring hospitalization	9 (1)	2 (< 1)
• Ischemia-driven coronary revascularization procedure	48 (3)	24 (3)
EQ-5D utility score mean (SD) baseline	0.8581 (0.1969)	0.8399 (0.2101)
EQ-5D utility score week 52 LS mean (SE) change from baseline	−0.018 (0.004)	−0.012 (0.006)
LS mean difference (95% CI) vs. placebo	−0.006 (−0.021 to 0.009), *P* = 0.4483	
Harms		
AE, patients, n (%)	1255 (81)	650 (83)
SAE, patients, n (%)	290 (19)	154 (20)
WDAE, patients, n (%)	111 (7)	46 (6)

AE = adverse event; CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; SAE = serious adverse event; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time-point interaction.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

Other Four Studies Not Considered Relevant to Reimbursement Criteria

TABLE 4: SUMMARY OF RESULTS FOR OPTIONS 1

	OPTIONS 1						
	Atorvastatin 20 mg Background			Atorvastatin 40 mg Background			
Result	Aliro N = 57	EZE N = 55	ATV 40 N = 57	Aliro N= 47	EZE N = 47	ATV 80 N = 47	ROS 40 N = 45
Mean (SD) calculated LDL baseline (mmol/L)	2.679 (0.904)	2.627 (0.760)	2.603 (0.800)	3.036 (0.968)	2.569 (0.763)	2.813 (0.970)	2.844 (1.011)
Estimated LS mean (SE) from baseline at week 24 (%)[a]	−44.1 (4.5)	−20.5 (4.7)	−5.0 (4.6)	−54.0 (4.3)	−22.6 (4.3)	−4.8 (4.2)	−21.4 (4.2)
Estimated mean difference, % (95% CI)	Versus EZE: −23.6 (−40.7 to −6.5), *P* = 0.0004 Versus ATV: −39.1 (−55.9 to −22.2), *P* = 0.0001			Versus EZE: −31.4 (−47.4 to −15.4), *P* < 0.0001 Versus ATV: −49.2 (−65.0 to −33.5), *P* < 0.0001 Versus ROS: −32.6 (−48.4 to −16.9), *P* < 0.0001			
Proportion of very-high CV risk patients reaching a calculated LDL-C < 1.81 mmol/L or high CV risk patients reaching a calculated LDL-C < 2.59 mmol/L at week 24	87.2	68.4	34.5	84.6	65.1	18.5	62.2
Combined estimate for odds ratio (95% CI)[b]	Versus EZE: 3.4 (0.8 to 14.6), *P* = 0.0284[c] Versus ATV: 16.7 (3.9 to 71.7), *P* < 0.0001			Versus EZE: 9.1 (1.6 to 52.2), *P* = 0.0011 Versus ATV: 83.2 (11.6 to 596.8), *P* < 0.0001 Versus ROS: 7.2 (1.3 to 38.3), *P* = 0.0025			
Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24	79.2	50.3	16.0	77.2	54.2	42.2	10.2
Combined estimate for odds ratio (95% CI)[b]	Versus EZE: 4.7 (1.3 to17.0)[c] Versus ATV: 28.9 (6.5 to127.8), *P* < 0.0001			Versus EZE: 9.9 (1.9 to 51.9) *P,* = 0.0004 Versus ATV: 13.2 (2.5 to 68.8), *P* < 0.0001 Versus ROS: 116.8 (14.7 to 927.5), *P* < 0.0001			
Deaths (pooled), n (%)	0	2 (2)	0	NA	NA	NA	NA
CHD death (including undetermined) (pooled), n (%)	0	1 (1)	0	NA	NA	NA	NA
Any patients with treatment-emergent CV events confirmed by adjudication (pooled), n (%)	1 (1)	1 (1)	0	NA	NA	NA	NA
EQ-5D	NR	NR	NR	NA	NA	NA	NA
Harms				NA	NA	NA	NA
AE, patients, n (%), pooled	68 (65)	65 (64)	95 (64)	NA	NA	NA	NA
SAE, patients, n (%), pooled	4 (4)	7 (7)	8 (5)	NA	NA	NA	NA
WDAE, patients, n (%), pooled	7 (7)	4 (4)	8 (5)	NA	NA	NA	NA

AE = adverse event; Aliro = alirocumab; ATV = atorvastatin; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; NA = not applicable; NR = not reported; ROS = rosuvastatin; SD = standard deviation; SE = standard error

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point interaction, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets using Rubin's formula. The logistic regression models stratified by randomization factors as per interactive voice response system include the fixed categorical effect of treatment group and the continuous fixed covariate of baseline calculated LDL-C value.

[c] Not statistically significant after adjustment for multiplicity (*P* = 0.01) or not tested after previous end point failed to achieve statistical significance.

Source: Clinical Study Report for OPTIONS 1,[13] Bays 2015.[14]

TABLE 5: SUMMARY OF RESULTS FOR OPTIONS 2

	OPTIONS 2					
	Rosuvastatin 10 mg Background			Rosuvastatin 20 mg Background		
Result	Alirocumab N = 49	EZE N = 48	ROS 20 N = 48	Alirocumab N = 54	EZE N = 53	ROS 40 N = 53
Mean (SD) calculated LDL baseline (mmol/L)	2.791 (0.687)	2.643 (1.095)	2.743 (0.933)	3.059 (0.841)	3.092 (1.257)	2.946 (1.122)
Estimated LS mean (SE) change from baseline at week 24 (%)[a]	−50.6 (4.2)	−14.4 (4.4)	−16.3 (4.1)	−36.3 (7.1)	−11.0 (7.2)	−15.9 (7.1)
Difference versus comparator	Versus EZE: −36.1 (−51.5 to −20.7), *P* < 0.0001 Versus ROS: −34.2(−49.2 to −19.3), *P* < 0.0001			Versus EZE: −25.3 (−50.9 to 0.3), *P* = 0.0136[c] Versus ROS: −20.3 (−45.8 to 5.1), *P* = 0.0453[c]		
Proportion of patients reaching target LDL-C < 1.8 mmol/L (very-high CV risk) or < 2.6 mmol/L (high CV risk); at week 24	84.9%	57.2%	45.0%	66.7%	52.2%	40.1%
Combined estimate for odds ratio (95% CI) versus comparator[b]	Versus EZE: 8.4 (1.8 to 40.5), *P* = 0.0007 Versus ROS: 12.4 (2.6 to 59.5), *P* < 0.0001			Versus EZE: 2.1 (0.6 to 7.0)[c] Versus ROS: 4.6 (1.3 to 15.9)[c]		
Proportion of patients reaching target LDL-C < 1.8 mmol/L (regardless of CV risk) at week 24	77.8%	43.1%	31.3%	60.1%	43.6%	29.9%
Combined estimate for odds ratio (95% CI) versus comparator[b]	Versus EZE: 11.6 (2.5 to 53.1), *P* < 0.0001 Versus ROS: 18.6 (3.6 to 96.2), *P* < 0.0001			Versus EZE: 2.5 (0.7 to 8.5)[c] Versus ROS: 6.1 (1.6 to 22.8)[c]		
Deaths (pooled), n (%)	0	1 (1.0)	0	NA	NA	NA
CHD death (including undetermined cause)	0	0	0	NA	NA	NA
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	0 (pooled)	1 (1) (pooled)	1 (1) (pooled)	NA	NA	NA
EQ-5D	NR			NA	NA	NA
Harms				NA	NA	NA
AE, patients, n (%), pooled	58 (56)	54 (54)	68 (67)	NA	NA	NA
SAE, patients, n (%), pooled	6 (6)	8 (8)	8 (8)	NA	NA	NA
WDAE, patients, n (%), pooled	5 (5)	8 (8)	5 (5)	NA	NA	NA

AE = adverse event; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; NA = not applicable NR = not reported; ROS = rosuvastatin; SAE = standard error; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point interaction, strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets using Rubin's formula. The logistic regression models stratified by randomization factors as per interactive voice response system include the fixed categorical effect of treatment group and the continuous fixed covariate of baseline calculated LDL-C value.

[c] Not statistically significant after adjustment for multiplicity (*P* = 0.0125) or not tested after previous end point failed to achieve statistical significance.

Source: Clinical Study Report for OPTIONS 2,[15] Farnier et al. 2016.[16]

TABLE 6: SUMMARY OF RESULTS FOR ALTERNATIVE AND MONO

	ALTERNATIVE			MONO	
Result	Alirocumab N = 126	Ezetimibe N = 124	ATV N = 63	Alirocumab N = 52	Ezetimibe N = 51
Mean (SD) baseline (mmol/L)				3.654 (0.702)	3.583 (0.636)
Estimated LS mean (SE) from baseline at week 24 (%)[a]	−45.0 (2.2)	−14.6 (2.2)	NR	−47.2 (3.0)	−15.6 (3.1)
LS mean difference (SE) vs. ezetimibe	−30.4 (−36.6 to −24.2), $P < 0.0001$			−31.6 (−40.2, −23.0), $P < 0.0001$	
Proportion of patients reaching calculated LDL-C < 2.6 mmol/L at week 12	NR	NR	NR	88.3	30.7
Combined estimate for odds ratio (95% CI)[b]	NA			47.4 (11.0 to 204.2), $P < 0.0001$	
Proportion of patients reaching calculated LDL-C < 1.8 mmol/L at week 12	NR	NR	NR	30 (58)	0
Combined estimate for odds ratio (95% CI)[b]	NA			138.7 (21.1 to > 9,999), $P < 0.0001$	
Proportion of very-high CV risk patients reaching a calculated LDL-C < 1.81 mmol/L or moderate or high CV risk patients reaching a calculated LDL-C < 2.59 mmol/L	41.9	4.4	NR	NR	NR
Combined estimate for odds ratio (95% CI)[b]	19.5 (6.9 to 55.2) $P <$ 0.0001		NR	NA	
Deaths	0	0	0	0	0
CHD death (including undetermined cause)	0	0	0	0	0
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	4 (3)	1 (1)	1 (2)	0	0
• Non-fatal myocardial infarction	1 (1)	0	0	0	0
• Ischemia-driven coronary revascularization procedure	3 (2)	1 (1)	1 (2)	0	0
Mean (SD) EQ-5D utility score	NR	NR	NR	0.94 (0.10)	0.92 (0.12)
Week 24 change from baseline LS mean (SE)	NR	NR	NR	0.01 (0.02)	−0.02 (0.02)
LS mean difference (95% CI) vs. ezetimibe	NA			0.03 (−0.02 to 0.07), $P = 0.2464$	
Harms					
AE, patients, n (%)	104 (83)	100 (81)	54 (86)	36 (69)	40 (78)
SAE, patients, n (%)	12 (10)	10 (8)	7 (11)	1 (2)	1 (2)
WDAE, patients, n (%)	23 (18)	31 (25)	16 (25)	5 (10)	4 (8)

AE = adverse event; ATV = atorvastatin; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; NR = not reported; SD = standard deviation; SE = standard error; vs. = versus; WDAE = withdrawal due to adverse event.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, time point, and treatment-by-time-point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time-point interaction; MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula. The logistic regression models include the fixed categorical effect of the treatment group and the continuous fixed covariate of baseline LDL-C value.

Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Low-density lipoprotein cholesterol (LDL-C) is the key component in total cholesterol, and is believed to play a crucial role in the formation of atherosclerotic plaques. Familial hypercholesterolemia (FH) is a common genetic disorder of lipid metabolism affecting between 14 and 34 million people worldwide.[1] FH is characterized by markedly elevated plasma levels of LDL-C, the chronic exposure to which leads to an increased susceptibility to premature coronary artery disease and cardiac death,[1] sometimes before the age of 10 in the most severe presentation of the disease.[22] Patients with untreated FH have a twentyfold increased risk, irrespective of the underlying genetic mutation, of developing premature coronary artery disease compared with people without FH.[22] FH is subdivided into heterozygous (HeFH) and homozygous disease,[1,22-24] with homozygous FH being the more severe and rare form.[1,25] In Canada, it is estimated that HeFH affects 83,500 people, while homozygous FH affects 60 people. In their input to the CADTH Common Drug Review (CDR), patients with FH describe the fear of death from their disease and the challenges associated with trying to get their LDL-C levels down to target. Patients describe being made to feel guilty about their weight or lack of exercise, and caregivers describe the challenges associated with getting those under their care to take medications regularly for an asymptomatic condition where the benefits of drug therapy are not readily apparent.

Hyperlipidemia is typically defined by an elevated LDL-C, and although the cut-off for therapy is also impacted by the patient's risk factors, for patients with established cardiovascular disease (CVD), the recommended target LDL-C is ≤ 2.0 mmol/L. For primary prevention in FH, and for treatment in patients in whom therapy is limited by intolerance, and who fail to achieve an LDL-C of ≤ 2.0 mmol/L, the Canadian Cardiovascular Society guidelines recommend a reduction in LDL-C of at least 50% from baseline.[2]

1.2 Standards of Therapy

Initial interventions for hyperlipidemia include diet and lifestyle modifications. The standard lipid-lowering therapy for the last few decades has been the use of HMG-CoA reductase inhibitors, more commonly known as statins. These drugs reduce cholesterol synthesis and have been the standard of care since their entry onto the market. The next most common drug used in management of hyperlipidemia is ezetimibe, an inhibitor of cholesterol absorption. Ezetimibe is typically used in combination with a statin, most commonly atorvastatin. Other drugs sometimes used in the management of hyperlipidemia include the bile acid sequestrants, which work by reducing the availability of bile acids, a precursor to cholesterol, and fibrates, which through a variety of mechanisms reduce triglyceride levels and increase high-density lipoprotein cholesterol. Niacin has also been used for hyperlipidemia for a number of years, although its use is waning according to the clinical expert, due to poor evidence regarding its use. The proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, described below, represent the newest class of lipid-lowering therapy, with evolocumab being the first drug approved in Canada.

1.3 Drug

Alirocumab is administered as a subcutaneous injection, 75 mg or 150 mg every two weeks. The recommended starting dose is 75 mg once every two weeks, and an increase to the maximum dose of 150 mg every two weeks can be considered if LDL-C response is inadequate. It is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CVD who require additional lowering of LDL-C.

Alirocumab is a fully human monoclonal antibody that binds to human PCSK9. Binding of PCSK9 to LDL-C receptors leads to destruction of those receptors. Therefore, when alirocumab binds to PCSK9, it prevents PCSK9 from destroying LDL-C receptors, which leads to an increase in LDL-C receptor density at the surface of the liver and enhanced clearance of LDL-C from the blood.

Indication under review
As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
Reimbursement criteria requested by sponsor
As an adjunct to diet and maximally tolerated statin (MTS) therapy with or without other lipid lowering therapies (LLT) for adults with HeFH or high-risk patients who have had prior cardiovascular (CV) events and require additional lowering of LDL-C.

TABLE 7: KEY CHARACTERISTICS OF PCSK9 INHIBITORS

	Alirocumab	Evolocumab
Indication[a]	As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CVD, who require additional lowering of LDL-C	
Route of Administration	Subcutaneous	
Recommended Dose	75 mg or 150 mg every two weeks. The recommended starting dose is 75 mg every two weeks, and this can be increased to 150 mg every two weeks if there is an inadequate LDL-C response.	140 mg every two weeks or 420 mg once monthly
Serious Side Effects/Safety Issues	None so far	

CVD = cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.
[a] Health Canada indication.

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of alirocumab for the treatment of primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 8.

TABLE 8: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia Subgroups: • Baseline LDL-C • Patients with a prior CV event (MI, ischemic stroke, unstable angina requiring hospitalization, or coronary revascularization) • Concomitant use of antihyperlipidemics during study • Patients who are not candidates for or are intolerant to statins
Intervention	Alirocumab 75 mg or 150 mg subcutaneously once every two weeks, as monotherapy or in combination with a statin with or without other lipid-modifying therapy
Comparators	Evolocumab Ezetimibe Statins Placebo

Outcomes	**Key efficacy outcomes:**
	• Mortality (all-cause and CV related)[a]
	• Morbidity (CV related)[a]
	  ○ CV events
	  ○ Hospitalizations
	  ○ Minimally invasive CV interventions (e.g., PCI)
	• Changes in LDL-C[a]
	• Quality of life[a]
	  ○ HRQoL
	Other efficacy outcomes:
	• Health care resource utilization
	• Vascular imaging
	Harms outcomes:
	AEs, SAEs, WDAEs
	Notable harms: immune reactions, injection site reactions, muscle symptoms, neurocognitive changes, hepatitis C, liver enzymes

Study Design	Published and unpublished phase 3 DB RCTs

AE = adverse event; DB RCT = double-blind randomized controlled trial; CV = cardiovascular; HRQoL = health-related quality of life; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAE = serious adverse event; SC = subcutaneous; WDAE = withdrawal due to adverse event.
[a] Outcomes identified as important in patient input to CDR.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records & daily updates through Ovid, Embase (1974–) through Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Praluent (alirocumab).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on February 3, 2016. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on June 15, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Devices Regulatory Approvals, Advisories and Warnings, Drug Class Review, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Figure 1; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings From the Literature

A total of 10 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 9: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

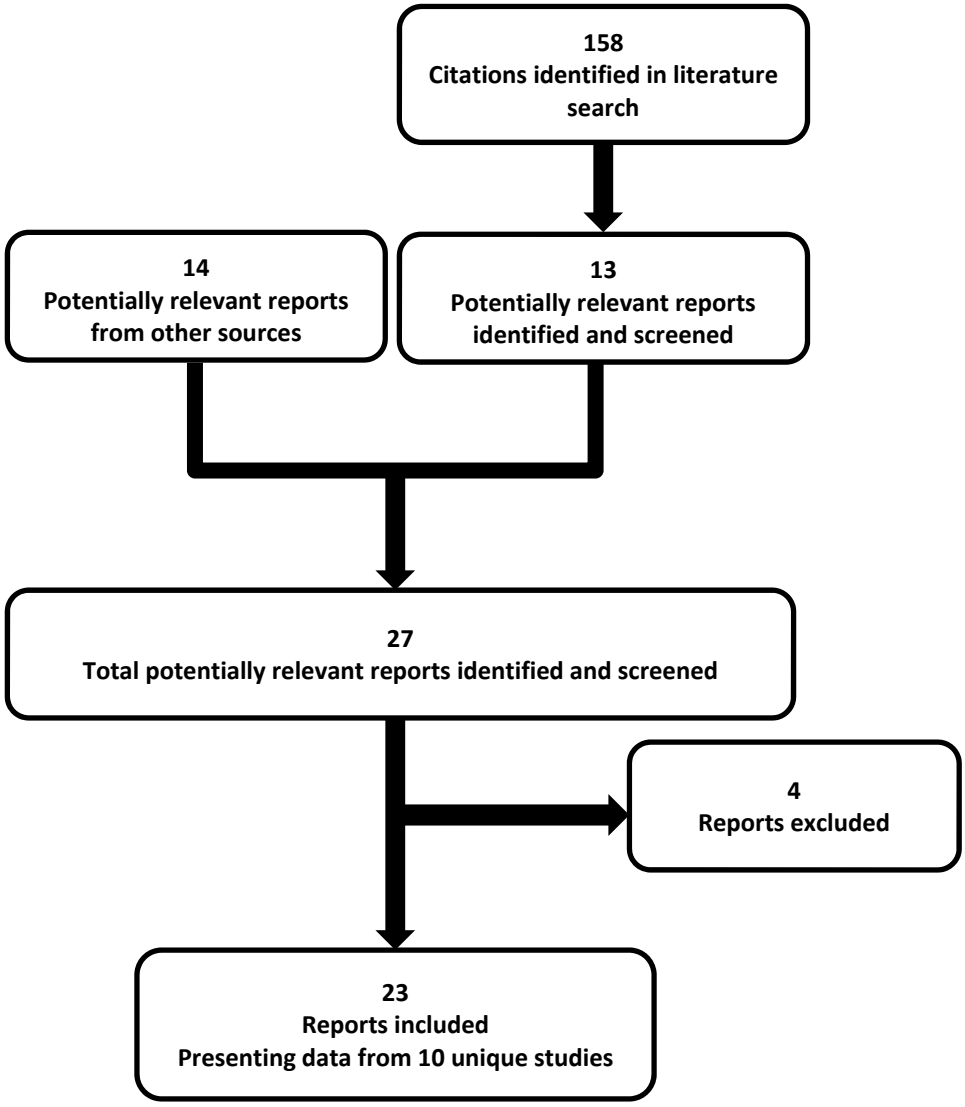

TABLE 9: DETAILS OF INCLUDED STUDIES FOR COMBO 1 AND COMBO 2

		COMBO 1	COMBO 2
DESIGNS AND POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	US: 76 sites	126 sites (Europe, Israel, North America, South Africa, South Korea)
	Randomized (N)	316	720
	Study Period	July 2012 to April 2014	August 2012 to May 2013
	Inclusion Criteria	Patients aged ≥ 18 years could participate if they had either (a) LDL-C ≥ 1.81 mmol/L and established CVD or (b) LDL-C ≥ 2.59 mmol/L with CHD risk equivalents (e.g., diabetes mellitus with other risk factors or chronic kidney disease). Receiving a stable, maximally tolerated statin dose (defined as atorvastatin, 40 mg to 80 mg; rosuvastatin, 20 mg to 40 mg; or simvastatin, 80 mg daily; or lower doses provided the investigator had a documented reason for not using the higher dose, e.g., intolerance and local practice) with or without other LLT (bile acid sequestrant, ezetimibe, niacin, or omega-3 ≥ 1,000 mg/day with stable dose ≥ 4 weeks; or fenofibrate with stable dose ≥ 6 weeks before enrolment)	Hypercholesterolemia and established CHD or CHD risk equivalents (ischemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes mellitus plus ≥ 2 additional risk factors) and be treated with a maximally tolerated dose of statin therapy (i.e., rosuvastatin 20 mg or 40 mg, atorvastatin 40 mg or 80 mg, or simvastatin 80 mg [if on this dose for > 1 year]) or on a lower dose provided the reason for doing so was documented. Statin dose had to be stable for ≥ 4 weeks before the screening visit and use of other LLT was not permitted. At screening, patients with documented CVD and LDL-C ≥ 1.8 mmol/L or no documented history of CVD but who were at high CV risk and had LDL-C ≥ 2.6 mmol/L were eligible to participate.
	Exclusion Criteria	Uncontrolled diabetes with A1C > 8.5% or diagnosed within 3 months, clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins, blood pressure > 160/100 mm Hg, major CV event within 3 months, New York Heart Association class III or IV heart failure within 12 months, fasting serum triglycerides > 4.52 mmol/L, thyroid-stimulating hormone either below or above the upper limit of normal, alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase > 3 × upper limit of normal	Recent (within 3 months before the screening visit or between screening and randomization visits) MI, unstable angina leading to hospitalization, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, TIA, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease
DRUGS	**Intervention**	Alirocumab 75 mg Q2W Add-on therapy to stable, maximally tolerated daily statin therapy (with or without other LLT) If LDL-C level was ≥ 1.81 mmol/L at week 8, alirocumab was increased in an automated and blinded fashion to 150 mg SC Q2W at the week 12 visit.	Alirocumab 75 mg SC Q2W (plus oral placebo or ezetimibe daily) The dose in the alirocumab group (only) was automatically increased in a blinded fashion, per protocol, at week 12 to 150 mg Q2W (1 mL volume) if the week 8 LDL-C value was ≥ 1.8 mmol/L. Continued to receive their background statin therapy
	Comparator(s)	Matching placebo Add-on therapy to stable, maximally tolerated daily statin therapy (with or without other LLT)	Ezetimibe (oral) 10 mg PO daily (plus placebo SC Q2W for alirocumab) Continued to receive their background statin therapy

		COMBO 1	COMBO 2
DURATION			
	Screening	Up to 2 weeks	Up to 3 weeks
	Double-blind	52 weeks	104 weeks
	Follow-up	8 weeks	8 weeks
OUTCOMES	**Primary End Point**	Per cent change in LDL-C from baseline to week 24 (ITT)	Per cent change in calculated LDL-C from baseline to week 24
	Other End Points	Per cent change in calculated LDL-C from baseline to week 24 (on-treatment) Per cent change in calculated LDL-C from baseline to week 12 (ITT) Per cent change in calculated LDL-C from baseline to week 12 (on-treatment) Per cent change in calculated LDL-C from baseline to week 52 (ITT) Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (ITT) Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (on-treatment)	
NOTES	**Publications**	Kereiakes et al. 2015[5]	Cannon et al. 2015[6]

A1C = hemoglobin A1C; CABG = coronary artery bypass graft; CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DB RCT = double-blind randomized controlled trial; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention; PO = by mouth; Q2W = every 2 weeks; SC = subcutaneous; TIA = transient ischemic attack.
Note: Four additional reports were included (Food and Drug Administration clinical and statistical reviews,[26,27] manufacturer's submission,[28] and Clinical Study Report).
Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes 2015,[5] Cannon et al. 2015.[6]

TABLE 10: DETAILS OF INCLUDED STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

		FH 1 and FH 2	HIGH FH
DESIGNS AND POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	FH 1: 89 sites North America, Europe, S Africa FH 2: 26 sites in Europe	
	Randomized (N)	FH 1: 486 FH 2: 249	107
	Study Period	FH 1: July 2012 to April 2014 FH 2: Nov 2012 to May 2014	June 2012 to May 2014
	Inclusion Criteria	Patients with HeFH who did not have a history of CV events, and those who had suffered an MI or ischemic stroke, if their LDL-C levels were not at goal according to current guidelines for primary (≥ 2.6 mmol/L) or secondary (≥ 1.8 mmol/L) prevention, respectively HeFH diagnosis was either by genotyping or clinical criteria (Simon Broome criteria or World Health Organization/Dutch Lipid Network criteria with a score of > 8 points). All patients were receiving stable high-dose statin therapy (rosuvastatin 20 mg to 40 mg, atorvastatin 40 mg to 80 mg, or simvastatin 80 mg; lower doses were allowed with an investigator-documented justification, e.g., intolerance to higher statin doses), with or without other LLT for at least 4 weeks before screening (6 weeks for fenofibrate; other fibrates were not allowed).	Adult patients with HeFH who were not adequately controlled with a maximally tolerated stable daily dose of statin for at least 4 weeks before the screening visit, with or without other LLT

		FH 1 and FH 2	HIGH FH
	Exclusion Criteria	Patients with known homozygous FH or fasting serum triglyceride levels > 4.5 mmol/L	LDL-C < 4.14 mmol/L at the screening visit Fasting serum TGs > 4.52 mmol/L at the screening visit Known history of homozygous FH
DRUGS	**Intervention**	Alirocumab 75 mg Q2W Alirocumab was increased in a blinded fashion to 150 mg Q2W at week 12 if the patient's LDL-C level at week 8 was ≥ 1.8 mmol/L. In addition to stable, maximally tolerated daily statin therapy (atorvastatin, rosuvastatin, or simvastatin) with or without other LLT	Alirocumab 150 mg Q2W
	Comparator(s)	Placebo In addition to stable, maximally tolerated daily statin therapy (atorvastatin, rosuvastatin, or simvastatin) with or without other LLT	Placebo
DURATION	Screening	Up to 3 weeks	3 weeks
	Double-blind	78 weeks	78 weeks
	Follow-up	8 weeks (or 3-year open-label extension study)	8 weeks
OUTCOMES	**Primary End Point**	Per cent change in calculated LDL-C from baseline to week 24 in the intention-to-treat (ITT) population	Per cent change in calculated LDL-C from baseline to week 24
	Other End Points	The key secondary end points were as follows: Per cent change in calculated LDL-C from baseline to week 24 (on-treatment) Per cent change in calculated LDL-C from baseline to week 12 (ITT estimand) Per cent change in calculated LDL-C from baseline to week 12 (on-treatment) Per cent change in calculated LDL-C from baseline to week 52 (ITT estimand) Proportion of very-high CV risk patients reaching calculated LDL-C < 1.81 mmol/L or high CV risk patients reaching calculated LDL-C < 2.59 mmol/L at week 24 (ITT estimand) Proportion of very-high CV risk patients reaching calculated LDL-C < 1.81 mmol/L or high CV risk patients reaching calculated LDL-C < 2.59 mmol/L at week 24 (on-treatment) Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (ITT estimand) Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (on-treatment)	
NOTES	**Publications**	Kastelein et al. 2015[9]	None

CV = cardiovascular; DB RCT = double-blind randomized controlled trial; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; Q2W = every 2 weeks.
Note: Four additional reports were included (FDA clinical and statistical reviews,[26,27] manufacturer's submission,[28] and Clinical Study Report).
Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein 2015,[9] Clinical Study Report for HIGH FH.[10]

TABLE 11: DETAILS OF INCLUDED STUDIES FOR MIXED POPULATION

		LONG TERM
DESIGNS AND POPULATIONS	**Study Design**	DB RCT
	Locations	320 sites in 27 countries: Africa, Europe, and North and South America
	Randomized (N)	2,341
	Study Period	January 2012 to May 2014
	Inclusion Criteria	Adult patients with HeFH with or without established CHD or CHD risk equivalents who are not adequately controlled with a maximally tolerated, stable daily dose of statin for at least 4 weeks before the screening visit with or without other LLT **OR** Patients with hypercholesterolemia and established CHD or CHD risk equivalents who are not adequately controlled with a maximally tolerated, stable daily dose of statin for at least 4 weeks before the screening visit with or without other LLT Definition of maximally tolerated dose (any of the following were acceptable): • Rosuvastatin 20 mg or 40 mg daily • Atorvastatin 40 mg or 80 mg daily • Simvastatin 80 mg daily (if already on this dose for > 1 year)
	Exclusion Criteria	Without established history of CHD or CHD risk equivalents, or without a diagnosis of HeFH based on genotyping or clinical criteria LDL-C < 1.81 mmol/L at screening (week 3) Not on a stable dose of LLT (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, before screening (week -3) and from screening to randomization Currently taking a statin that is not simvastatin, atorvastatin, or rosuvastatin Simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than one year, who are eligible)
DRUGS	**Intervention**	Alirocumab 150 mg SC Q2W
	Comparator(s)	Placebo
DURATION	Screening	3 weeks
	Double-blind	78 weeks
	Follow-up	8 weeks
OUTCOMES	**Primary End Point**	Percentage change in calculated LDL cholesterol level from baseline to week 24, analyzed with the use of an ITT approach
	Other End Points	The key secondary efficacy variables were: Per cent change in calculated LDL-C from baseline to week 24 (on-treatment) Per cent change in calculated LDL-C from baseline to week 12 (ITT estimand) Per cent change in calculated LDL-C from baseline to week 12 (on-treatment) Per cent change in measured LDL-C from baseline to week 24 (ITT estimand) Proportion of very-high CV risk patients reaching calculated LDL-C < 1.81 mmol/L or high CV risk patients reaching calculated LDL-C < 2.59 mmol/L at week 24 (ITT) Proportion of very-high CV risk patients reaching calculated LDL-C < 1.81 mmol/L or high CV risk patients reaching calculated LDL-C < 2.59 mmol/L at week 24 (on-treatment) Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (ITT) Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (on-treatment)

		LONG TERM
NOTES	**Publications**	Robinson et al. 2015[12]

CHD = coronary heart disease; CV = cardiovascular; DB RCT = double-blind randomized controlled trial; HeFH = heterozygous familial hypercholesterolemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; Q2W = every 2 weeks; SC = subcutaneous.
Note: Four additional reports were included (FDA clinical and statistical reviews,[26,27] manufacturer's submission,[28] and Clinical Study Report).
Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

Other Four Studies Considered Less Relevant to Reimbursement Criteria

TABLE 12: DETAILS OF INCLUDED STUDIES FOR OPTIONS 1 AND OPTIONS 2

		OPTIONS 1	OPTIONS 2
DESIGNS AND POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	85 sites: N America (incl. Canada), EU, Australia	79 sites: EU, N America (incl. Canada), Australia
	Randomized (N)	355	305
	Study Period	October 2012 and May 2014	November 2012 to May 2014
	Inclusion Criteria	Men and women aged 18 years or older at very-high CVD risk (a history of CVD including CHD, or type 2 diabetes with target organ damage) and LDL-C of 1.8 mmol/L or greater or at high risk (no history of CVD or CHD but with other risk factors: calculated 10-year risk of fatal CVD of 5% or greater [Systematic Coronary Risk Evaluation], moderate chronic kidney disease, or diabetes with no target organ damage) and LDL-C of 2.6 mmol/L or greater Patients presenting with these LDL-C levels despite receiving atorvastatin 20 mg or 40 mg/day with or without other LLT (but not ezetimibe) for at least 4 weeks before screening If not already on stable atorvastatin 20 mg or 40 mg/day, patients were enrolled into a run-in period to receive atorvastatin 20 mg or 40 mg/day for at least 4 weeks before screening and randomization.	Adults with hypercholesterolemia at very-high or high CV risk receiving rosuvastatin 10 or 20 mg/day for at least 4 weeks before screening Very-high CV risk patients with a history of CHD, non-CHD CVD, or diabetes mellitus with target organ damage were included if LDL-C was ≥ 1.8 mmol/L at screening. High-risk CV patients without documented CHD or CVD but with a 10-year risk of fatal CVD ≥ 5% (Systematic Coronary Risk Evaluation), moderate chronic kidney disease, or diabetes with no target organ damage were included if LDL-C was ≥ 2.6 mmol/L.
	Exclusion Criteria	LDL-C < 1.81 mmol/L at the screening visit (week -2) in patients with history of documented CHD or non-CHD CVD LDL-C < 2.59 mmol/L at the screening visit (week -2) in patients without history of documented CHD or non-CHD CVD but with other risk factors Homozygous FH (clinically or from previous genotyping) Currently taking a statin that is not atorvastatin taken daily at 20 mg or 40 mg[a] Currently taking ezetimibe or had received ezetimibe within 4 weeks of screening visit 1 (week -2)	

		OPTIONS 1	OPTIONS 2
		Not on a stable dose of allowable lipid-modifying therapy (excluding ezetimibe) for at least 4 weeks and/or fenofibrate for at least 6 weeks prior to the screening visit (week -2) or from screening to randomization, as applicable Use of fibrates, other than fenofibrate, within 6 weeks of the screening visit (week -2) or between screening and randomization visits Recent (within 3 months prior to the screening visit [week -2]) MI, unstable angina leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft surgery, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease Planned to undergo scheduled percutaneous coronary intervention, coronary artery bypass graft surgery, or carotid or peripheral revascularization during the study Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg at screening visit and/or randomization visit History of New York Heart Association Class III or IV heart failure within the past 12 months Known history of hemorrhagic stroke Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit (week -2) Newly diagnosed (within 3 calendar months prior to randomization visit [week 0]) or poorly controlled (hemoglobin A1c > 9%) diabetes Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins History of bariatric surgery within 12 months prior to the screening visit (week -2) Unstable weight defined by a variation > 5 kg within 2 months prior to the screening visit (week -2)	
DRUGS	**Intervention**	Alirocumab 75 mg Q2W If, at week 8, patient was above the pre-specified, protocol-defined LDL-C treatment goal (≥ 1.8 mmol/L or 2.6 mmol/L in patients with or without documented CVD, respectively), the dose of alirocumab was increased to 150 mg Q2W at week 12. Plus baseline atorvastatin (20 mg or 40 mg/day)	Alirocumab 75 mg Q2W If week 8 LDL-C levels were ≥ 1.8 mmol/L in patients with documented CVD or diabetes mellitus with target organ damage, or ≥ 2.6 mmol/L in all of the other patients, the alirocumab dose was increased to 150 mg Q2W at week 12 in a blinded manner. Plus baseline rosuvastatin (10 mg or 20 mg/day)
	Comparator(s)	Ezetimibe 10 mg/day Atorvastatin doubling of baseline dose (i.e., 40 mg/day or 80 mg/day depending on baseline regimen) or a switch to rosuvastatin 40 mg/day (only patients on baseline atorvastatin 40 mg/day had this option) Plus baseline atorvastatin (20 mg or 40 mg/day)	Ezetimibe 10 mg/day Doubling of the rosuvastatin dose Plus baseline rosuvastatin (10 mg or 20 mg/day)

		OPTIONS 1	OPTIONS 2
DURATION	Screening	2 to 6 weeks	2 to 6 weeks
	Double-blind	24-week	24 weeks
	Follow-up	8-week	
OUTCOMES	**Primary End Point**	Percentage change in calculated LDL-C from baseline to week 24 (ITT analysis)	
	Other End Points	Percentage change in LDL-C from baseline to week 24 (on-treatment analysis) Percentage change in LDL-C at week 12 Percentage change in other lipid parameters Proportion of patients achieving their protocol-defined LDL-C treatment goal (< 2.6 mmol/L for high CV risk patients, < 1.8 mmol/L for very-high CV risk patients) Proportion of patients reaching calculated LDL-C < 1.8 mmol/L at week 24, in both ITT and on-treatment analyses as well as the impact on other lipid parameters	Per cent change from baseline in calculated LDL-C at week 24 (modified ITT population) Per cent change in LDL-C from baseline to week 12 (ITT and on-treatment) Per cent change in other lipid parameters Proportion of very-high and high CV risk patients reaching LDL-C < 1.8 mmol/L or < 2.6 mmol/L at week 24, respectively, in both ITT and on-treatment analyses
NOTES	**Publications**	Bays et al. 2015[14]	Farnier et al. 2016[16]

CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DB RCT = double-blind randomized controlled trial; EU = European Union; FH = familial hypercholesterolemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; Q2W = every 2 weeks.
Note: Four additional reports were included (FDA clinical and statistical reviews,[26,27] manufacturer's submission,[28] and Clinical Study Report).
[a] Daily 10 mg or 20 mg rosuvastatin in Options 2
Source: Clinical Study Report for OPTIONS 1[13] and OPTIONS 2,[15] Bays et al. 2015,[14] Farnier et al. 2016.[16]

TABLE 13: DETAILS OF INCLUDED STUDIES FOR MONO AND ALTERNATIVE

		MONO	ALTERNATIVE
DESIGNS AND POPULATIONS	**Study Design**	DB RCT	DB RCT
	Locations	8 sites: US, EU	67 sites: N America (incl. Canada), EU, Israel
	Randomized (N)	103	314
	Study Period	July 2012 to July 2013	November 2012 to October 2013
	Inclusion Criteria	Male and female patients aged ≥ 18 years with a 10-year risk of fatal CV events of ≥ 1% and < 5%, based on the European Systematic Coronary Risk Estimation, a level of risk for which LDL-C lowering drug therapy can be considered Patients were not receiving statin or any other lipid-lowering therapy for at least 4 weeks before screening	18 years of age with primary hypercholesterolemia Patients at moderate or high CV risk and statin intolerance were eligible if they had a calculated serum LDL-C concentration ≥ 2.6 mmol/L at screening; those at very-high risk were eligible if they had a calculated serum LDL-C ≥ 1.8mmol/L.
	Exclusion Criteria	LDL-C < 2.59 mmol/L or >4.91 mmol/L, respectively) at Week-2 Established CHD or CVD risk equivalents defined as manifestations of non-coronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm	Use of a statin that was at or above the lowest approved daily dose within 4 weeks prior to the screening visit (week -7) Not on a stable dose of LMT for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit (week -7) or

		MONO	ALTERNATIVE
		and carotid artery disease Use of any LLT within 4 weeks or a fibrate within 6 weeks of the screening visit Fasting serum triglycerides > 4.52 mmol/l during the screening period Systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening (week-2) or randomization (week 0) visits Transient ischemic attacks or ischemic stroke and "clinically significant carotid artery obstruction by invasive or non-invasive testing (such as angiography or ultrasound)". Use of a fibrate within 6 weeks of the screening visit (Week -2, V1) or between screening and randomization visits. Planned to undergo scheduled percutaneous coronary intervention, coronary artery bypass graft surgery, or carotid or peripheral revascularization during the study History of New York Heart Association Class III or IV heart failure within the past 12 months Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit (Week-2). Newly diagnosed (within 3 months prior to randomization visit [Week 0]) or poorly controlled (hemoglobin A1c >8 .5% at the screening visit [Week-2]) diabetes. History of bariatric surgery within 12 months prior to the screening visit (Week -2). Unstable weight defined by a variation > 5 kg within 2 months prior to the screening visit Week -2). Known history of homozygous or heterozygous FH	from screening to randomization, as applicable Use of fibrates, other than fenofibrate, within 6 weeks of the screening visit (week -7) Diagnosis of fibromyalgia History of severe neuropathic pain, rheumatologic disease associated with symptoms that could be confounded with symptoms of statin intolerance, eg, rheumatoid arthritis, myalgia or myopathy that began or increased during treatment with LMT, other than statin therapy, and stopped when the LMT was discontinued, seizure disorder, previous transplant surgery, myopathy, other than statin-associated myopathy, rhabdomyolysis (defined as evidence of organ damage with CPK >10,000 IU/L), hemorrhagic stroke Recent (within 3 months prior to the screening visit [week -7]) MI, unstable angina leading to hospitalization, percutaneous coronary intervention, coronary artery bypass graft surgery, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins History of bariatric surgery within 12 months prior to the screening visit (week -7) History of New York Heart Association Class III or IV heart failure within the past 12 months Unstable weight (variation > 5 kg) within 2 months prior to the screening visit (week -7) Systolic blood pressure > 160 mm Hg or diastolic blood pressure > 100 mm Hg at the screening visit (week -7) or time of randomization (week 0/day 1) Newly diagnosed (within 3 calendar months prior to randomization visit [week 0/day 1]) diabetes mellitus or poorly controlled diabetes (hemoglobin A1c > 9%) Known history of homozygous FH

		MONO	ALTERNATIVE
DRUGS	**Intervention**	Alirocumab 75 mg Q2W Up-titrated in a blinded manner to alirocumab 150 mg SC Q2W at week 12 if their week 8 LDL-C value was ≥ 2.6 mmol/L. However, due to an administrative error during the study, an up-titration threshold of 1.8 mmol/L instead of 2.6 mmol/L was utilized.	Alirocumab 75 mg Q2W At week 12 of the 24-week double-blind treatment period, the alirocumab dose was increased to 150 mg Q2W if the patient's week 8 LDL-C concentration remained elevated (≥ 1.8 mmol/L in very-high CV risk patients or ≥ 2.6 mmol/L in moderate or high CV risk patients).
	Comparator(s)	Ezetimibe 10 mg/day orally	Ezetimibe 10 mg daily or atorvastatin 20 mg daily Efficacy comparisons vs. atorvastatin were not assessed as this treatment group was only included as an essential control to define the appropriate patient population.
DURATION	Screening	2 weeks	1 week screening, 2 weeks washout, 4 weeks run-in
	Double-blind	24 weeks	24 weeks
	Follow-up	8 weeks	8 weeks
OUTCOMES	**Primary End Point**	Per cent change from baseline in calculated LDL-C at 24 weeks	Per cent change in calculated LDL-C from baseline to week 24 (ITT)
	Other End Points	Per cent change from baseline to week 12 in calculated LDL-C Proportion of patients at week 24 with LDL-C < 2.59 mmol/L Proportion of patients at week 24 with LDL-C < 1.81 mmol/L	Change from baseline to 24 weeks using on-treatment (modified ITT) LDL-C values Per cent change from baseline to 12 weeks and 24 weeks in LDL-C
NOTES	**Publications**	Roth et al. 2014,[19] 2015[20]	Moriarty et al. 2015[21]

CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; DB RCT = double-blind randomized controlled trial; EU = European Union; FH = familial hypercholesterolemia; ITT = intention to treat; LDL-C = low-density lipoprotein cholesterol; LLT = lipid lowering therapies; LMT = lipid moderating therapies; MI = myocardial infarction; Q2W = every 2 weeks; vs. = versus.
Note: Four additional reports were included (FDA clinical and statistical reviews,[26,27] manufacturer's submission,[28] and Clinical Study Report).
Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

3.2 Included Studies

3.2.1 Description of Studies

Ten multi-centre, manufacturer-sponsored, phase 3 double-blind randomized controlled trials were included in this review. Six of the studies were considered to be key studies with respect to evidence in support of the manufacturer's proposed reimbursement criteria, as they included patients who were at high risk of CV events (COMBO 1 and COMBO 2), or who had HeFH (FH 1, FH 2, and HIGH FH), or who were a mixed population of both types of patient (LONG TERM). The findings from these studies will be presented in these groups (high risk, HeFH, mixed) throughout the review, in accordance with the proposed reimbursement criteria. The additional four studies (OPTIONS 1, OPTIONS 2, MONO, and ALTERNATIVE) included a wider mix of patients, notably those with non-FH with lower CV risk. As these four studies are less relevant for the manufacturer's proposed reimbursement criteria, less emphasis was placed on them in this review. The primary outcome of all 10 studies was the per cent change from baseline in LDL-C after 24 weeks.

Clinical Cardiovascular Disease Studies
COMBO 1 and COMBO 2 were of similar design, randomizing patients with either established coronary heart disease and an LDL-C > 1.8 or high coronary heart disease risk equivalents and an LDL-C > 2.6 on maximally tolerated statin therapy. COMBO 1 randomized 316 patients 2:1 to either alirocumab or placebo for 52 weeks, and COMBO 2 randomized 720 patients 2:1 to either alirocumab or ezetimibe for 104 weeks. In COMBO 1, randomization was stratified by history of myocardial infarction or ischemic stroke and intensity of concomitant statin treatment (high intensity or not high intensity), and in COMBO 2 it was stratified by those parameters as well as geography.

Familial Hypercholesterolemia Studies
The FH 1 and FH 2 studies were also of similar design to each other and included patients with HeFH who were not at target for primary or secondary prevention, despite high-dose statin therapy (atorvastatin, rosuvastatin, or simvastatin). Both studies were placebo-controlled, with FH 1 randomizing 486 patients 1:1 to alirocumab or placebo for 78 weeks and FH 2 randomizing 249 patients 1:1 to either alirocumab or placebo for 78 weeks. The HIGH FH study included patients with HeFH who were not adequately controlled (LDL > 4.15 mmol/L) on maximally tolerated statin background and randomized 107 patients 1:1 to either alirocumab or placebo. Randomization was stratified by history of myocardial infarction or ischemic stroke and intensity of concomitant statin treatment (high intensity or not high intensity), as well as geography.

Mixed Population Study
The LONG TERM study included HeFH patients with or without established coronary heart disease and patients with hypercholesterolemia with established coronary heart disease or risk equivalents who were not adequately controlled on maximally tolerated statins (atorvastatin, rosuvastatin, or simvastatin). These 2,341 patients were randomized 2:1 to either alirocumab or placebo for 78 weeks. In all studies, the primary outcome was per cent change from baseline in LDL after 24 weeks. Randomization was stratified by HeFH population (Yes, No), prior history of acute or silent myocardial infarction or ischemic stroke (Yes, No), statin treatment (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily versus simvastatin at any daily dose, atorvastatin below 40 mg daily, or rosuvastatin below 20 mg daily), and region (North America, Western Europe, Eastern Europe, and Rest of World).

Other Four Studies Considered Less Relevant to Proposed Reimbursement Criteria
OPTIONS 1 and OPTIONS 2 were similarly designed, with all patients established for four weeks on a background of one of two doses of a statin (atorvastatin 20 mg or 40 mg in OPTIONS 1, rosuvastatin 10 mg or 20 mg in OPTIONS 2) and comparing alirocumab with ezetimibe or a doubling of the background statin dose. In OPTIONS 1 there was an additional group that could be switched to rosuvastatin 40 mg. Both were 24-week studies. In OPTIONS 1, patients either had LDL > 1.8 mmol/L or CV risk factors and LDL > 2.6 mmol/L; in OPTIONS 2, patients had high CV risk and LDL > 2.6 mmol/L or high or very-high CV risk and LDL > 1.8 mmol/L. In MONO, 103 patients with moderate CV risk scores were randomized 1:1 to either alirocumab or ezetimibe, and in ALTERNATIVE, 314 patients with moderate or high CV risk and who were statin intolerant were randomized 1:1:1 to alirocumab, ezetimibe, or atorvastatin 20 mg. In ALTERNATIVE, the atorvastatin group was not included in the formal statistical analysis plan. These studies were also of 24 weeks' duration.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The COMBO studies both enrolled patients with a high risk of CV events, defined as either established CVD (a previous CV event) or risk equivalents (examples included diabetes mellitus with other risk

factors including chronic kidney disease, peripheral vascular disease, and ischemic stroke)(Table 9). Patients who did not have established CVD had to have a baseline LDL-C of at least 2.6 mmol/L while on maximally tolerated statins while patients with established CVD had to have a baseline LDL-C of only 1.8 mmol/L while on maximally tolerated statins. In both cases, patients had to have been receiving a defined maximally tolerated dose of statin (at least 40 mg of atorvastatin, at least 20 mg of rosuvastatin, or exactly 80 mg of simvastatin), unless the investigator could document intolerance to this higher dose; in COMBO 1, patients could also have been receiving other lipid-lowering therapy. Both studies excluded patients with recent CV events.

The FH-specific studies enrolled patients who had HeFH (Table 10). Patients could have either had a previous CV event or not, but were not able to achieve target LDL-C for either primary or secondary prevention (same LDL-C thresholds as in COMBO studies) on maximally tolerated statins (same doses as defined in COMBO studies). Patients could also have received additional lipid-lowering therapy although this was not a requirement. HIGH FH enrolled patients who were not adequately controlled on maximally tolerated statins with or without other lipid-lowering therapy (Table 10).

LONG TERM enrolled a mixed population of patients who either had HeFH with or without a prior history of established CVD and were not adequately controlled on maximally tolerated statin or who had established CVD or risk equivalents not adequately controlled on maximally tolerated statins (Table 11).

Other Four Studies Considered Less Relevant to Proposed Reimbursement Criteria
In the OPTIONS studies, patients were enrolled who were at very high or high CV risk but were not adequately controlled on maximally tolerated statins (Table 12). In MONO and ALTERNATIVE, patients could be at a risk level that would warrant treatment with a lipid-lowering therapy or at moderate to high CV risk, respectively (Table 13).

b) Baseline Characteristics

Clinical Cardiovascular Disease Studies
The mean age in all these studies was approximately 62, and the majority of patients were male. Patients in COMBO 1 and COMBO 2 had lower LDL-C (approximately 2.7 mmol/L) compared with patients in the FH-specific studies. The majority of patients across the COMBO studies had coronary heart disease (Table 14). With respect to between-group differences within studies, COMBO 1 had a numerically lower proportion of males in alirocumab-treated patients compared with placebo (63% versus 72%). A numerically higher proportion of alirocumab-treated patients versus placebo patients in COMBO 1 had type 2 diabetes (45% versus 39%).

Familial Hypercholesterolemia Studies
Mean ages of patients in the FH-specific studies (FH 1, FH 2, and HIGH FH) were in the low 50s. Patients in the FH-specific studies had higher LDL-C levels than in the COMBO studies, from 3.6 mmol/L in FH 1 and FH 2 to 5.1 mmol/L in HIGH FH (Table 15). In the FH-specific studies, the proportion of patients with coronary heart disease ranged from 36% in FH 2 to 53% in HIGH FH.

There was a numerically smaller proportion of males in the alirocumab-treated group in HIGH FH than in the placebo group (49% versus 63%). This group was the only one, across all studies, where the majority of patients were not male. This alirocumab group in HIGH FH also had a numerically lower proportion of patients with coronary heart disease at baseline compared with placebo (43% versus 63% of patients).

Mixed Population Study

The mean age of patients in LONG TERM was 60, and the majority (62%) of patients were male and Caucasian (93%). The majority of patients in the study (82%) had non-FH, and 69% of patients had a prior history of coronary heart disease. There were no notable differences in baseline characteristics between groups (Table 16).

Other Studies

In the other four studies, patients were in their early 60s (Table 17, Table 18, Table 19). LDL-C varied between studies, around 2.8 mmol/L in OPTIONS, 3.6 mmol/L in MONO, and 4.9 mmol/L in ALTERNATIVE. The majority of patients (> 60%) in the OPTIONS studies had coronary heart disease; ALTERNATIVE about 47% had coronary heart disease; MONO did not report this characteristic.

TABLE 14: SUMMARY OF BASELINE CHARACTERISTICS FOR CLINICAL CARDIOVASCULAR DISEASE STUDIES

	COMBO 1		COMBO 2	
Characteristic	**Alirocumab N = 209**	**Placebo N = 107**	**Alirocumab N = 479**	**Ezetimibe 10 mg N = 241**
Mean (SD) age, years	63.0 (9.5)	63.0 (8.8)	61.7 (9.4)	61.3 (9.2)
Male, n (%)	131 (63)	77 (72)	360 (75)	170 (71)
Race, n (%)				
Caucasian	170 (81)	88 (82)	404 (84)	206 (86)
Black or African American	34 (16)	17 (16)	21 (4)	7 (3)
Asian	2 (1)	1 (1)	32 (7)	21 (9)
Other	3 (1)	1 (1)	22 (5)	7 (3)
Mean (SD) LDL-C, mmol/L • Calculated	2.595 (0.764)	2.746 (0.915)	2.812 (0.945)	2.710 (0.884)
• Measured	2.456 (0.760)	2.596 (0.891)	2.689 (0.902)	2.619 (0.908)
CHD, n (%)	164 (79)	83 (78)	437 (91)	212 (88)
CHD risk equivalents, n (%)	85 (41)	51 (48)	151 (32)	72 (30)
Any CV history/ risk factors, n (%)	206 (99)	106 (99)	477 (100)	241 (100)
Hypertension, n (%)	185 (89)	95 (89)	382 (80)	198 (82)
Type 2 diabetes, n (%)	94 (45)	42 (39)	145 (30)	76 (32)
Statin use, n (%)	209 (100)	107 (100)	479 (100)	241 (100)
High-intensity statin, n (%)	124 (59)	63 (59)	307 (64)	153 (64)
Low/moderate intensity statin, n (%)	85 (41)	44 (41)	172 (36)	88 (37)
Other LLT use, n (%)	80 (38)	53 (50)	29 (6)	12 (5)
Ezetimibe use, n (%)	15 (7)	11 (10)	0	0
Prior history of MI or ischemic stroke, n (%)				
Yes	120 (57)	61 (57)	311 (65)	157 (65)
No	46 (43)	89 (43)	168 (35)	84 (35)

CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; Q2W = every 2 weeks; SD = standard deviation.
Alirocumab 75 mg SC Q2W with a dose increase to 150 mg Q2W week 12 if week 8 LDL-C was ≥ 1.8 mmol/L.
LDL-C levels were calculated with the use of the Friedewald formula and also measured by means of beta-quantification.
CHD risk equivalents were defined as peripheral artery disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate: 30 to < 60 mL per minute for 1.73 m^2 of body-surface area), or diabetes mellitus plus two or more additional risk factors (hypertension, ankle-brachial index of ≤ 0.90, microalbuminuria, macroalbuminuria, or a urinary dipstick result of > 2 + protein, preproliferative or proliferative retinopathy or laser treatment for retinopathy, or a family history of premature CHD).
High-dose statin therapy was defined as a daily dose of 40 mg to 80 mg of atorvastatin, 20 mg to 40 mg of rosuvastatin, or 80 mg of simvastatin.
Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes 2015,[5] Cannon et al. 2015.[6]

TABLE 15: SUMMARY OF BASELINE CHARACTERISTICS FOR STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

	FH 1		FH 2		HIGH FH	
Characteristic	**Alirocumab N = 323**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**	**Alirocumab N = 72**	**Placebo N = 35**
Mean (SD) age, years	52.1 (12.9)	51.7 (12.3)	53.2 (12.9)	53.2 (12.5)	49.8 (14.2)	52.1 (11.2)
Male, n (%)	180 (56)	94 (56)	86 (52)	45 (55)	35 (49)	22 (63)
Race, n (%)						
• Caucasian	300 (93)	144 (88)	164 (98)	80 (98)	64 (89)	30 (86)
• Black or African American	2 (1)	3 (2)	0	2 (2)	1 (1)	1 (3)
• Asian	5 (2)	1 (1)	3 (2)	0	3 (4)	3 (9)
• Other	16 (5)	15 (10)	–	–	4 (6)	1 (3)
Mean (SD) LDL-C, mmol/L) • Calculated	3.749 (1.325)	3.739 (1.213)	3.485 (1.065)	3.471 (1.071)	5.083 (1.499)	5.205 (1.125)
• Measured	3.631 (1.287)	3.627 (1.128)	3.434 (1.053)	3.372 (0.948)		
FH diagnosis, n (%)						
Genotyping	129 (40)	62 (38)	117 (70)	66 (80.5)	14 (19)	5 (14)
Clinical criteria	193 (60)	101 (62)	50 (30)	16 (19.5)	58 (81)	30 (86)
CHD history, n (%)	147 (46)	78 (48)	57 (34)	31 (38)	31 (43)	22 (63)
Any CV history/risk factors, n (%)	164 (51)	85 (52)	64 (38)	32 (39)	38 (53)	23 (66)
Hypertension, n (%)	139 (43)	71 (44)	57 (34)	24 (29)	40 (56)	21 (60)
Type 2 diabetes, n (%)	32 (10)	25 (15)	7 (4)	3 (4)	9 (13)	6 (17)
High-intensity statin, n (%)	262 (81)	132 (81)	138 (83)	68 (83)	51 (71)	25 (71)
Low/moderate intensity statin, n (%)	61 (19)	31 (19)	29 (17)	14 (17)	21 (29)	10 (29)
Other LLT use, n (%)	198 (61)	107 (66)	117 (70)	57 (70)	16 (22)	13 (37)
Ezetimibe use, n (%)	180 (56)	97 (60)	112 (67)	53 (65)	14 (19)	12 (34)
Prior history of MI or ischemic stroke, n (%)						
Yes	89 (28)	46 (28)	37 (22)	18 (22)	18 (25)	9 (26)
No	234 (72)	117 (72)	130 (78)	64 (78)	54 (75)	26 (74)

CHD = coronary heart disease; CV = cardiovascular; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; SD = standard deviation.
LDL-C levels were calculated with the use of the Friedewald formula and also measured by means of beta-quantification.
CHD risk equivalents were defined as peripheral artery disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate 30 to
< 60 mL per minute for 1.73 m^2 of body-surface area), or diabetes mellitus plus two or more additional risk factors (hypertension, ankle-brachial index of ≤ 0.90, microalbuminuria, macroalbuminuria, or a urinary dipstick result of > 2 + protein, preproliferative or proliferative retinopathy or laser treatment for retinopathy, or a family history of premature CHD).
High-dose statin therapy was defined as a daily dose of 40 mg to 80 mg of atorvastatin, 20 mg to 40 mg of rosuvastatin, or 80 mg of simvastatin.
Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein 2015,[9] Clinical Study Report for HIGH FH.[10]

TABLE 16: SUMMARY OF BASELINE CHARACTERISTICS FOR MIXED POPULATION STUDY

	LONG TERM	
Characteristic	**Alirocumab N = 1553**	**Placebo N = 788**
Mean (SD) age, years	60.4 (10.4)	60.6 (10.4)
Male, n (%)	983 (63)	474 (60)
Race, n (%)		
Caucasian	1441 (93)	730 (93)
Black or African American	53 (3)	24 (3)
American Indian or Alaska native	28 (2)	18 (3)
Asian	12 (1)	6 (1)
Other	19 (1)	10 (< 1)
Mean (SD) LDL-C, mmol/L) • Calculated	3.178 (1.102)	3.157 (1.073)
• Measured	3.036 (1.011)	2.994 (0.987)
HeFH, n (%)	276 (18)	139 (18)
Non-FH, n (%)	1,277 (82)	649 (82)
HeFH diagnosis, n (%)		
Genotyping	111 (40)	56 (40)
Clinical criteria	165 (60)	83 (60)
CHD, n (%)	1,055 (68)	552 (70)
Any CV history/ risk factors, n (%)	1,403 (90)	718 (91)
CHD risk equivalents, n (%)	639 (41)	323 (41)
Type 2 diabetes mellitus, n (%)	542 (35)	267 (34)
Statin use, n (%)	1,552 (> 99)	787 (> 99)
High-intensity statin, n (%)	676 (44)	344 (44)
Low/moderate intensity statin, n (%)	877 (57)	444 (56)
Other LLT use, n (%)	437 (28)	220 (28)
Ezetimibe use, n (%)	216 (14)	118 (15)
Prior history of MI or ischemic stroke, n (%)		
Yes	745 (48)	380 (48)
No	808 (52)	408 (52)

CHD = coronary heart disease; CV = cardiovascular; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; SD = standard deviation.
LDL-C levels were calculated with the use of the Friedewald formula and also measured by means of beta-quantification.
CHD risk equivalents were defined as peripheral artery disease, ischemic stroke, moderate chronic kidney disease (estimated glomerular filtration rate 30 mL to < 60 mL per minute for 1.73 m^2 of body-surface area), or diabetes mellitus plus two or more additional risk factors (hypertension, ankle-brachial index of ≤ 0.90, microalbuminuria, macroalbuminuria, or a urinary dipstick result of > 2 + protein, preproliferative or proliferative retinopathy or laser treatment for retinopathy, or a family history of premature CHD).
High-dose statin therapy was defined as a daily dose of 40 mg to 80 mg of atorvastatin, 20 mg to 40 mg of rosuvastatin, or 80 mg of simvastatin.
Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

Other Four Studies Considered Less Relevant to Proposed Reimbursement Criteria

TABLE 17: SUMMARY OF BASELINE CHARACTERISTICS FOR OPTIONS 1

	OPTIONS 1						
	Atorvastatin 20 mg Background			Atorvastatin 40 mg Background			
Characteristic	Alirocumab N = 57	Ezetimibe N = 55	ATV 40 N = 57	Alirocumab N = 47	Ezetimibe N = 47	ATV 80 N = 47	ROS 40 N = 45
Mean (SD) age, years	62.2 (10.0)	65.7 (9.0)	63.0 (9.9)	64.2 (10.4)	63.9(10.3)	63.2 (10.9)	57.5 (10.0)
Male, n (%)	33 (58)	31 (56)	35 (61)	31 (66)	36 (77)	33 (70)	32 (71)
Race, n (%)							
Caucasian	48 (84)	48 (87)	50 (88)	43 (92)	43 (92)	41 (87)	33 (73)
Mean (SD) BMI (kg/m2)	32.2 (7.7)	31.6 (6.0)	31.4 (6.8)	29.8 (5.4)	30.8 (5.9)	30.2 (6.0)	30.8 (6.9)
Mean (SD) LDL-C, mmol/L) • Calculated	2.68 (0.90)	2.63 (0.76)	2.60(0.80)	3.04 (0.97)	2.57 (0.76)	2.81(0.97)	2.84 (1.01)
Measured							
CHD, n (%)	22 (39)	28 (51)	29 (51)	33 (70)	35 (75)	31 (66)	22 (49)
CHD risk equivalents, n (%)	16 (28)	16 (29)	19 (33)	10 (21)	15 (32)	16 (34)	8 (18)
CV history/ risk factors, n (%)							
Hypertension	44 (77)	45 (82)	46 (81)	36 (77)	37 (79)	37 (79)	33 (73)
Type 2 diabetes	33 (58)	29 (53)	31 (54)	25 (53)	16 (34)	25 (53)	18 (40)
Other LLT use, n (%)	23 (22)	21 (21)	32 (22)				
Ezetimibe use	0	0	0				
Prior history of MI or ischemic stroke, n (%)							
Yes	15 (26)	15 (27)	15 (26)	18 (38)	18 (38)	18 (38)	17 (38)
No	42 (74)	40 (73)	42 (74)	29 (62)	29 (62)	29 (62)	28 (62)

ATV = atorvastatin; CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; SD = standard deviation.
Source: Clinical Study Report for OPTIONS 1,[13] Bays et al. 2015.[14]

TABLE 18: SUMMARY OF BASELINE CHARACTERISTICS FOR OPTIONS 2

	OPTIONS 2					
	Rosuvastatin 10 mg Background			Rosuvastatin 20 mg Background		
Characteristic	Alirocumab N = 49	Ezetimibe N = 48	ROS 20 N = 48	Alirocumab N = 54	Ezetimibe N = 53	ROS 40 N = 53
Mean (SD) age, years	62.2 (11.1)	60.4(10.4)	61.5 (11.1)	57.9 (8.9)	63.1 (10.2)	60.6 (10.1)
Male, n (%)	31 (63)	26 (54)	33 (69)	28 (52)	31 (59)	38 (72)
Race, n (%)						
Caucasian	45 (92)	42 (88)	37 (77)	42 (78)	46 (87)	44 (83)
Black or African American	2 (4)	6 (13)	6 (13)	6 (11)	2 (4)	5 (9)
Other	2 (4)	0	5 (10)	6 (11)	5 (9)	4 (8)
Mean (SD) LDL-C, mmol/L) • Calculated	2.78 (0.68)	2.65 (1.09)	2.74 (0.93)	3.07 (0.83)	3.08 (1.24)	2.92 (1.12)
• Measured	2.75 (0.75)	2.45 (0.87)	2.59 (0.96)	2.96 (0.78)	2.98 (1.25)	2.81 (1.12)
Patients with HeFH, n (%)	8 (16)	6 (13)	4 (8)	6 (11)	8 (15)	9 (17)
CHD, n (%)	23 (47)	29 (60)	25 (52)	32 (59)	32 (60)	36 (68)
CHD risk equivalents, n (%)	16 (33)	12 (25)	15 (31)	11 (20)	11 (21)	14 (26)
CV history/ risk factors, n (%)						
Hypertension	36 (74)	33 (69)	34 (71)	40 (74)	36 (68)	42 (79)
Type 2 diabetes	19 (39)	23 (48)	28 (58)	18 (33)	21 (40)	17 (32)
Other LLT use, n (%)	11 (22)	8 (17)	11 (23)	11 (20)	13 (25)	9 (17)

CHD = coronary heart disease; CV = cardiovascular; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; ROS = rosuvastatin; SD = standard deviation.
Source: Clinical Study Report for OPTIONS 2,[15] Farnier 2016.[16]

TABLE 19: SUMMARY OF BASELINE CHARACTERISTICS FOR ALTERNATIVE AND MONO

	ALTERNATIVE			MONO	
Characteristic	Alirocumab N = 126	Ezetimibe N = 124	Atorvastatin N = 63	Alirocumab N = 52	Ezetimibe N = 51
Mean (SD) age, years	64.1 (9.0)	62.8 (10.1)	63.4 (8.9)	60.8 (4.6)	59.6 (5.3)
Male, n (%)	70 (56)	67 (53)	35 (56)	28 (54)	27 (53)
Race, n (%)					
Caucasian	117 (93)	116 (93)	62 (98)	46 (88)	47 (92)
Black or African American	5 (4)	7 (6)	0	6 (12)	4 (8)
Other	4 (3)	2 (2)	1 (2)		
Mean (SD) LDL-C, mmol/L)	4.95 (1.88)	5.01 (1.84)	4.85 (1.54)	3.65 (0.70)	3.58 (0.64)
CHD, n (%)	64 (51)	54 (43)	28 (44)		
10-year risk of fatal CVD (SCORE), %[a]				2.97 (1.29)	2.68 (1.14)
Very-high CV risk,[a] n (%)	73 (58)	62 (50)	35 (56)		
High CV risk,[b] n (%)	29 (23)	47 (38)	13 (21)		
Any CV history/ risk factors, n (%)					
Hypertension	85 (68)	77 (62)	35 (56)	NR	NR
Diabetes mellitus	36 (29)	24 (19)	15 (24)	3 (6)	1 (2)
Statin use				6 (12)	4 (8)
High-intensity statin				NR	NR
Other LLT use	41 (33)	48 (38)	31 (49)	NR	NR
Ezetimibe use				2 (4)	0
Prior history of MI or ischemic stroke, n (%)					

	ALTERNATIVE			MONO	
Yes	26 (21)	26 (21)	13 (21)		
No	100 (79)	99 (79)	50 (79)		

CHD = coronary heart disease; CV = cardiovascular; CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MI = myocardial infarction; NR = not reported; SCORE = Systematic Coronary Risk Evaluation; SD = standard deviation.
[a]Very-high risk: Documented history of coronary heart disease, ischemic stroke, peripheral artery disease, transient ischemic attack, abdominal aortic aneurysm, or carotid artery occlusion. 50% without symptoms; carotid endarterectomy or carotid artery stent procedure; renal artery stenosis or renal artery stent procedure; or diabetes mellitus with target organ damage.
[b]High risk: 10-year fatal cardiovascular risk SCORE ≥ 5%, moderate chronic kidney disease, diabetes mellitus without target organ damage, or familial hypercholesterolemia.
Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

3.2.3 Interventions

In most studies, patients were initiated on a dose of alirocumab 75 mg every two weeks which could then be up-titrated to 150 mg after 12 weeks if LDL was still not at target at 8 weeks. In LONG TERM and HIGH FH, patients were initiated on alirocumab 150 mg every two weeks.

Statin and other lipid-lowering therapies (if applicable) were to be stable (including dose) for at least four weeks and fenofibrate for at least six weeks before the screening visit, from screening to randomization, and during the first 24 weeks of the double-blind treatment period, barring exceptional circumstances whereby overriding concerns (including but not limited to a triglycerides alert posted by the central laboratory) warranted changes, as per the investigator's judgment. From week 24 onward, background lipid-lowering therapy might be modified only under certain conditions including the triglycerides alert and the LDL-C rescue alert. Additionally, the site might receive an alert related to two consecutive calculated LDL-C < 0.65 mmol/L under certain provisions

3.2.4 Outcomes

The primary outcome of all included studies was the per cent change from baseline in calculated LDL-C after 24 weeks. Secondary end points typically included per cent change from baseline in LDL-C at other time points (typically weeks 12 and 52) and in various populations (intention-to-treat [ITT], on-treatment), calculated or measured. Studies also typically reported the proportion of patients achieving target LDL-C, either 1.8 mmol/L or 2.6 mmol/L, often depending on baseline risk. Changes in other lipids were also reported as secondary outcomes, but were not of interest for this review.

Total cholesterol, high-density lipoprotein cholesterol, triglycerides, apolipoprotein B, apolipoprotein A-1, and lipoprotein(a) were directly measured by the central laboratory. LDL-C was calculated using the Friedewald formula at all visits (except week 1 and the follow-up visit). In addition, LDL-C was systematically measured (via the beta-quantification method) at week 0 and week 24 for efficacy analysis purpose. The central laboratory was also to reflexively measure (via the beta-quantification method) the LDL-C if triglycerides values exceeded 4.52 mmol/L, rather than calculate it. Non-high-density lipoprotein cholesterol was calculated by subtracting high-density lipoprotein cholesterol from the total cholesterol. Ratios of apolipoprotein B to apolipoprotein A-1 and total cholesterol to high-density lipoprotein cholesterol were calculated as well.

Cardiovascular events were collected as adverse events (AEs), not as an efficacy outcome. Adjudicated CV events included all CV AEs positively adjudicated as:

- coronary heart disease death
- non-fatal myocardial infarction

- fatal and non-fatal ischemic stroke
- unstable angina requiring hospitalization (of note, a strict definition was applied for the end point "unstable angina requiring hospitalization," which was only considered when there was definite evidence of progression of the ischemic condition)
- congestive heart failure requiring hospitalization
- ischemia-driven coronary revascularization procedure.

The EQ-5D questionnaire was assessed at baseline and at week 12, week 24, week 36, and week 52 or at early termination in the six studies considered relevant to the manufacturer's proposed reimbursement criteria. The European Quality of Life scale (EQ-5D) is a generic health-related quality-of-life instrument that may be applied to a wide range of health conditions and treatments.[29,30] Index scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively. The scale has not been fully evaluated in hypercholesterolemia, and therefore no minimal clinically important difference specific to this condition is available. Reported general minimal clinically important differences for the 3L version of the scale have ranged from 0.033 to 0.074.[31]

3.2.5 Statistical Analysis

Power calculations were performed and described for all studies included in this review. In COMBO 1, it was estimated that 45 randomized patients (30 alirocumab, 15 placebo) would provide 95% power to detect a mean per cent change in LDL-C of ≥ 30% from baseline to 24 weeks with a 0.05 two-sided significance level, assuming a standard deviation of 25%. To accommodate a maximum estimated patient dropout rate of 30% (based on previous trials) at 52 weeks and to provide greater safety data to the ODYSSEY phase 3 program, the sample size was increased to 306 patients. In COMBO 2, it was estimated that a sample of 96 participants would have 95% power to detect a difference in mean per cent change in LDL-C of 20% at a significance level of 0.05 for a two-sided test, assuming a common standard deviation of 25% and all 96 patients having an evaluable primary end point. However, the sample size was set at 660 (2:1 randomization) to better assess the safety of alirocumab in the context of this study and in the overall integrated safety database of the ODYSSEY program. In FH 1 and FH 2, a total sample size of 45 patients (30 alirocumab, 15 placebo) was calculated to provide 95% power to detect a difference in mean per cent change in LDL-C of 30% with a 0.05 two-sided significance level, assuming a common standard deviation of 25% and all 45 patients having an evaluable primary end point. Nevertheless, to meet regulatory requirements across the program, sample size was increased to 471 (FH 1) and 250 (FH 2) to assess the safety of alirocumab in a larger population. In LONG TERM, for safety assessment, a sample size of 2,100 patients (randomization ratio 2:1; i.e., 1,400 alirocumab and 700 placebo) allowed for the collection of long-term safety data in a broad database (at least 1,000 patients exposed to alirocumab for a minimum of 12 months, of which approximately 900 patients were exposed to alirocumab for 78 weeks). In OPTIONS 1, a sample size of 50 patients per treatment group was calculated to have 90% power to detect a difference in means of at least 20% in any one pairwise comparison of LDL-C percentage change from baseline to week 24 using a two-sided t-test with 1% significance level for each of the five pairwise comparisons (thereby maintaining an overall 5% significance level), assuming a common standard deviation of 25% based on previous experience with alirocumab. In OPTIONS 2, a total sample size of 300 patients (50 in each of the six treatment groups), was determined to provide 90% power to detect a difference in means of at least 20% in any of the four pairwise comparisons of the primary efficacy end point, using a two-sided t-test with an adjusted significance level of 1.25% for each of the four pairwise comparisons (i.e., Bonferroni adjustment giving 5% significance overall). In MONO, a sample size of 45 patients per treatment group was calculated to have 95% power to detect a mean difference between alirocumab and ezetimibe of 20% in LDL-C per

cent change from baseline to week 24 using a two-sided t-test with 5% significance, assuming a common standard deviation of 25% based on a previous alirocumab trial and with an expected rate of exclusion of 5%. In ALTERNATIVE, a sample of 42 patients in both the alirocumab and ezetimibe treatment groups would provide 95% power to detect a 20% difference between alirocumab and ezetimibe in least squares (LS) mean per cent change from baseline to week 24 in LDL-C, using a two-sided t-test and assuming a common standard deviation of 25%.

A mixed-effect model with repeated measures was used for analysis of the primary outcomes. All available post-baseline data were used regardless of status on or off treatment. The model included fixed categorical effects of treatment group, randomization strata, time point, treatment-by-time-point interaction, and strata-by-time-point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time-point interaction. This model provided baseline adjusted LS means estimates at week 24 for both treatment groups with their corresponding 95% CIs. LDL-C reduction at week 24 was analyzed "on treatment" in the pre-specified modified ITT population (i.e., all patients in the ITT population who had an evaluable primary efficacy end point while on treatment, defined as the period between first dose of study treatment up to 21 days after last injection, or 3 days after taking the last capsule, whichever came first). For the on-treatment analysis, all available on-treatment measurements (i.e., up to 21 days after last injection or 3 days after the last capsule, whichever came first) at planned time points from weeks 4 to 52 were used in the mixed-effect model with repeated measures.

Sensitivity analyses in all studies were performed based on a pattern mixture model conducted to evaluate the impact of missing data on the primary end point, in addition to the mixed-effect model with repeated measures. In this approach, missing calculated LDL-C values during the on-treatment period were multiply imputed using a model assuming "missing at random"; missing calculated LDL-C values during the post-treatment period were multiply imputed using random draws from a normal distribution where the mean was equal to the patient's own baseline value. A tipping-point approach was also used in addition to the pattern mixture approach.

Secondary end points were analyzed in a predefined order using a hierarchical testing procedure to control type I error. These end points were analyzed with the same methodology as for the primary end point, except lipoprotein(a) and triglycerides, which were analyzed using a multiple imputation approach for the handling of missing values followed by robust regression. The proportion of patients achieving target LDL-C was analyzed using a multiple imputation approach for the handling of missing values followed by logistic regression.

To assess the homogeneity of the treatment effect across various subgroups, treatment-by-subgroup-factor, time-point-by-subgroup-factor, and treatment-by-time-point-by-subgroup-factor interaction terms and a subgroup factor term were added in the primary mixed-effect model with repeated measures. LS mean difference versus placebo at week 24 was provided, as well as the corresponding standard error and 95% CI, within each subgroup. The significance level of the treatment-by-subgroup-factor interaction term at week 24 was also provided for each factor for descriptive purposes. In order to handle imbalances between randomization stratification factor levels, population weights were used as in the primary analysis model.

Subgroups typically of interest included:

- statin treatment (atorvastatin 40 mg to 80 mg daily or rosuvastatin 20 mg to 40 mg daily versus simvastatin at any daily dose, atorvastatin below 40 mg daily, or rosuvastatin below 20 mg daily)

- statins with versus without other lipid-modifying therapy at randomization
- prior history of myocardial infarction or ischemic stroke (Yes, No)
- baseline LDL-C (e.g., < 2.59, ≥ 2.59 to < 3.37, ≥ 3.37 to < 4.14, ≥ 4.14 mmol/L): For this specific subgroup factor, the mixed-effect model with repeated measures included fixed categorical effects for treatment group, randomization strata (as per interactive voice response system), baseline LDL-C category, time point, and the interactions treatment-by-time-point, strata-by-time-point, baseline-LDL-C-category-by-time-point, treatment-group-by-baseline-LDL-C-category, and treatment-group-by-baseline-LDL-C-category-by-time-point.

If the subgroup factor was a randomization stratification factor, then the interactive voice response system strata were used.

a) Analysis Populations

The ITT population was defined as all randomized patients who had an evaluable primary efficacy end point. The primary efficacy end point was evaluable when the following two conditions were met:

- availability of baseline calculated LDL-C value
- availability of at least one calculated LDL-C value on treatment or off treatment within one of the analysis windows up to week 24.

Patients in the ITT population were analyzed according to the treatment group allocated by randomization (i.e., as-randomized treatment group).

The modified ITT population was defined as all randomized patients who took at least one dose or part of a dose of the double-blind injection of investigative medicinal product and had an evaluable primary efficacy end point during the efficacy treatment period. The primary efficacy end point was evaluable when the following two conditions were met:

- availability of baseline calculated LDL-C value
- availability of at least one calculated LDL-C value on treatment, i.e., during the efficacy treatment period and within one of the analysis windows up to week 24.

The efficacy treatment period was defined as the time period from the first double-blind injection of investigative medicinal product up to the day of last injection + 21 days. Patients in the modified ITT population were analyzed according to the treatment group allocated by randomization (i.e., as-randomized treatment group). The analyses using the on-treatment estimand (on-treatment analyses) were performed on the modified ITT population.

The primary end point was assessed in the ITT population, which included all randomized patients regardless of treatment adherence with ≥ 1 available LDL-C value both at baseline and at one of the planned time points between weeks 4 and 24.

3.3 Patient Disposition

Clinical Cardiovascular Disease Studies

Studies tended to have a high proportion of patients not completing. In COMBO 1, 24% of alirocumab patients and 30% of placebo patients did not complete the study. In COMBO 2, 15% of patients in each of the alirocumab and ezetimibe groups did not complete. AE was the most common identified reason for not completing the treatment period, although in COMBO 1 many patients were identified as not completing due to “other” reasons (Table 20).

Familial Hypercholesterolemia Studies

High withdrawal were also seen in two of the three FH-specific studies. In FH 1, 24% of alirocumab patients and 20% of placebo patients did not complete. In HIGH FH, 21% versus 17% of alirocumab-treated versus placebo-treated patients did not complete the study. In FH 2, 10% of alirocumab and 12% of placebo patients did not complete the study period. Among identified reasons for discontinuation (i.e., not "other"), AEs were typically the most common reason for study discontinuation (Table 21).

Mixed Population Study

In LONG TERM, 28% of alirocumab patients and 25% of placebo patients did not complete the study, and AEs were again the most common reason for not continuing (7% of alirocumab-treated patients and 6% of placebo patients)(Table 22).

Other Studies

In the other studies, there were some groups in OPTIONS 1 and OPTIONS 2 with withdrawal rates above 20%. In MONO, withdrawal rates were around 15%, and in ALTERNATIVE, withdrawal rates were highest, above 25% (Table 23, Table 24).

TABLE 20: PATIENT DISPOSITION FOR CLINICAL CARDIOVASCULAR DISEASE STUDIES

	COMBO 1		COMBO 2	
Patient Disposition	**Alirocumab N = 209**	**Placebo N = 107**	**Alirocumab N = 479**	**Ezetimibe N = 241**
Screened	640		1112	
Randomized	209	107	479	241
Randomized and treated, n (%)	207 (99)	107 (100)	479 (100)	241 (100)
Did not complete study treatment period as per CRF, n (%)	51 (24)	32 (30)	73 (15)	35 (15)
• Adverse event	13 (6)	8 (8)	36 (8)	13 (5)
• Poor compliance to protocol	10 (5)	9 (8)	13 (3)	7 (3)
• Other	28 (13)	15 (14)	24 (5)	15 (6)
Completed 12 months of DB treatment period (at least 50 weeks' exposure and visit week 52 performed), n (%)	167 (80)	80 (75)	71 (15)	33 (14)
ITT, n (%)	205 (98)	106 (99)	467 (98)	240 (100)
mITT, n (%)	204 (98)	105 (98)	464 (97)	235 (98)
Safety, n (%)	207 (99)	107 (100)	479 (100)	241 (100)

CRF = clinical report form; DB = double-blind; ITT = intention to treat; mITT = modified intention to treat.
Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes 2015,[5] Cannon et al. 2015.[6]

TABLE 21: PATIENT DISPOSITION FOR STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

	FH 1		FH 2		Hi FH	
Patient Disposition	**Alirocumab N = 322**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**	**Alirocumab N = 72**	**Placebo N = 35**
Screened	597		322		206	
Randomized	323	163	167	82	72 (100)	35 (100)
Randomized and treated, n (%)	322	163	167	81	72 (100)	35 (100)
Did not complete study, n (%)	76 (24)	33 (20)	17 (10)	10 (12)	15 (21)	6 (17)
• Adverse event	13 (4)	10 (6)	6 (4)	1 (1)	3 (4)	1 (3)
• Poor compliance to protocol	10 (3)	4 (2)	2 (1)	2 (2)	4 (6)	1 (3)
• Other	53 (16)	19 (12)	9 (5)	7 (9)	8 (11)	4 (11)
Treatment ongoing, n (%)					51 (71)	25 (71)
ITT, n (%)	322	163	166	81	71 (99)	35 (100)
mITT, n (%)	321 (99)	163 (100)	166 (99)	81 (99)	71 (99)	35 (100)
Safety, n (%)	322	163	167	81	72 (100)	35 (100)
Entered open-label extension, n (%)	254	138	136	63	6 (11)	4 (8)

ITT = intention to treat; mITT = modified intention to treat.
Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein 2015,[9] Clinical Study Report for HIGH FH.[10]

TABLE 22: PATIENT DISPOSITION FOR MIXED POPULATION STUDIES

	LONG TERM	
Patient Disposition	**Alirocumab N = 1,553**	**Placebo N = 788**
Screened	5,142	NR
Randomized	1,553	788
Randomized and treated, n (%)	1,550 (99.8)	788 (100)
Did not complete study, n (%)	437 (28.1)	193 (24.5)
• Adverse event	113 (7.3)	47 (5.9)
• Poor compliance to protocol	60 (3.9)	38 (4.8)
• Other	264 (16.9)	108 (13.7)
ITT, n (%)	1,530 (98.5)	780 (99.0)
mITT, n (%)	1,523 (98.1)	777 (98.6)
Safety, n (%)	1,550 (99.8)	788 (100)

ITT = intention to treat; mITT = modified intention to treat.
Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

Other Four Studies Considered Less Relevant to Proposed Reimbursement Criteria

TABLE 23: PATIENT DISPOSITION FOR OPTIONS 1 AND OPTIONS 2

	OPTIONS 1							OPTIONS 2					
	Atorvastatin 20 mg Background			Atorvastatin 40 mg Background				Rosuvastatin 10 mg Background			Rosuvastatin 20 mg Background		
Patient Disposition	Aliro N = 57	EZE 10 N = 55	ATV 40 N = 57	Aliro N = 47	EZE 10 N = 47	ATV 80 N = 47	ROS 40 N = 45	Aliro N = 49	EZE 10 N = 48	ROS 20 N = 48	Aliro N= 54	EZE 10 N = 53	ROS 40 N = 53
Screened	859							672					
Randomized	57	55	57	47	47	47	45	49	48	48	54	53	53
Randomized and treated													
Did not complete study, n (%)	11 (19)	15 (27)	13 (23)	9 (19)	6 (13)	8 (17)	6 (13)	11 (22)	14 (29)	5 (10)	13 (24)	9 (17)	8 (15)
• Adverse event	5 (9)	3 (6)	4 (7)	2 (4)	1 (2)	3 (6)	1 (2)	3 (6)	6 (13)	2 (4)	2 (4)	2 (4)	3 (6)
• Poor compliance to protocol	0	4 (7)	2 (4)	1 (2)	0	0	0	2 (4)	2 (4)	1 (2)	3 (4)	0	0
• Other	6 (11)	8 (15)	7 (12)	6 (13)	5 (11)	5 (11)	5 (11)	6 (12)	6 (13)	2 (4)	9 (17)	7 (13)	5 (9)
ITT, n (%)	55	53	53	46	46	47	45	48	47	48	53	50	52
mITT, n (%)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Safety, n (%)	57	55	57	47	46	47	45	49	48	48	54	53	53

Aliro = alirocumab; ATV = atorvastatin; EZE = ezetimibe; ITT = intention to treat; mITT = modified intention to treat, NR = not reported; ROS = rosuvastatin.
Source: Clinical Study Report for OPTIONS 1[13] and OPTIONS 2,[15] Bays et al. 2015,[14] Farnier et al. 2016.[16]

TABLE 24: PATIENT DISPOSITION FOR ALTERNATIVE AND MONO

	ALTERNATIVE			MONO	
Patient Disposition	Alirocumab	Ezetimibe	Atorvastatin	Alirocumab	Ezetimibe
Screened	519			204	
Randomized	126	125	63	52	51
Randomized and treated	126	124	63	52	51
Discontinued intervention, n (%)	30 (24)	42 (34)	21 (33)	8 (15)	7 (14)
• Adverse event	23 (18)	31 (25)	16 (25)	5 (10)	4 (8)
• Poor compliance to protocol	0	0	2 (3)	0	1 (2)
• Patient moved				1 (2)	0
• Withdrew consent				1 (2)	0
• Other	7 (6)	11 (9)	3 (5)	1 (2)	2 (4)
ITT	126	122	62	52	51
On treatment	123	118	60	51	50
Safety	126	124	63	52	51

ITT = intention to treat.
Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

3.4 Exposure to Study Treatments

In COMBO 1, the mean duration of exposure was 46 weeks with alirocumab and 45 weeks with placebo, while in COMBO 2 it was 58 weeks in each of the alirocumab and ezetimibe groups.

In the FH-specific studies, mean exposure across studies was consistently around 60 weeks, with no clear differences in exposure between groups within studies.

In LONG TERM, the mean duration of exposure was 65 weeks in each of the alirocumab and placebo groups.

In the other four studies, duration of exposure was consistently around 22 weeks in the OPTIONS studies and in MONO, and around 20 weeks in ALTERNATIVE.

3.5 Critical Appraisal

3.5.1 Internal Validity

The proportion of patients discontinuing the study often exceeded 20% across the included studies. This high rate of discontinuations may mean that the population whose data were being analyzed at the end of the study was different from the population that was randomized into the study. None of the included studies had run-in periods where patients received injections, and this might partially explain the high withdrawal rates; however, it does not explain why the rate of withdrawal varied between studies or between groups within studies. The numerical difference in withdrawal between groups within studies was generally less than 5% in the six studies submitted for the proposed reimbursement criteria, however in COMBO 1 it was 24% with alirocumab and 30% with placebo. In the other four studies, larger between-group differences within studies were noted, such as in OPTIONS 1 where the proportion of withdrawal ranged from a low of 13% to a high of 27%, and in OPTIONS 2, 10% to 29%.

In the six studies submitted for the proposed reimbursement criteria, the manufacturer employed a mixed-effect model with repeated measures method in their primary analysis and performed a number of sensitivity analyses that appeared to support the robustness of the primary analysis in an effort to

assess the potential for bias from missing data. The results in these studies for the primary outcome (per cent change in LDL-C at 24 weeks) were consistently large, therefore it is unlikely that the large proportion of withdrawal or differences in withdrawal between groups would have introduced enough bias to alter the conclusions for these outcomes. However, the differences between groups for the primary outcomes in the other four studies were smaller, and the between-group differences in discontinuations were larger, therefore it is possible that conclusions for the primary outcome for these studies might have been impacted by the high rate of discontinuations. The other key outcomes identified in our protocol were either not assessed as efficacy outcomes (quality of life, which was assessed as a safety outcome) or were included as part of the safety analysis (mortality, morbidity), and therefore no statistical analyses were provided.

The included studies were all double blinded, and patients in control groups were required to administer placebo injections. Training appears to have been provided for injections to increase the likelihood of adequate delivery of drug and to reduce risk of injection site reactions. Adequate measures appear to have been taken during the randomization process to ensure allocation concealment. Injection site reactions and, more notably, hypersensitivity reactions are known complications associated with the use of monoclonal antibodies; however, neither were common in the included studies and therefore such reactions are unlikely to have compromised blinding.

Adjustments for multiplicity were made for the testing of multiple study end points in a hierarchical approach and the hierarchy appears to have been adhered to. In the other four studies, two of which featured multiple comparison groups, statistical adjustments were also made to adjust for multiple comparisons between groups, and this hierarchy also appears to have been adhered to.

3.5.2 External Validity

The included studies were not designed to assess hard clinical outcomes such as mortality and morbidity, therefore the evidence supporting the efficacy of alirocumab relative to comparators such as ezetimibe and placebo relies on a surrogate marker, LDL-C. LDL-C is considered to be a well-validated and widely accepted surrogate for this indication.

The baseline characteristics across studies were generally consistent with the population that would be expected to use alirocumab in Canada according to the clinical expert. There were Canadian sites in the included studies.

None of the included studies compared alirocumab with evolocumab, the other PCSK9 inhibitor currently approved in Canada and therefore a key comparator for alirocumab. Given the timing of the approval of these two drugs, a direct comparison between the two would not necessarily be expected at this time, but this is still a limitation.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 8). See 0 for detailed efficacy data.

3.6.1 Mortality

There were few deaths across the studies, and no clear differences between groups in the proportion of deaths or CV deaths. The largest number of deaths or CV deaths was in LONG TERM, where 8 (0.5%) alirocumab patients and 10 (1.3%) placebo patients died. In FH 1, six (2%) of alirocumab-treated patients died versus none in placebo, although only two of these deaths were CV related.

In COMBO 1, two (1.0%) alirocumab patients died versus three (2.8%) placebo patients, and in COMBO 2, two (0.4%) alirocumab patients died versus four (1.7%) ezetimibe patients.

3.6.2 Cardiovascular Deaths

There were few CV deaths across all the studies and no notable differences between comparison groups in any study. In COMBO 1, there was one (0.5%) CV death with alirocumab and one with placebo (0.9%), and in COMBO 2, there were two CV deaths with alirocumab (0.4%) and two with ezetimibe (0.8%). In FH 1, there were two (1%) CV deaths with alirocumab and none with placebo, and none in the other studies. In LONG TERM, there were four (0.3%) CV deaths with alirocumab and seven (0.9%) with placebo.

In the OPTIONS studies, there was one (1%) CV death in OPTIONS 1 with ezetimibe and none in OPTIONS 2, nor were there any in MONO or ALTERNATIVE.

3.6.3 Cardiovascular Morbidity

Across the studies, CV morbidity was assessed as a safety outcome and as adjudicated CV events, although no statistical comparisons were planned. Non-fatal myocardial infarction tended to be the most common CV AE across studies.

Clinical Cardiovascular Disease Studies

The proportion of patients with a CV event was similar between the alirocumab and placebo groups in COMBO 1 (6 [2.9%] versus 3 [2.8%]) and between the alirocumab and ezetimibe groups in COMBO 2 (23 [4.8%] versus 9 [3.7%]) (Table 25). In both studies, the most common CV event was ischemia-driven coronary revascularization.

Familial Hypercholesterolemia Studies

There was a numerically higher proportion of alirocumab-treated versus placebo-treated patients experiencing a CV event in the HIGH FH study (6 [8.3%] versus 0), although this was a small study and was clearly not powered to assess this outcome in a formal manner. Again, non-fatal myocardial infarction was the most common CV event, occurring in 6% of alirocumab-treated patients (four patients) and none in placebo. There were also numerically more CV events with alirocumab than placebo in FH 1 (8 [2.5%] versus 3 [1.8%] of patients), but similar proportions of patients with CV events between the alirocumab and placebo groups in FH 2 (1% in each group) (Table 26).

Mixed Population Study

The largest number of CV events across all studies was in LONG TERM, occurring in 72 (4.6%) alirocumab-treated patients and 40 (5.1%) placebo patients (Table 27).

Other Studies

There were numerically more alirocumab-treated patients than ezetimibe-treated patients with a CV event in ALTERNATIVE (4 [3%] versus 1 [1%]), and in this case the most common event was a revascularization procedure (Table 30). In the other studies, only a small proportion of patients experienced a CV event, no more than one patient in any group, with no notable differences between groups.

3.6.4 Quality of Life

The EQ-5D was used to assess quality of life in all of the six studies that focused on the proposed reimbursement criteria, however it was only reported as a safety outcome in each of these studies and

therefore was not part of the hierarchy for statistical testing. There was no statistically significant difference between groups in utility scores after 52 weeks in any of the included studies. The manufacturer noted that although the *P* value for COMBO 1 was below 0.05, this was not adjusted for multiple comparisons, and it concluded that no statistically significant difference existed (Table 25).

3.6.5 Change in Low-Density Lipoprotein Cholesterol

Per cent change from baseline in LDL-C after 24 weeks was the primary outcome of all studies.

Clinical Cardiovascular Disease Studies

The per cent reductions from baseline in LDL-C after 24 weeks in alirocumab-treated patients were relatively consistent across both COMBO 1 (48%) and COMBO 2 (51%). In COMBO 1, the difference after 24 weeks between the alirocumab and placebo groups was statistically significant (estimated LS mean difference between groups: −45.9%; 95% CI, −52.5 to −39.3; $P < 0.0001$) (Table 25). In COMBO 2, the difference between alirocumab and ezetimibe was also statistically significant (estimated LS mean difference between groups: −29.8%; 95% CI, −34.4 to −25.3; $P < 0.0001$) (Table 25).

The COMBO studies also reported the proportion of patients reaching target LDL as a secondary outcome (target of < 1.8 mmol/L for everyone), and these differences between alirocumab and comparators were statistically significant. When compared with placebo in COMBO 1, 75% of alirocumab patients versus 9% of placebo patients achieved target (combined estimate for odds ratio 38.5; 95% CI, 16.5 to 89.8; $P < 0.0001$), while in COMBO 2, 77% of alirocumab patients versus 46% of ezetimibe patients reached target (combined estimate for odds ratio 5.4; 95% CI, 3.7 to 7.9; $P < 0.0001$) (Table 25).

Subgroups

Regarding subgroups, there were no consistent interactions found based on any of the subgroups identified in our protocol. In COMBO 1, there was a greater per cent reduction in LDL-C in patients who had a prior history of myocardial infarction or stroke (estimated LS mean difference between groups −52.8; 95% CI, −61.4 to −44.1) versus those who did not (estimated LS mean difference between groups −36.9; 95% CI, −46.8 to −27.0) (Table 36). Also in COMBO 1, patients with other lipid-modifying therapy at randomization had larger reductions in LDL (estimated LS mean difference between groups −55.1; 95% CI, −64.9 to −45.2) than those who did not have lipid-modifying therapy (estimated LS mean difference between groups −37.9; 95% CI, −46.9 to −28.9) (Table 36).

Familial Hypercholesterolemia Studies

The per cent reductions from baseline in LDL were relatively consistent across studies, ranging from a low of 46% in HIGH FH to 49% in each of the FH 1 and FH 2 studies. In HIGH FH, the difference after 24 weeks between the alirocumab and placebo groups was statistically significant (estimated LS mean difference between groups −39.1%; 95% CI, −51.1 to −27.1; $P < 0.0001$) (Table 26). This was also the case in FH 1 (estimated LS mean difference between groups −57.9; 95% CI, −63.3 to −52.6; $P < 0.0001$) and FH 2 (estimated LS mean difference between groups −51.4; 95% CI, −58.1 to −44.8; $P < 0.0001$) (Table 26).

The FH 1 and FH 2 studies also reported the proportion of patients reaching target LDL as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of 1.8 mmol/L for those with prior CV events and < 2.6 mmol/L for those without) or not taking it into account (target of < 1.8 mmol/L for everyone), and these differences between alirocumab and comparators were statistically significant, where reported, in all cases. Taking into account baseline CV risk, in the alirocumab versus placebo groups, 72% versus 2% of patients reached target in FH 1 (combined estimate for odds ratio 156.0; 95%

CI, 48.9 to 498.1; *P* < 0.0001) and 81% versus 11% reached target in FH 2 (combined estimate for odds ratio 52.2; 95% CI, 20.9 to 130.0; *P* < 0.0001). In patients who achieved target without accounting for baseline risk, in FH 1 the proportions achieving target were 60% for alirocumab versus 1% for placebo (combined estimate for odds ratio 244.9; 95% CI, 34.4 to 1,744.4; *P* < 0.0001), and for FH 2 the proportions were 68% alirocumab versus 1% placebo (combined estimate for odds ratio 239.7; 95% CI, 31.6 to 1820.3; *P* < 0.0001). In HIGH FH, targets were again adjusted for baseline risk (very-high CV risk: < 1.8 mmol/L; high CV risk: < 2.6 mmol/L) and the difference between the alirocumab and placebo groups was again statistically significant, with 41% of alirocumab-treated patients and 6% of placebo patients reaching target (combined estimate for odds ratio 11.7; 95% CI, 2.5 to 53.5; *P* = 0.0016) (Table 26).

Subgroups

Re subgroups, there were no consistent interactions found based on any of the subgroups identified in our protocol. In HIGH FH, patients with other lipid-modifying therapy at randomization had larger reductions in LDL (estimated LS mean difference between groups −59.0; 95% CI, −80.1 to −37.9) than those who did not have lipid-modifying therapy (estimated LS mean difference between groups −29.7; 95% CI, −44.2 to −15.3) (Table 38).

Mixed Population Study

In LONG TERM, there was a statistically significant reduction in LDL-C for alirocumab versus placebo after 24 weeks (estimated LS mean difference between groups −61.9; 95% CI, −64.3 to −59.4; *P* < 0.001) (Table 27).

The LONG TERM study also reported the proportion of patients reaching target LDL as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of < 1.8 mmol/L for those with prior CV events and < 2.6 mmol/L for those without) or not taking it into account (target of < 1.8 mmol/L for everyone), and these differences between the alirocumab and placebo groups were statistically significant, where reported, in both cases. Taking into account baseline CV risk, in the alirocumab versus placebo groups, 81% versus 9% of patients reached target (combined estimate for odds ratio 71.5; 95% CI, 51.6 to 99.1; *P* < 0.0001), while 79% versus 8% reached target when baseline CV risk was not taken into account (combined estimate for odds ratio 74.6; 95% CI, 53.3 to 104.4; *P* < 0.0001) (Table 27).

Subgroups

In LONG TERM, there was a statistically significant interaction based on baseline LDL, with a larger reduction versus placebo in patients with lower baseline LDL. For example, patients with the lowest baseline LDL (< 2.59 mmol/L) had the largest difference between the alirocumab and placebo groups (estimated LS mean difference between groups −75.0; 95% CI, −79.3 to −70.6), while patients with the highest baseline LDL (> 4.14 mmol/L) had the smallest difference between the alirocumab and placebo groups (estimated LS mean difference between groups −41.3; 95% CI, −47.8 to −34.8) (Table 39).

Other Studies

In the other four studies, differences between alirocumab and various comparators were consistently statistically significant, regardless of background therapy, with one exception. In OPTIONS 2, in the patients on a background of rosuvastatin 20 mg, there was no statistically significant difference between alirocumab and ezetimibe (estimated LS mean difference between groups −25.3; 95% CI, −50.9 to 0.3; *P* = 0.0136) or alirocumab and rosuvastatin 40 mg (estimated LS mean difference between groups −20.3; 95% CI, −45.8 to 5.1; *P* = 0.0453)(Table 29). These comparisons did not reach the threshold for statistical significance of *P* = 0.0125, which had been adjusted for multiple comparisons between groups.

In the OPTIONS studies, the proportion of patients reaching target LDL was reported as a secondary outcome, either taking into account baseline CV risk (lower LDL-C target of < 1.8 mmol/L for those with prior CV events and < 2.6 mmol/L for those without) or not taking it into account (target of < 1.8 mmol/L for everyone). Differences between alirocumab and the various comparison groups were generally statistically significant, but there were exceptions. When taking into account CV risk, in OPTIONS 1, in patients on a background of atorvastatin 20 mg, differences in the proportion of alirocumab versus ezetimibe patients achieving target (87% versus 68%, respectively) were not statistically significant (combined estimate for odds ratio 3.4; 95% CI, 0.8 to 14.6; *P* = 0.0284), and the subsequent end point, when not taking into account baseline CV risk, was therefore not formally tested after failure to reach statistical significance in the previous end point. Similar results were seen in OPTIONS 2, where patients were on a background of rosuvastatin 10 mg or 20 mg daily. When taking into account CV risk, in OPTIONS 2, in patients on a background of rosuvastatin 20 mg, differences in the proportion of alirocumab patients versus ezetimibe patients achieving target (67% versus 52%, respectively) were not formally tested after failure of the primary end point, and this was also the case when not taking into account baseline CV risk. ALTERNATIVE did not report the proportion of patients achieving target, and in MONO, differences for alirocumab versus placebo were statistically significant whether baseline risk was taken into account or not.

No statistically significant interactions were found based on any of the reported subgroups in OPTIONS 1, OPTIONS 2, ALTERNATIVE, or MONO.

3.6.6 Other Efficacy Outcomes

Health care resource utilization and imaging were not investigated in any of the included studies.

TABLE 25: KEY EFFICACY OUTCOMES FOR CLINICAL CARDIOVASCULAR DISEASE STUDIES

	COMBO 1		COMBO 2	
Outcome	**Alirocumab N = 209**	**Placebo N = 107**	**Alirocumab N = 467**	**Ezetimibe N = 240**
Mean (SD) calculated LDL baseline (mmol/L)	2.597 (0.770)	2.709 (0.836)	2.805 (0.946)	2.706 (0.884)
Estimated LS mean (SE) % change from baseline at week 24[a]	−48.2 (1.9)	−2.3 (2.7)	−50.6 (1.4)	−20.7 (1.9)
Estimated mean difference % (95% CI)	−45.9 (−52.5 to −39.3), *P* < 0.0001		−29.8 (−34.4 to −25.3), *P* < 0.0001	
Proportion of patients reaching calculated LDL-C < 1.8 mmol/L	75.0	9.0	77.0	45.6
Combined estimate for odds ratio (95% CI)[b]	38.5 (16.5 to 89.8), *P* < 0.0001		5.4 (3.7 to 7.9), *P* < 0.0001	
Deaths, n (%)	2 (1.0)	3 (2.8)	2 (0.4)	4 (1.7)
CHD death (including undetermined cause), n (%)	1 (0.5)	1 (0.9)	2 (0.4)	2 (0.8)
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	6 (2.9)	3 (2.8)	23 (4.8)	9 (3.7)
• CHD death (including undetermined cause)	0	0	2 (< 1)	2 (1)
• Non-fatal MI	1 (0.5)	1 (0.9)	12 (3)	3 (1)
• Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	2 (1.0)	0	1 (< 1)	1 (< 1)
• Unstable angina requiring hospitalization	0	0	1 (< 1)	0
• CHF requiring hospitalization	0	1 (0.9)	1 (< 1)	1 (< 1)
• Ischemia-driven coronary revascularization procedure	3 (1.4)	1 (0.9)	16 (3)	4 (2)

	COMBO 1		COMBO 2	
EQ-5D utility score mean (SD) baseline	0.826 (0.208) N = 200	0.847 (0.204) N = 102	0.84 (0.19) N = 458	0.83 (0.19) N = 233
EQ-5D utility score week 52 LS mean (SE) change from baseline	−0.021 (0.014)	0.039 (0.021)	−0.004 (0.008)	0.002 (0.011)
LS difference (SE) vs. placebo	−0.060 (−0.110 to −0.010), *P* = 0.0183		−0.006 (−0.032 to 0.021), *P* = 0.6747	

CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 Dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; SD = standard deviation; SE = standard error; vs. = versus.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes 2015,[5] Cannon et al. 2015.[6]

TABLE 26: KEY EFFICACY OUTCOMES FOR STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

	FH 1		FH 2		HIGH FH	
Outcome	Alirocumab N = 322	Placebo N = 163	Alirocumab N = 167	Placebo N = 82	Alirocumab N = 71	Placebo N = 35
Calculated LDL-C, mean (SD) baseline, mmol/L	3.748 (1.326)	3.739 (1.213)	3.486 (1.069)	3.470 (1.078)	5.083 (1.499)	5.205 (1.125)
Estimated LS mean (SE) % change from baseline at week 24[a]	−48.8 (1.6)	9.1 (2.2)	−48.7 (1.9)	2.8 (2.8)	−45.7 (3.5)	−6.6 (4.9)
Estimated mean difference % (95% CI)	−57.9 (−63.3 to −52.6), *P* < 0.0001		−51.4 (−58.1 to −44.8), *P* < 0.0001		−39.1 (−51.1 to −27.1), *P* < 0.0001	
Patients (%) with or without prior CV events achieving LDL-C < 1.8 mmol/L or < 2.6 mmol/L, respectively, week 24	72.2	2.4	81.4	11.3	NR	NR
Combined estimate for odds ratio (95% CI)[b]	156.0 (48.9 to 498.1), *P* < 0.0001		52.2 (20.9 to 130.0), *P* < 0.0001			
Patients (%) achieving LDL-C < 1.8 mmol/L at week 24 (regardless of prior CV events)	59.8	0.8	68.2	1.2	NR	NR
Combined estimate for odds ratio (95% CI)[b]	244.9 (34.4 to 1,744.4), *P* < 0.0001		239.7 (31.6 to 1,820.3), *P* < 0.0001			
Very-high CV risk patients (%) reaching calculated LDL-C < 1.8 mmol/L or high CV risk patients reaching calculated LDL-C < 2.6 mmol/L at week 24	NR	NR	NR	NR	41.0	5.7
Combined estimate for odds ratio (95% CI)[b]					11.7 (2.5 to 53.5), *P* = 0.0016	
Deaths, n (%)	6 (1.9)	0	0	0	0	0
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	8 (2.5)	3 (1.8)	2 (1)	1 (1)	6 (8.3)	0
• CHD death (including undetermined cause)	2 (1)	0	0	0	0	0
• Non-fatal MI	1 (< 1)	0	0	1	4 (6)	0
• Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	1 (< 1)	0	0	0	0	0
• Unstable angina requiring hospitalization	1 (< 1)	0	0	0	0	0
• Congestive heart failure requiring hospitalization	1 (< 1)	0	0	1	1 (1)	0
• Ischemia-driven coronary revascularization procedure	2 (1)	2 (1)	2 (1)	1	5 (7)	0
EQ-5D utility score mean (SD) baseline	0.908 (0.139)	0.912 (0.127)	0.917 (0.151)	0.907 (0.154)	0.926 (0.122)	0.883 (0.208)

	FH 1		FH 2		HIGH FH	
Outcome	Alirocumab N = 322	Placebo N = 163	Alirocumab N = 167	Placebo N = 82	Alirocumab N = 71	Placebo N = 35
EQ-5D utility score week 52 LS mean (SE) change from baseline	−0.002 (0.007)	0.007 (0.010)	−0.027 (0.011)	0.000 (0.015)	−0.030 (0.022)	−0.013 (0.030)
LS mean difference (SE) vs. placebo	−0.010 (−0.034 to 0.014), *P* = 0.4287		0.027 (−0.010 to 0.064), *P* = 0.1481		−0.017 (−0.092 to 0.057), *P* = 0.6424	

CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; NR = not reported; SD = standard deviation; SE = standard error; vs. = versus.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time-point interaction. Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein 2015,[9] Clinical Study Report for HIGH FH.[10]

TABLE 27: KEY EFFICACY OUTCOMES FOR MIXED POPULATION STUDY

	LONG TERM	
Outcome	**Alirocumab N = 1,530**	**Placebo N = 780**
Mean (SD) baseline LDL-C (mmol/L)	3.18 (1.10)	3.15 (1.08)
Estimated LS mean (SE) % change from baseline at week 24	−61.0 (0.7)	0.8 (1.0)
Estimated mean difference % (95% CI)[a]	−61.9 (−64.3 to −59.4), *P* < 0.001	
Patients achieving LDL-C < 1.8mmol/L in patients at very-high risk or < 2.6mmol/L in patients at high risk, %	80.7	8.5
Combined estimate for odds ratio (95% CI)[b]	71.5 (51.6 to 99.1), *P* < 0.0001	
Patients achieving LDL-C < 1.8mmol/L regardless of risk, %	79.3	8.0
Combined estimate for odds ratio (95% CI)[b]	74.6 (53.3 to 104.4), *P* < 0.0001	
Deaths, n (%)	8 (0.5)	10 (1.3)
Patients with treatment-emergent CV events confirmed by adjudication, n (%)	72 (4.6)	40 (5.1)
CHD death (including undetermined cause) , n (%)	4 (0.3)	7 (0.9)
• Non-fatal MI	14 (1)	18 (2)
• Fatal and non-fatal ischemic stroke (including stroke NOS)	9 (1)	2 (< 1)
• Unstable angina requiring hospitalization	0	1 (< 1)
• CHF requiring hospitalization	9 (1)	2 (< 1)
• Ischemia-driven coronary revascularization procedure	48 (3)	24 (3)
EQ-5D utility score mean (SD) baseline	0.858 (0.197) N = 1490	0.840 (0.210) N = 758
EQ-5D utility score week 52 LS mean (SE) change from baseline	−0.018 (0.004)	−0.012 (0.006)
LS mean difference (SE) vs. placebo	−0.006 (−0.021 to 0.009), *P* = 0.4483	

CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 Dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; MI = myocardial infarction; MMRM = mixed-effect model with repeated measures; NOS = not otherwise specified; SD = standard deviation; SE = standard error; vs. = versus.

[a] LS means, SEs, and *P* values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time-point interaction.

[b] Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

Other Four Studies Not Considered Relevant to Reimbursement Criteria

TABLE 28: KEY EFFICACY OUTCOMES FOR OPTIONS 1

	OPTIONS 1						
	Atorvastatin 20 mg Background			Atorvastatin 40 mg Background			
Outcome	Aliro n = 57	EZE N = 55	ATV 40 N = 57	Aliro n = 47	EZE N = 47	ATV 80 N = 47	ROS 40 N = 45
Mean (SD) calculated LDL baseline (mmol/L)	2.68 (0.90)	2.63 (0.76)	2.60 (0.80)	3.04 (0.97)	2.57 (0.76)	2.81 (0.97)	2.84 (1.01)
Estimated LS mean (SE) from baseline at week 24 (%)[a]	−44.1 (4.5)	−20.5 (4.7)	−5.0 (4.6)	−54.0 (4.3)	−22.6 (4.3)	−4.8 (4.2)	−21.4 (4.2)
Estimated mean difference % (95% CI)	Versus EZE: −23.6 (−40.7 to −6.5), *P* = 0.0004 Versus ATV: −39.1 (−55.9 to −22.2), *P* = 0.0001			Versus EZE: −31.4 (−47.4 to −15.4), *P* < 0.0001 Versus ATV: −49.2 (−65.0 to −33.5), *P* < 0.0001 Versus ROS: −32.6 (−48.4 to −16.9), *P* < 0.0001			
Proportion of very-high CV risk patients reaching calculated LDL-C < 1.81 mmol/L or high CV risk patients reaching calculated LDL-C < 2.59 mmol/L at week 24 (ITT)	87.2%	68.4%	34.5%	84.6%	65.1%	18.5%	62.2%
Combined estimate for odds ratio (95% CI)[b]	Versus EZE: 3.4 (0.8 to 14.6), *P* = 0.0284[c] Versus ATV: 16.7 (3.9 to 71.7), *P* < 0.0001			Versus EZE: 9.1 (1.6 to 52.2), *P* = 0.0011 Versus ATV: 83.2 (11.6 to 596.8), *P* < 0.0001 Versus ROS: 7.2 (1.3 to 38.3), *P* = 0.0025			
Proportion of patients reaching calculated LDL-C < 1.81 mmol/L at week 24 (ITT analysis)	79.2%	50.3%	16.0%	77.2%	54.2%	42.2%	10.2%
Combined estimate for odds ratio (95% CI)[b]	Versus EZE: 4.7 (1.3 to17.0)[c] Versus ATV: 28.9 (6.5 to127.8), *P* < 0.0001			Versus EZE: 9.9 (1.9 to 51.9), *P* = 0.0004 Versus ATV: 13.2 (2.5 to 68.8), *P* < 0.0001 Versus ROS: 116.8 (14.7 to 927.5), *P* < 0.0001			
Deaths (pooled), n (%)	0	2 (2)	0	NA	NA	NA	NA
CHD death (including undetermined), n (%)	0	1 (1)	0	NA	NA	NA	NA
Any patients with treatment-emergent CV events confirmed by adjudication (pooled), n (%)	1 (1)	1 (1)	0	NA	NA	NA	NA
EQ-5D	NR	NR	NR	NR	NR	NR	NR

Aliro = alirocumab; ATV = atorvastatin; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 Dimensions; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; LS = least squares; NR = not reported; ROS = rosuvastatin; SD = standard deviation; SE = standard error; ITT = intention to treat.

[a] LS means, SEs, and P values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point interaction, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest. Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets using Rubin's formula.

[c] Not statistically significant after adjustment for multiplicity (*P* = 0.01) or not tested after previous end point failed to achieve statistical significance.

Source: Clinical Study Report for OPTIONS 1,[13] Bays et al. 2015.[14]

TABLE 29: KEY EFFICACY OUTCOMES FOR OPTIONS 2

	OPTIONS 2					
	Rosuvastatin 10 mg Background			Rosuvastatin 20 mg Background		
Outcome	Alirocumab n = 49	EZE N = 48	ROS 20 N = 48	Aliro n = 54	EZE N = 53	ROS 40 N = 53
Mean (SD) calculated LDL baseline (mmol/L)	2.791 (0.687)	2.643 (1.095)	2.743 (0.933)	3.059 (0.841)	3.092 (1.257)	2.946 (1.122)
Estimated LS mean (SE) from baseline at week 24 (%)[a]	−50.6 (4.2)	−14.4 (4.4)	−16.3 (4.1)	−36.3 (7.1)	−11.0 (7.2)	−15.9 (7.1)
Estimated mean difference % (95% CI) versus comparator	Versus EZE: −36.1 (−51.5 to −20.7), $P < 0.0001$ Versus ROS: −34.2(−49.2 to −19.3), $P < 0.0001$			Versus EZE: −25.3 (−50.9 to 0.3), $P = 0.0136$[c] Versus ROS: −20.3 (−45.8 to 5.1), $P = 0.0453$[c]		
Proportion of patients reaching target LDL-C < 1.8 mmol/L (very-high CV risk) or < 2.6 mmol/L (high CV risk) at week 24	84.9%	57.2%	45.0%	66.7%	52.2%	40.1%
Combined estimate for odds ratio (95% CI) versus comparator[b]	Versus EZE: 8.4 (1.8 to 40.5), $P = 0.0007$ Versus ROS: 12.4 (2.6 to 59.5), $P < 0.0001$			Versus EZE: 2.1 (0.6 to 7.0)[c] Versus ROS: 4.6 (1.3 to 15.9)[c]		
Proportion of patients reaching target LDL-C < 1.8 mmol/L (regardless of CV risk) at week 24	77.8%	43.1%	31.3%	60.1%	43.6%	29.9%
Combined estimate for odds ratio (95% CI) versus comparator[b]	Versus EZE: 11.6 (2.5 to 53.1), $P < 0.0001$ Versus ROS: 18.6 (3.6 to 96.2), $P < 0.0001$			Versus EZE: 2.5 (0.7 to 8.5)[c] Versus ROS: 6.1 (1.6 to 22.8)[c]		
Deaths (pooled), n (%)	0	1 (1.0)	0	NA	NA	NA
CHD death (including undetermined cause), n (%)	0	0	0	NA	NA	NA
Any patients with treatment-emergent CV events confirmed by adjudication	0 (pooled)	1 (1) (pooled)	1 (1) (pooled)	NA	NA	NA
EQ-5D	NR	NR	NR	NR	NR	NR

Aliro = alirocumab; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 Dimensions; EZE = ezetimibe; LDL-C = low-density lipoprotein cholesterol; LS = least squares; NR = not reported; ROS = rosuvastatin; SD = standard deviation; SE = standard error.

[a] LS means, SEs, and P values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per interactive voice response system, time point, treatment-by-time-point interaction, and strata-by-time-point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline value by time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest. Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets using Rubin's formula.

[c] Not statistically significant after adjustment for multiplicity ($P = 0.0125$) or not tested after previous end point failed to achieve statistical significance.

Source: Clinical Study Report for OPTIONS 2,[15] Farnier et al. 2016.[16]

TABLE 30: KEY EFFICACY OUTCOMES FOR ALTERNATIVE AND MONO

	ALTERNATIVE			MONO	
Outcome	**Alirocumab n = 126**	**Ezetimibe N = 124**	**ATV N = 63**	**Alirocumab N = 52**	**Ezetimibe N = 51**
Mean (SD) baseline (mmol/L)				3.654 (0.702)	3.583 (0.636)
Estimated LS mean (SE) from baseline at week 24 (%)	−45.0 (2.2)	−14.6 (2.2)	NR	−47.2 (3.0)	−15.6 (3.1)
LS mean difference (SE) vs. ezetimibe	−30.4 (−36.6 to −24.2), $P < 0.0001$			−31.6 (−40.2 to −23.0), $P < 0.0001$	
Proportion of patients reaching calculated LDL-C < 2.6 mmol/L at week 12	NR	NR	NR	88.3	30.7
Combined estimate for odds ratio (95% CI)[b]	NA			47.4 (11.0 to 204.2), $P < 0.0001$	
Proportion of patients reaching calculated LDL-C < 1.8 mmol/L at week 12	NR	NR	NR	30 (58)	
Combined estimate for odds ratio (95% CI)	NA			138.7 (21.1 to > 9,999), $P < 0.0001$	
Proportion of very-high CV Risk patients reaching calculated LDL-C < 1.81 mmol/L or moderate or high CV risk patients reaching a calculated LDL-C < 2.59 mmol/L	41.9	4.4			
Combined estimate for odds ratio (95% CI)[b]	19.5 (6.9 to 55.2), $P < 0.0001$		NR	NA	NA
Deaths, n (%)	0	0	0	0	0
CHD death (including undetermined cause), n (%)	0	0	0	0	0
Any patients with treatment-emergent CV events confirmed by adjudication, n (%)	4 (3)	1 (1)	1 (2)	0	0
• Non-fatal myocardial infarction	1 (1)	0	0	0	0
• Ischemia-driven coronary revascularization procedure	3 (2)	1 (1)	1 (2)	0	0
Mean (SD) EQ-5D utility score	NR	NR	NR	0.94 (0.10)	0.92 (0.12)
Week 24 change from baseline LS mean (SE)	NR	NR	NR	0.01 (0.02)	−0.02 (0.02)
LS mean difference (95% CI)				0.03 (−0.02 to 0.07), $P = 0.2464$	

ATV = atorvastatin; CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; EQ-5D = EuroQoL-5 Dimensions; LDL-C = low-density lipoprotein cholesterol; LS = least squares; NR = not reported; SD = standard deviation; SE = standard error; vs. = versus.

[a] LS means, SEs, and P values taken from MMRM analysis. The model includes the fixed categorical effects of treatment group, time point, treatment-by-time-point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time-point interaction. MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[b] Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest. Combined estimate for odds ratio is obtained by combining the logarithm of odds ratio from logistic regression model analyses of the different imputed data sets, using Rubin's formula.

Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

3.7 Harms

Only those harms identified in the review protocol are reported below. See 0 for detailed harms data.

3.7.1 Adverse Events

Clinical Cardiovascular Disease Studies

The proportion of patients experiencing any AE was similar between the alirocumab and placebo groups in COMBO 1 (76% in each group after 52 weeks) and COMBO 2 (71% versus 67% after 104 weeks). Upper respiratory tract infection and dizziness were common AEs across studies, but still occurred in only 5% to 7% of patients (Table 31). Among notable harms, there were no clear and consistent numerical differences between groups, and the most commonly occurring notable harm in both studies was allergic event, occurring in between 5% and 9% of patients across studies.

Familial Hypercholesterolemia Studies

The proportion of patients with an AE after 78 weeks was numerically lower with alirocumab than placebo in FH 2 (75% versus 82%) and HIGH FH (61% versus 71%), and similar between the alirocumab and placebo groups in FH 2 (82% versus 79%). The most common AE across studies was nasopharyngitis (Table 32).

The most common notable harm across studies was injection site reaction, and there was a numerically larger proportion of alirocumab-treated versus placebo-treated patients in HIGH FH (8% versus 3%) with this AE.

Mixed Population Study

In LONG TERM, 81% of alirocumab versus 83% of placebo patients experienced an AE after 78 weeks. The most common AE was nasopharyngitis (Table 33). The most common notable harm was allergic reaction, occurring in 10% of alirocumab and placebo patients.

Other Studies

The proportion of patients experiencing an AE ranged between 64% and 86% across studies (Table 34, Table 35). Numerical differences in AEs between groups were noted in OPTIONS 2, where AEs occurred in 56% of alirocumab patients and 54% of ezetimibe patients versus 67% of atorvastatin 40 mg patients, and in MONO, where AEs occurred in 69% of alirocumab patients and 78% of ezetimibe patients. Among notable harms, there were no clear and consistent differences between groups in the risk of notable harms.

3.7.2 Serious Adverse Events

Clinical Cardiovascular Disease Studies

The proportion of patients experiencing a serious adverse event (SAE) were similar between the alirocumab and placebo groups in COMBO 1 (13% in each group after 52 weeks) and alirocumab versus ezetimibe in COMBO 2 (19% versus 18% after 104 weeks)(Table 31).

Familial Hypercholesterolemia Studies

The proportion of patients experiencing an SAE was similar between the alirocumab and placebo groups in FH 1 (14% in each after 78 weeks), FH 2 (9% in alirocumab, 10% in placebo after 78 weeks), and HIGH FH (11% in each after 78 weeks) (Table 32).

Mixed Population Study
There were similar proportions of alirocumab-treated versus placebo-treated patients experiencing an SAE in LONG TERM (19% versus 20% after 78 weeks) (Table 33).

Other Studies
Across studies, SAEs were reported in between 2% and 11% of patients, with no more than a 3% difference between groups in any study (Table 34, Table 35).

3.7.3 Withdrawal Due to Adverse Events

Clinical Cardiovascular Disease Studies
In COMBO 1, withdrawal due to adverse event (WDAEs) occurred in 6% of alirocumab-treated patients and 8% of placebo patients, and in COMBO 2, WDAEs occurred in 8% of alirocumab-treated patients and 5% of ezetimibe patients (Table 31).

Familial Hypercholesterolemia Studies
In FH 1, WDAEs occurred in 3% of alirocumab patients versus 6% of placebo patients. In FH 2, WDAEs occurred in 4% of alirocumab versus 1% of placebo patients. In HIGH FH, WDAEs occurred in 4% of alirocumab versus 3% of placebo patients (Table 32).

Mixed Population Study
WDAEs occurred in 7% of alirocumab patients versus 6% of placebo patients in LONG TERM (Table 33).

Other Studies
The ALTERNATIVE study had a notably higher rate of WDAEs (~25%) compared with the other studies. WDAEs ranged between 4% and 10% (Table 34,Table 35).

TABLE 31: HARMS FOR CLINICAL CARDIOVASCULAR DISEASE STUDIES

	COMBO 1		COMBO 2	
Harm	Alirocumab N = 209	Placebo N = 107	Alirocumab N = 479	Ezetimibe N = 241
TEAEs, n (%)	157 (76)	81 (76)	341 (71)	162 (67)
Most common (5% in any group), n (%)				
Upper respiratory tract infection	16 (8)	11 (10)	31 (7)	14 (6)
Arthralgia	8 (4)	8 (8)	–	–
Nasopharyngitis	15 (7)	5 (5)	–	–
Urinary tract infection	13 (6)	4 (4)	–	–
Dizziness	11 (5)	6 (6)	23 (5)	13 (5)
Non-cardiac chest pain	2 (1)	7 (7)	–	–
Sinusitis	11 (5)	4 (4)	–	–
Myalgia	–	–	21 (4)	12 (5)
Treatment-emergent SAEs, n (%)	26 (13)	14 (13)	90 (19)	43 (18)
TEAEs leading to discontinuation, n (%)	13 (6)	8 (8)	36 (8)	13 (5)
Notable AEs, n (%)				
• Local injection site reactions	11 (5)	3 (3)	12 (3)	2 (1)
• Potential general allergic reaction events	18 (9)	7 (7)	30 (6)	12 (5)
• Neurologic events	5 (2)	2 (2)	13 (3)	7 (3)
• Neurocognitive disorders	0 (0)	1 (1)	4 (1)	3 (1)

	COMBO 1		COMBO 2	
• ALT > 3 × ULN	3 (2)	2 (2)	8/470 (1.7)	1/240 (0.4)
• CK > 3 × ULN			13/467 (2.8)	6/236 (2.5)
Mean (SD) duration of IMP injection exposure (weeks)	46.08 (13.82)	45.39 (14.24)	57.97 (18.74)	57.70 (18.99)
Patients up-titrated, n (%)	32/191 (17)	NA	82/446 (18)	NA

AE = adverse event; ALT = alanine aminotransferase; CK = creatinine kinase; IMP = investigative medicinal product; LDL-C = low-density lipoprotein cholesterol; NA = not applicable; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.
Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes et al. 2015,[5] Cannon et al. 2015.[6]

TABLE 32: HARMS FOR STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

	FH 1		FH 2		HIGH FH	
Harm	**Alirocumab N = 322**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**	**Alirocumab N = 72**	**Placebo N = 35**
Patients with an AE, n (%)	263 (82)	129 (79)	125 (75)	66 (82)	44 (61)	25 (71)
Most common (5% in any group), n (%)						
• Nasopharyngitis	36 (11)	12 (7)	21 (13)	18 (22)	8 (11)	4 (11)
• Upper respiratory tract infection	22 (7)	14 (9)	5 (3)	1 (1)	–	–
• Arthralgia	20 (6)	9 (6)	8 (5)	7 (9)	–	–
• Influenza	20 (6)	10 (6)	24 (14)	7 (9)	8 (11)	1 (3)
• Back pain	18 (6)	7 (4)	12 (7)	6 (7)	–	–
• Sinusitis	17 (5)	7 (4)	1 (1)	2 (3)	4 (6)	2 (6)
• Headache	15 (5)	9 (6)	16 (10)	7 (9)	4 (6)	0
• Diarrhea	10 (3)	5 (3)	11(6)	1 (1)	4 (6)	3 (9)
• Bronchitis	10 (3)	9 (6)	4 (2)	1 (1)	4 (6)	1 (3)
• Dizziness	7 (2)	6 (4)	8 (5)	5 (6)	–	–
• Myalgia	6 (2)	11 (7)	10 (6)	5 (6)	3 (4)	3 (9)
• Influenza-like illness	6 (2)	1 (1)	9 (5)	5 (6)	–	–
Treatment-emergent SAEs, n (%)	44 (14)	22 (14)	15 (9)	8 (10)	8 (11)	4 (11)
Ischemic coronary artery disorders, n (%)					5 (7)	0
AEs leading to discontinuation, n (%)	11 (3)	10 (6)	6 (4)	1 (1)	3 (4)	1 (3)
Notable AEs, n (%)						
• Local injection site reactions	40 (12)	18 (11)	19 (11)	6 (7)	6 (8)	1 (3)
• General allergic reaction events	28 (9)	16 (10)	19 (11)	5 (6)	3 (4)	1 (3)
• Neurologic events	12 (4)	7 (4)	7 (4)	2 (3)	1 (1)	1 (3)
• Neurocognitive disorders	2 (1)	2 (1)	0	1 (1)	1 (1)	1 (3)
• ALT > 3X ULN	5/322 (2)	2/163 (1)	6/166 (4)	1/81 (1)	3 (4)	1 (3)
• CK > 3X ULN	13/318 (4)	10/163 (6)	8/165 (5)	6/80 (8)	2 (3)	0
Mean (SD) duration of injection exposure (weeks)	59.1 (14.2)	59.0 (14.7)	58.8 (12.5)	60.7 (8.3)	58.3 (17.6)	60.7 (13.2)
Patients up-titrated, n (%)	135/311 (43)	NA	61/158 (39)	NA		

AE = adverse event; ALT = alanine aminotransferase; CK = creatinine kinase; NA = not applicable; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse events; ULN = upper limit of normal.
Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein 2015,[9] Clinical Study Report for HIGH FH.[10]

TABLE 33: HARMS FOR MIXED POPULATION STUDY

	LONG TERM	
Harm	**Alirocumab 150 (N = 1,550)**	**Placebo (N = 788)**
Patients with an AE, n (%)	1,255 (81)	650 (83)
Most common (5% in any group), n (%)		
• Upper respiratory tract infection	109 (7)	63 (8)
• Arthralgia	70 (5)	47 (6)
• Nasopharyngitis	196 (13)	100 (13)
• Urinary tract infection	81 (5)	49 (6)
• Influenza	84 (5)	43 (6)
• Bronchitis	80 (5)	37 (5)
• Headache	74 (5)	44 (6)
• Diarrhea	82 (5)	40 (5)
• Back pain	73 (5)	47 (6)
Treatment-emergent SAEs, n (%)	290 (19)	154 (20)
AEs leading to discontinuation, n (%)	111 (7)	46 (6)
Notable AEs, n (%)		
• Local injection site reactions	91 (6)	33 (4)
• General allergic reaction events	156 (10)	75 (10)
• Neurologic events	65 (4)	35 (4)
• Neurocognitive disorders	18 (1)	4 (1)
Mean (SD) duration of IMP injection exposure (weeks)	64.59 (19.15)	64.63 (19.11)

AE = adverse event; IMP = investigative medicinal product; SAE = serious adverse event; SD = standard deviation.
Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

Other Four Studies Not Considered Relevant to Reimbursement Criteria

TABLE 34: HARMS FOR OPTIONS 1 AND OPTIONS 2

	OPTIONS 1			OPTIONS 2		
	Pooled			Pooled		
Harm	**Alirocumab N = 104**	**Ezetimibe N = 101**	**ATV 40 N = 149**	**Alirocumab n = 103**	**Ezetimibe N = 101**	**ATV 40 N = 101**
Patients with an AE, n (%)	68 (65)	65 (64)	95 (64)	58 (56)	54 (54)	68 (67)
Most common (5% in any group), n (%)						
• Upper respiratory tract infection	5 (5)	9 (9)	7 (5)	6 (6)	4 (4)	9 (9)
• Nasopharyngitis	5 (5)	3 (3)	8 (5)	4 (4)	5 (5)	7 (7)
• Urinary tract infection	3 (3)	8 (8)	8 (5)	–	–	–
• Nausea	1 (1)	4 (4)	11 (7)	–	–	–
• Diarrhea	2 (2)	3 (3)	8 (5)	–	–	–
• Back pain	7 (7)	3 (3)	6 (4)	–	–	–
• Dizziness	–	–	–	3 (3)	2 (2)	5 (5)
• Pain in extremity	–	–	–	2 (2)	3 (3)	8 (8)
Treatment-emergent SAEs, n (%)	4 (4)	7 (7)	8 (5)	6 (6)	8 (8)	8 (8)
AEs leading to discontinuation, n (%)	7 (7)	4 (4)	8 (5)	5 (5)	8 (8)	5 (5)

	OPTIONS 1			OPTIONS 2		
Notable AEs, n (%)						
• Local injection site reactions	3 (3)	3 (3)	3 (2)	4 (4)	0	2 (2)
• Potential general allergic reaction events	2 (2)	5 (5)	6 (4)	9 (9)	2 (2)	7 (7)
• Neurologic events	3 (3)	1 (1)	3 (2)	2 (2)	3 (3)	2 (2)
• Neurocognitive disorders				1 (1)	1 (1)	1 (1)
• ALT > 3 × ULN	0	0	1 (1)	1 (1)	0	0
• CK > 3 × ULN	3 (3)	1 (1)	8 (5)	0	3 (3)	2 (2)
Mean (SD) duration of injection exposure (weeks)	21.98 (6.30)	22.05 (5.37)	22.70 (4.81)	22.05 (5.53)	21.52 (6.23)	22.99 (4.13)

AE = adverse event; ALT = alanine aminotransferase; ATV = atorvastatin; CK = creatinine kinase; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal.
Source: Clinical Study Report for OPTIONS 1[13] and OPTIONS 2,[15] Bays et al. 2015,[14] Farnier et al. 2016.[16]

TABLE 35: HARMS FOR ALTERNATIVE AND MONO

	ALTERNATIVE			MONO	
Harm	Alirocumab N = 126	Ezetimibe N = 124	Atorvastatin N = 63	Alirocumab N = 52	Ezetimibe N = 51
Patients with an AE, n (%)	104 (83)	100 (81)	54 (86)	36 (69)	40 (78)
Most common (5% in any group) , n (%)					
• Nasopharyngitis	8 (6)	10 (8)	2 (3)	12 (23)	8 (16)
• Diarrhea	–	–	–	6 (12)	2 (4)
• Influenza	–	–	–	6 (12)	3 (6)
• Arthralgia	7 (6)	5 (4)	2 (3)	3 (6)	2 (4)
• Headache	6 (5)	6 (5)	4 (6)	3 (6)	2 (4)
• Nausea	–	–	–	3 (6)	3 (6)
• Upper respiratory tract infection	7 (6)	5 (4)	2 (3)	2 (4)	5 (10)
• Urinary tract infection	–	–	–	0	3 (6)
• Back pain	–	–	–	1 (2)	3 (6)
• Dizziness	–	–	–	1 (2)	3 (6)
• Myalgia	31 (25)	29 (23)	17 (27)	–	–
• Sinusitis	6 (5)	4 (3)	1 (2)	–	–
Treatment-emergent SAEs, n (%)	12 (10)	10 (8)	7 (11)	1 (2)	1 (2)
AEs leading to discontinuation, n (%)	23 (18)	31 (25)	16 (25)	5 (10)	4 (8)
Notable AEs, n (%)					
• Local injection site reactions	6 (5)	6 (5)	1 (2)	1 (2)	2 (4)
• Potential general allergic reaction events				6 (12)	5 (10)
• Neurologic events				0	0
• Neurocognitive disorders				0	0
• ALT > 3X ULN	0	0	0	0	0
• CK > 3X ULN	3 (2)	2 (2)	3 (5)	0	1 (2)
Mean (SD) duration of injection exposure (weeks)	21.47 (5.91)	19.82 (7.25)	19.43 (7.76)	22.05 (5.62)	22.39 (5.16)

AE = adverse event; ALT = alanine aminotransferase; CK = creatinine kinase; SAE = serious adverse event; SD = standard deviation; ULN = upper limit of normal.
Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

4. DISCUSSION

4.1 Summary of Available Evidence

Ten phase 3 double-blind randomized controlled trials were included in this review, of which six were considered to be key studies with respect to evidence in support of the manufacturer's proposed reimbursement criteria, as these studies included patients who were at high risk of CV events (COMBO 1 and COMBO 2), or who had HeFH (FH 1, FH 2, and HIGH FH), or who were a mixed population of both types of patient (LONG TERM). These six studies were also the ones chosen by Health Canada to be included in the Canadian Product Monograph. The remaining four studies (OPTIONS 1, OPTIONS 2, MONO, and ALTERNATIVE) included broader populations of patients that were less well-aligned with the manufacturer's proposed reimbursement criteria, including patients without FH and a relatively lower risk of CV events. The primary outcome for all 10 studies was the per cent change from baseline in LDL-C after 24 weeks, and the comparators included placebo, ezetimibe, or statins. None of the included studies was powered to assess clinical outcomes such as mortality, CV death, or CV morbidity, nor were any they powered to assess potential harms. Quality of life was not assessed as an efficacy outcome but rather as a safety outcome (and thus not part of the statistical hierarchy) in all studies in which it was assessed.

4.2 Interpretation of Results

4.2.1 Efficacy

The evidence relevant to the manufacturer's proposed reimbursement criteria included two studies in primarily clinical CVD patients (COMBO 1 and COMBO 2), defined as patients with established coronary heart disease or risk equivalents, three studies in HeFH patients (FH 1, FH 2, and HIGH FH), and one study in a mixed population of both clinical CVD and HeFH patients (LONG TERM). In all of these studies, 24 weeks of alirocumab treatment was associated with a statistically and clinically significant per cent reduction from baseline in LDL-C versus placebo (five studies) or ezetimibe (one study, COMBO 2). The treatment effect versus placebo was largest in the LONG TERM and FH 1 studies (approximately a 60% reduction) and smallest in HIGH FH (approximately a 40% reduction); therefore, there did not appear to be evidence of a differential treatment effect size in HeFH patients compared to patients with clinical CVD. The magnitude of the reduction in LDL-C observed in alirocumab-treated patients in the included studies was similar to the effect of another PCSK9 inhibitor, evolocumab, which reduces LDL-C by > 50%.

Although each of the studies that focused on HeFH patients, clinical CVD patients, or HeFH patients with or without clinical CVD demonstrated that alirocumab treatment caused a statistically and clinically significant reduction in LDL-C, the clinical relevance of these reductions in LDL levels is unclear. Because none of these studies was powered to assess clinical end points such as mortality, CV mortality, or CV morbidity, the frequencies of these events were too low to draw any definitive conclusions. Nevertheless, LDL-C is widely accepted as a valid indicator of CV risk, based on evidence from clinical studies that have shown that changes in LDL-C are correlated with the incidence of CAD-related clinical events,[32,33] and LDL-C has been used as a surrogate end point in other studies of PCSK9 inhibitors, including evolocumab. The ongoing ODYSSEY OUTCOMES study, with an expected enrolment of 18,000 patients, is designed to assess the effects of alirocumab on major CVD events and should be completed by late 2017. The primary end point in ODYSSEY OUTCOMES is the proportion of patients with a major adverse CV event, a composite end point that includes death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization. When this composite was applied in a post-hoc analysis to the LONG TERM study, the proportion of

patients experiencing a major CV event was lower with alirocumab than with placebo (1.7% versus 3.3% of patients, *P* = 0.02).

An important consideration is the extent to which patients who are not at a target LDL-C level are maximized in their statin therapy. There are side effects with statins that limit the maximum dose that can be tolerated by some patients, most notably muscle-related issues that range from myalgia (which is relatively common but highly subjective) to myositis and rhabdomyolysis (which are serious and easier to detect, but relatively uncommon). The results of the six included studies that focused on patients with HeFH, clinical CVD, or both, in which the comparator was either placebo (five studies) or ezetimibe (one study), demonstrated that alirocumab treatment was effective in lowering LDL-C levels in patients who were on a maximally tolerated dose of a statin (atorvastatin, rosuvastatin, or simvastatin). Data from the smaller, shorter-term OPTIONS studies suggest that alirocumab may not be superior to a high dose of rosuvastatin (40 mg daily) administered to patients who fail to achieve a target LDL-C level on a moderate dose of rosuvastatin (20 mg daily). However, as noted above, the broader population used in the OPTIONS studies limits the generalizability of these findings to patients with HeFH, clinical CVD, or both. In addition, it is also unclear whether this result applies to statins other than rosuvastatin, which is a relatively potent statin (according to the clinical expert).

Patient input submitted to CDR suggested that quality of life is an important consideration for patients with hypercholesterolemia. Much of the connection between quality of life and hypercholesterolemia is based on patient concerns about the difficulty in achieving a target LDL level and about the potential clinical consequences of elevated cholesterol levels. Quality of life was studied only as a safety rather than an efficacy outcome in the included studies, using the EQ-5D instrument, and there were no clear and consistent differences in changes to the EQ-5D across studies. Although it is debatable whether the lowering of LDL-C levels would necessarily improve changes in quality of life, as patients are unlikely to feel a clear improvement in their health status with treatment, the available evidence does not support the conclusion that achieving a target LDL level improves quality of life. It is possible that an improvement in quality of life attributable to achieving a target LDL level might be mitigated by other factors, such as the fact that PCSK9 inhibitors are administered by injection (whereas statins are administered orally). However, the impact of the route of administration was not assessed in any of the included studies. Moreover, as noted above, quality of life was not an efficacy outcome in the included studies, and it is unclear whether the EQ-5D is the most appropriate tool to measure changes in quality of life in the included studies, as this is a generic EQ-5D health-related quality-of-life instrument that has not been evaluated specifically in hypercholesterolemia patients. Most respondents in the patient impact submission to CDR indicated that they were not concerned or only somewhat concerned about administering an injection, and suggested that they would not find it difficult to adhere to the treatment regimen since the injection is only once or twice a month. Others appeared to focus on the less-frequent administration as an advantage rather than the route of administration being a disadvantage. It is also worth noting that the alternative PCSK9 inhibitor available in Canada, evolocumab, is also administered by subcutaneous injection at a frequency similar to that of alirocumab.

4.2.2 Harms

Overall, the harms reported in the included studies suggest that alirocumab is relatively well tolerated, which is consistent with the findings for the other drug in this class, evolocumab. The overall frequencies of AEs observed in the included studies tended to be similar to those of the comparator groups (or lower in some cases), while serious AE frequencies were similar among treatment groups across all studies.

Among several notable potential harms that were identified for this review, including immune reactions, injection site reactions, muscle symptoms, neurocognitive changes, hepatitis C, and changes in liver enzymes, there were no major differences with respect to the frequency of these harms among treatment groups across the included studies. One caveat is the fact that none of the included studies was sufficiently powered or sufficiently long to assess harms, which is particularly pertinent to rarer harms. Harms that are normally associated with the use of monoclonal antibodies, such as hypersensitivity reactions and injection site reactions, were often more frequent in patients treated with alirocumab than other treatments in the included studies. Although formal statistical comparisons were not appropriate due to the limitation noted above, such AEs are not unexpected for a subcutaneously administered antibody treatment, and these side effects are generally mild, are easily managed, and do not often lead to discontinuation of treatment. The safety profile of alirocumab is similar to that of the other PCSK9 inhibitor in this class, evolocumab.

4.3 Potential Place in Therapy[1]

Statins are used routinely for primary and secondary prevention of CVD. However, although statins are generally well tolerated, a small percentage of people are intolerant to statins and either cannot take a statin or can achieve only a suboptimal dose of statin. The inability of some patients to tolerate statins, and therefore to secure the beneficial effects of these drugs, represents an unmet need in the management of dyslipidemia, and having available an effective and well-tolerated drug for such patients would be a useful addition to current therapies. Another major potential unmet need is for adjunctive therapy to further reduce cholesterol levels in patients considered at high risk of a CV event, in whom cholesterol levels remain high despite optimal statin therapy. This population would comprise primarily adult patients (≥ 18 years of age) with HeFH or established coronary heart disease with LDL-C levels that are higher than the recommended target despite taking maximally tolerated doses of statins.

The results of clinical studies suggest that PCSK9 inhibitors such as alirocumab could reduce LDL-C levels in this population, but it is uncertain whether this translates into a reduction in clinically significant CV events. Coupled with an absence of long-term safety data for alirocumab, this uncertainty means that many physicians and their patients may decide to await further evidence before incorporating this drug into routine practice.

[1] This information is based on information provided by the clinical expert consulted for the purpose of this review.

5. CONCLUSIONS

Ten multi-centre, manufacturer-sponsored, phase 3 double-blind randomized controlled trials included in this review assessed the effects of treatment with alirocumab compared with placebo or ezetimibe on LDL-C levels over 24 weeks. Six studies included patients who were at high risk of CV events (COMBO 1 and COMBO 2), or who had HeFH (FH 1, FH 2, and HIGH FH), or who were a mixed population of both types of patient (LONG TERM), while the remaining four studies (OPTIONS 1, OPTIONS 2, MONO, and ALTERNATIVE) included broader populations of patients, including patients without FH or with clinical CVD. The results of COMBO 1 and COMBO 2 suggested that treatment of patients with clinical CVD with alirocumab for 24 weeks is associated with a statistically significant reduction in LDL-C levels of between 30% and 46% versus ezetimibe or placebo and allows statistically significantly more patients to achieve a target LDL-C level of < 1.8 mmol/L. The results of FH 1, FH 2, and HIGH FH suggested that treatment of HeFH patients with alirocumab for 24 weeks is associated with a statistically significant reduction in LDL-C levels of between 51% and 58% versus placebo and allows statistically significantly more patients to achieve a target LDL-C level of < 1.8 mmol/L, even in FH patients who had not experienced a prior CV event. The results of LONG TERM suggested that treatment of patients with HeFH or clinical CVD or both HeFH and CVD with alirocumab for 24 weeks is associated with a statistically significant reduction in LDL-C levels of up to 62% versus placebo and allows statistically significantly more such patients to achieve a target LDL-C level of < 1.8 mmol/L. The results of the other studies suggested that treatment of patients who are not necessarily at high risk of a CV event with alirocumab for 24 weeks statistically significantly reduces LDL-C levels compared with ezetimibe or a doubling of background statin therapy, although it is uncertain whether this applies to patients treated with rosuvastatin. There were no important or consistent differences among treatment groups across all of the included studies with respect to harms such as mortality, AEs, SAEs, or WDAEs, except for harms related to administration (such as injection site reactions). Therefore, alirocumab treatment did not appear to be associated with a substantial risk of serious harm, but there is still limited evidence regarding the long-term safety of alirocumab. Despite the availability of post-hoc analyses from the LONG TERM study, the effect of alirocumab on CV morbidity and mortality has not been determined. In addition, none of the included studies directly compared alirocumab with evolocumab, the other PCSK9 inhibitor approved for use in Canada, nor was there evidence available in the literature to compare these two drugs indirectly. Therefore, the relative efficacy and safety of alirocumab versus evolocumab is unknown.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups, the Heart and Stroke Foundation and the Familial Hypercholesterolemia Canada Patient Network, provided input for this review.

The Heart and Stroke Foundation is one of Canada's largest and most effective health charities. Its mission is to prevent disease, save lives, and promote recovery. During the last 60 years, the Heart and Stroke Foundation has invested more than $1.39 billion in heart and stroke research, and the death rate from heart disease and stroke has declined by more than 75% during this period. The Heart and Stroke Foundation has received unrestricted financial support from: Aegerion Pharmaceuticals, Amgen, Apotex, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb Canada, Eli Lilly Canada, GlaxoSmithKline Inc., Janssen, McKesson Canada, Merck, Merz Pharma Canada, Novartis, Novo Nordisk, Pfizer Canada Inc., Sanofi, Servier, Takeda, and Valeant. The Heart and Stroke Foundation and the individuals involved in the preparation of this submission have no conflict of interests to declare.

The Familial Hypercholesterolemia Canada Patient Network is a volunteer-led national non-profit organization. It was organized with the assistance of clinicians in Montreal and Vancouver and with outreach through the Familial Hypercholesterolemia Canada Registry Network and the FH Foundation in the United States. The objectives of the Network are to raise awareness about familial hypercholesterolemia to promote screening and diagnosis, to provide education about the condition, to improve access to appropriate treatment and care, and to provide a forum for advocacy and support. The Network receives unrestricted educational grants from Sanofi Canada, Pfizer Canada, Amgen, and Aegerion, and receives organizational and administrative support, including preparation of this submission on behalf of the Familial Hypercholesterolemia Canada Patient Network, from the not-for-profit Consumer Advocare Network at no cost. No other organizations were involved in the preparation of the submission.

2. Condition-Related Information

The Familial Hypercholesterolemia Canada Patient Network gathered information through one-on-one interviews, small group discussion via webcast, teleconferences, surveys, and forums. Of the 282 participants, 72 said they were managed "well" or "very well" on their current therapy, while the remainder indicated that they currently or previously had high cholesterol that was "at higher than target levels." The Heart and Stroke Foundation gathered information through online surveys and literature searches. In total, 65 participants were used to inform this submission.

Patients with hypercholesterolemia primarily expressed that lowering their cholesterol or achieving target levels was most important; however, almost all experienced challenges in achieving these goals. Patients conveyed the frustration, stress, anxiety, and even depression associated with the serious challenge of achieving or maintaining low cholesterol despite trying medications, low-fat diets, exercise, and other interventions. They reported being "accused" by their health professionals of not adhering to their medications: "I know I need to lose weight and probably get more aerobic exercise, but when I talk to my doctor and I know he doesn't believe I am trying, it just makes me more discouraged." Most patients have tried several different treatment regimens including different drugs or combinations of drugs, natural foods, and homeopathic therapies. Some patients reported that this condition does not

affect their day-to-day lives or their ability to conduct activities, but the majority felt that the condition affects their lives on a daily basis. They expressed that their relationships, work, social life, and activities were all affected by the condition. The challenges most frequently reported were daily medication regimens, frequent medical appointments, and self-management of their condition with other forms of therapy such as diet and exercise. Another concern expressed by patients is the stress and fear of death, especially from the risk of stroke or CV events: "Both my father and his father died of heart attacks before they were 50 years old. At the time they didn't know it was FH, so at least we can get a diagnosis now, but I don't know whether that helps."

3. Current Therapy–Related Information

Some patients suffering from hypercholesterolemia reported inadequate control with conventional therapy while others indicated adequate control using medications such as statins, ezetimibe, niacin, resins, homeopathic cholesterol-sterol, coenzyme Q10, or acetylsalicylic acid. Other patients indicated that they were not taking any medication to treat their high cholesterol, primarily due to intolerance with adverse events such as myopathy, muscle pain, chest pain, constipation, headaches, fatigue, weakness, anxiety, depression, elevated liver count, heat burn, cramps, upset stomach, flatulence, diarrhea, redness, burning, and itching. In some cases, adverse events were significant enough to require treatment dose adjustment, switching treatment, additional combination treatments, taking a break from treatment, or discontinuing treatment. Several patients suggested it is difficult to differentiate the symptoms of high cholesterol from those caused by the treatment. Some patients managed their hypercholesterolemia with nondrug therapies such as apheresis, although the treatments were not satisfactory: "I go for plasma exchange every couple of weeks, but it is just keeping me alive and is very time-consuming."

Most patients suffering from hypercholesterolemia expressed their challenges with the medication regimen and said that they have tried several different treatment regimens including different drugs or combination of drugs, natural foods, and homeopathic therapies. "I had switched statins and found myself spiralling into the worst depression. My doctor didn't believe it was related but switched me back and things are back to normal. I'd rather struggle with the cholesterol than experience that again." "I switched from atorvastatin to rosuvastatin because I was having extreme pains in my legs and hips. The pain has gone, but now I'm just exhausted all the time. Someone suggested taking CoQ10 and vitamin D, but that brings me up to 11 medications." Some patients expressed their difficulty convincing their health professional to let them try alternate medications, while others suggested that their treatment had been changed without their knowledge: "I told the doctor I was experiencing some side effects (dizziness, bladder control, and anxiety) from my new meds, and he said that was not possible. He said he had just moved me from the [brand] statin to the same generic version. I convinced him to switch me back, and the side effects went away." Some patients also expressed their challenges in adhering to strict dietary conditions: "I also have diabetes so was referred to a dietician, since I needed a diet that was low-carbohydrate as well as low-fat. I can't say it is easy."

Many of the caregivers were parents of children diagnosed with or at risk for hypercholesterolemia. While some were anxious and optimistic to start therapy and indicated no impacts or challenges on their routine or lifestyle, others expressed the "horror" of starting their children on statins. Some caregivers expressed frustration with getting their spouses or older children to stay on therapy, especially when they seemingly experienced no immediate benefit from therapy or negative outcome when regimens were not followed.

4. Expectations About the Drug Being Reviewed

When asked "Other than being cured, what would the best course of treatment look like for you?" in the Heart and Stroke Foundation survey, participants indicated therapy that did not include medication, or included medications with few to no side effects: "diet, exercise, I don't' tolerate pills very well," "getting off the statin," "medicine I could tolerate that would lower my levels without any side effects." Other responses included "continue with medication," "continue doing what I'm doing," and "no further progression of disease."

Patients suffering from hypercholesterolemia, regardless if they are adequately controlled or not on current conventional therapies, believe that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors could be a valuable alternative and are anticipating their approval. Some believe that all therapies are effective for only a limited time: "When I started on statins, I was excited to get my cholesterol levels down to normal but after a while my doctor had to double the dosage (increase the frequency) to get the same effect. Then he added another drug (ezetimibe). He said I could be a candidate for PCSK9, based on my history of increasing resistance." "I started getting side effects [to the statin] almost right away but my doctor said to give them a chance and they may go away. Not only didn't the side effects improve, my cholesterol levels didn't change very much. I am not sure how the PCSK9s work, but I am ready to try something else if it works and is easier to handle." "When I was diagnosed with lupus, I had to start two other medications, so my doctor took me off the statins temporarily. When I started back, they just didn't seem to have the same effect and my cholesterol was stuck well over 30. I like the fact that you don't have to take the PCSK9 every day so it might not be a problem with my other medications."

Patients suffering from inadequately controlled hypercholesterolemia have the highest expectations for PCSK9 inhibitors. They expect that PCSK9 inhibitors will more effectively control their cholesterol and that the treatment will have fewer adverse events compared with statins. Most participants indicated that they were not concerned or only somewhat concerned about administering an injection, and suggested that it would not be difficult to adhere to the treatment regimen since it is only once or twice a month. Some were aware of the potential stomach, digestive, and cognitive risks, but suggested that they were willing to try the treatment with appropriate monitoring to see if the treatment might be more efficacious and cause fewer adverse events when compared with statins. For patients with experience with PCSK9 inhibitors, all were satisfied or very satisfied with the impact on their cholesterol level and expressed both a physical and emotional benefit: "At first, I was worried I wouldn't be able to manage the injections, but it was actually quite easy, especially with those new injection devices." "I had no idea how liberating it would be not to have to remember statins four times a day. A monthly injection is almost like being drug free." Those with PCSK9 inhibitor experience expressed that they had very few or temporary adverse events: "I had some soreness with the injections initially but that has gone away almost completely." Two patients had direct experience with Praluent and indicated that it was helping to control cholesterol with no additional medication needed. One of the two patients reported the following adverse effects: throat, nose, or sinus infection; flu or cold-like symptoms (high temperature, sore throat, runny nose, cough, or chills); and reactions at the injection site (redness, swelling, bruising, or pain). Most of those well managed on statins said they would not want to switch at this time. However, when asked if they would choose a monthly injection over a pill if the injection "worked better" or if there were fewer serious side effects, all chose the injection. Parents were unsure whether they would start their children on statins, which have a history of effectiveness and safety, or PCSK9 inhibitors, which may be more effective and require less-demanding regimens.

5. Additional Information

The two patient groups acknowledged that a limitation of the patient input gathered was that it was not a population-based survey. The submissions did not suggest that the responses were representative of the entire hypercholesterolemia population.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 3, 2016
Alerts:	Bi-weekly search updates until June 15, 2016
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY		
1	(alirocumab* or Praluent* or (REGN adj1 "727") or REGN727 or (SAR adj1 "236553") or SAR236553).ti,ab,ot,hw,kf,rn,nm.	466
2	(PP0SHH6V16 or 1245916-14-6 or "1245916146").rn,nm.	273
3	1 or 2	466
4	3 use pmez	107
5	*alirocumab/	101
6	(alirocumab* or Praluent* or (REGN adj1 "727") or REGN727 or (SAR adj1 "236553") or SAR236553).ti,ab,kw.	237
7	5 or 6	263
8	7 use oemezd	177
9	conference abstract.pt.	2134146
10	8 not 9	134
11	4 or 10	241
12	remove duplicates from 11	158

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	February 2, 2016
Keywords:	Praluent (Alirocumab)/Hypercholesterolemia; Dyslipidemia; Low-density Lipoprotein Cholesterol (LDL-C)
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Zhang XL, Zhu QQ, Zhu L, Chen JZ, Chen QH, Li GN, et al. Safety and efficacy of anti-PCSK9 antibodies: A meta-analysis of 25 randomized, controlled trials. BMC Medicine [Internet]. 2015 [cited 2016 Feb 24];13(1).	Systematic review and meta-analysis
White CM. Therapeutic Potential and Critical Analysis of the PCSK9 Monoclonal Antibodies Evolocumab and Alirocumab. Ann Pharmacother. 2015 Dec;49(12):1327-35.	Review
McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol [Internet]. 2012 Jun 19 [cited 2016 Feb 24];59(25):2344-53.	Phase 2 trial / Wrong dose
Moriarty PM, Jacobson TA, Bruckert E, Thompson PD, Guyton JR, Baccara-Dinet MT, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol [Internet]. 2014 Nov [cited 2016 Feb 24];8(6):554-61.	Design and rationale not an RCT

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 36: SUBGROUP DATA FOR CLINICAL CARDIOVASCULAR DISEASE STUDIES

	COMBO 1		COMBO 2	
	Alirocumab N = 209	Placebo N = 107	Alirocumab N = 467	Ezetimibe N = 240
Prior History of MI or Ischemic Stroke				
Yes	n = 118	n = 60	n = 303	n = 157
LS means (SE)	−52.3 (2.5)	0.4 (3.6)	−52.2 (1.7)	−21.6 (2.4)
LS mean difference vs. placebo or ezetimibe (95% CI)	−52.8 (−61.4 to −44.1)		−30.6 (−36.2 to −24.9)	
No	n = 87	n = 46	n = 164	n = 83
LS means (SE)	−42.6 (3.0)	−5.7 (4.1)	−47.5 (2.3)	−19.0 (3.2)
LS mean difference vs. placebo or ezetimibe (95% CI)	−36.9 (−46.8 to −27.0)		−28.5 (−36.2 to −20.8)	
Interaction *P* value	*P* = 0.0183		*P* = 0.6769	
Baseline Calculated LDL-C				
< 2.59 mmol/L	[redacted]	[redacted]	N = 231	N = 126
LS means (SE)	[redacted]	[redacted]	−47.8 (1.9)	−14.9 (2.6)
LS mean difference vs. placebo or ezetimibe (95% CI)	[redacted]		−32.8 (−39.2 to −26.5)	
≥ 2.59 to < 3.37 mmol/L	[redacted]	[redacted]	N = 136	N = 64
LS means (SE)	[redacted]	[redacted]	−52.2 (2.5)	−24.9 (3.7)
LS mean difference vs. placebo or ezetimibe (95% CI)	[redacted]		−27.3 (−36.0 to −18.5)	
≥ 3.37 to < 4.14 mmol/L	[redacted]	[redacted]	N = 59	N = 33
LS means (SE)	[redacted]	[redacted]	−58.2 (3.9)	−28.7 (5.1)
LS mean difference vs. placebo or ezetimibe (95% CI)	[redacted]		−29.6 (−42.0 to −17.1)	
≥ 4.14 mmol/L	[redacted]	[redacted]	N = 41	N = 17
LS means (SE)	[redacted]	[redacted]	−51.9 (4.6)	−27.8 (7.3)
LS mean difference vs. placebo or ezetimibe (95% CI)	[redacted]		−24.1 (−40.8 to −7.3)	
Interaction *P* value	[redacted]		*P* = 0.6574	
LMT at Randomization				
Statin with other LMT at randomization	n = 77	n = 52		
LS means (SE)	−51.0 (3.2)	4.1 (3.9)		
LS mean difference vs. placebo (95% CI)	−55.1 (−64.9 to −45.2)			
Statin without other LMT at randomization	n = 128	n = 54		
LS means (SE)	−46.5 (2.4)	−8.6 (3.9)		
LS mean difference vs. placebo (95% CI)	−37.9 (−46.9 to −28.9)			
Interaction *P* value	*P* = 0.0122			
Statin Treatment as Per IVRS				
High-intensity statin	n = 121	n = 62	n = 302	n = 152
LS means (SE)	−46.8 (2.5)	−0.2 (3.6)	−49.8 (1.7)	−21.6 (2.4)
LS mean difference vs. placebo or ezetimibe (95% CI)	−46.6 (−55.2 to −38.0)		−28.2 (−33.9 to −22.5)	
No high-intensity statin	n = 84	n = 44	n = 165	n = 88
LS means (SE)	−50.2 (3.1)	−5.2 (4.2)	−52.0 (2.4)	−19.2 (3.2)

	COMBO 1		COMBO 2	
	Alirocumab N = 209	Placebo N = 107	Alirocumab N = 467	Ezetimibe N = 240
LS mean difference vs. placebo or ezetimibe (95% CI)	−44.9 (−55.1 to −34.7)		−32.8 (−40.4 to −25.1)	
Interaction *P* value	*P* = 0.8039		*P* = 0.3462	

IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; SE = standard error; vs. = versus.
Source: Clinical Study Report for COMBO 1[3] and COMBO 2,[4] Kereiakes et al. 2015,[5] Cannon et al. 2015.[6]

TABLE 37: SUBGROUP DATA FOR STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

	FH 1		FH 2	
Data	**Alirocumab N = 322**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**
Prior History of MI or Ischemic Stroke				
Yes	n = 89	n = 46	n = 36	n = 18
LS means (SE)	−50.0 (3.1)	4.8 (4.2)	−50.5 (4.2)	1.8 (5.8)
LS mean difference (95% CI) vs. placebo	−54.8 (−64.9 to −44.7)		−52.3 (−66.4 to −38.3)	
No	n = 233	n = 117	n = 130	n = 63
LS means (SE)	−48.3 (1.9)	10.9 (2.6)	−48.2 (2.2)	3.0 (3.1)
LS mean difference (95% CI) vs. placebo	−59.2 (−65.5 to −52.9)		−51.2 (−58.7 to −43.6)	
Interaction *P* value	*P* = 0.4702		*P* = 0.8854	
Baseline Calculated LDL-C				
< 2.59 mmol/L	[redacted]			
LS means (SE)	[redacted]			
LS mean difference (95% CI) vs. placebo	[redacted]			
≥ 2.59 to < 3.37 mmol/L	[redacted]			
LS means (SE)	[redacted]			
LS mean difference (95% CI) vs. placebo	[redacted]			
≥ 3.37 to < 4.14 mmol/L	[redacted]			
LS means (SE)	[redacted]			
LS mean difference (95% CI) vs. placebo	[redacted]			
≥ 4.14 mmol/L	[redacted]			
LS means (SE)	[redacted]			
LS mean difference (95% CI) vs. placebo	[redacted]			
Interaction *P* value	[redacted]			
LMT at Randomization				
Statin with other LMT at randomization	n = 197	n = 107	n = 116	n = 57
LS means (SE)	−51.8 (2.0)	8.9 (2.7)	−48.4 (2.3)	1.0 (3.3)
LS mean difference (95% CI) vs. placebo	−60.7 (−67.3 to −54.1)		−49.4 (−57.4 to −41.4)	
Statin without other LMT at randomization	n = 125	n = 56	n = 50	n = 24
LS means (SE)	−44.1 (2.6)	9.7 (4.0)	−49.3 (3.5)	7.0 (5.2)
LS mean difference (95% CI) vs. placebo	−53.8 (−63.0 to −44.7)		−56.2 (−68.5 to −43.9)	
Interaction *P* value	*P* = 0.2290		*P* = 0.3623	
Statin Treatment as Per IVRS				
High-intensity statin	n = 261	n = 132	n = 137	n = 68
LS means (SE)	−49.7 (1.8)	9.4 (2.5)	−48.4 (2.1)	2.3 (3.0)
LS mean difference (95% CI) vs. placebo	−59.1 (−65.0 to −53.1)		−50.6 (−57.9 to −43.3)	
No high-intensity statin	n = 61	n = 31	n = 29	n = 13

	FH 1		FH 2	
Data	**Alirocumab N = 322**	**Placebo N = 163**	**Alirocumab N = 167**	**Placebo N = 82**
LS means (SE)	−45.0 (3.7)	8.1 (5.2)	−50.1 (4.8)	5.4 (6.9)
LS mean difference (95% CI) vs. placebo	−53.0 (−65.4 to −40.6)		−55.5 (−72.0 to −39.0)	
Interaction *P* value	*P* = 0.3876		*P* = 0.5958	

CI = confidence interval; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; SE = standard error; vs. = versus.
Source: Clinical Study Report for FH 1 and FH 2,[7,8] Kastelein 2015.[9]

TABLE 38: SUBGROUP DATA FOR STUDIES SPECIFIC TO HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HIGH FH)

	HIGH FH	
Data	**Alirocumab N = 72**	**Placebo N = 35**
Prior History of MI or Ischemic Stroke		
Yes	n = 17	**n = 9**
LS means (SE)	−43.4 (7.1)	4.8 (9.7)
LS mean difference (95% CI) vs. placebo	−48.3 (−72.0 to −24.5)	
No	n = 54	n = 26
LS means (SE)	−46.5 (4.0)	−10.4 (5.7)
LS mean difference (95% CI) vs. placebo	−36.1 (−50.0 to −22.2)	
Interaction *P* value	*P* = 0.3822	
Baseline Calculated LDL-C		
< 4.91 mmol/L	[redacted]	[redacted]
LS means (SE)	[redacted]	[redacted]
LS mean difference (95% CI) vs. placebo	[redacted]	
≥ 4.91 mmol/L	[redacted]	[redacted]
LS means (SE)	[redacted]	[redacted]
LS mean difference (95% CI) vs. placebo	[redacted]	
Interaction *P* value	[redacted]	
LMT at Randomization		
Statin with other LMT at randomization	n = 16	n = 13
LS means (SE)	−55.1 (7.2)	3.9 (7.9)
LS mean difference (95% CI) vs. placebo	−59.0 (−80.1 to −37.9)	
Statin without other LMT at randomization	n = 55	n = 22
LS means (SE)	−42.9 (3.9)	−13.2 (6.1)
LS mean difference (95% CI) vs. placebo	−29.7 (−44.2 to −15.3)	
Interaction *P* value	*P* = 0.0257	
Statin Treatment as Per IVRS		
High-intensity statin	n = 50	n = 25
LS means (SE)	−50.2 (4.2)	−10.7 (5.8)
LS mean difference (95% CI) vs. placebo	−39.5 (−53.7 to −25.3)	
No high-intensity statin	n = 21	n = 10
LS means (SE)	−34.9 (6.6)	3.7 (9.5)
LS mean difference (95% CI) vs. placebo	−38.6 (−61.5 to −15.7)	
Interaction *P* value	*P* = 0.9495	

CI = confidence interval; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; SE = standard error; vs. = versus.
Source: Clinical Study Report for HIGH FH.[10]

TABLE 39: SUBGROUP DATA FOR MIXED POPULATION STUDY

	LONG TERM	
Data	**Alirocumab N = 1530**	**Placebo N = 780**
History of MI or Ischemic Stroke		
Yes	n = 734	n = 375
LS means (SE)	−63.0 (1.1)	0.3 (1.5)
LS mean difference (95% CI) vs. placebo	−63.3 (−66.8 to −59.7)	
No	n = 796	n = 405
LS means (SE)	−59.2 (1.0)	1.3 (1.4)
LS mean difference (95% CI) vs. placebo	−60.6 (−64.0 to −57.1)	
Interaction *P* value	*P* = 0.2835	
Baseline Calculated LDL-C		
< 2.59 mmol/L	n = 470	n = 241
LS means (SE)	−61.3 (1.3)	13.6 (1.8)
LS mean difference (95% CI) vs. placebo	−75.0 (−79.3 to −70.6)	
≥ 2.59 to < 3.37 mmol/L	n = 562	n = 285
LS means (SE)	−62.0 (1.2)	0.5 (1.7)
LS mean difference (95% CI) vs. placebo	−62.5 (−66.5 to −58.4)	
≥ 3.37 to < 4.14 mmol/L	n = 271	n = 143
LS means (SE)	−59.8 (1.7)	−5.2 (2.4)
LS mean difference (95% CI) vs. placebo	−54.6 (−60.3 to −48.8)	
≥ 4.14 mmol/L	n = 227	n = 111
LS means (SE)	−59.5 (1.9)	−18.2 (2.8)
LS mean difference (95% CI) vs. placebo	−41.3 (−47.8 to −34.8)	
Interaction *P* value	*P* < 0.0001	
LMT at Randomization		
Statin with other LMT at randomization	n = 433	n = 219
LS means (SE)	−62.3 (1.4)	1.5 (2.0)
LS mean difference (95% CI) vs. placebo	−63.8 (−68.5 to −59.1)	
Statin without other LMT at randomization	n = 1097	n = 561
LS means (SE)	−60.5 (0.9)	0.5 (1.2)
LS mean difference (95% CI) vs. placebo	−61.0 (−64.0 to −58.1)	
Interaction *P* value	*P* = 0.3210	
Statin Treatment as Per IVRS		
High-intensity statin	n = 670	n = 342
LS means (SE)	−61.5 (1.1)	0.8 (1.6)
LS mean difference (95% CI) vs. placebo	−62.3 (−66.0 to −58.6)	
No High-Intensity Statin	n = 860	n = 438
LS means (SE)	−60.7 (1.0)	0.8 (1.4)
LS mean difference (95% CI) vs. placebo	−61.5 (−64.8 to −58.2)	
Interaction *P* value	*P* = 0.7543	

CI = confidence interval; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; SE = standard error; vs. = versus.
Source: Clinical Study Report for LONG TERM,[11] Robinson 2015.[12]

TABLE 40: SUBGROUP DATA FOR OPTIONS 1

	OPTIONS 1						
	Atorvastatin 20 mg Background			Atorvastatin 40 mg Background			
Data	Aliro N = 57	Ezetimibe N = 55	ATV 40 N = 57	Aliro N = 47	Ezetimibe N = 47	ATV 80 N = 47	ROS 40 N = 45
Prior History of MI or Ischemic Stroke							
Yes, n	13	15	14	18	17	18	17
LS means (SE)	−38.3 (9.4)	−29.9 (9.1)	−3.0 (8.8)	−45.3 (6.7)	−13.8 (6.8)	−6.0 (6.9)	−29.7 (6.9)
LS mean difference (95% CI) vs. comparator	[redacted]			[redacted]			
No, n	42	38	39	28	29	29	28
LS means (SE)	−45.9 (5.2)	−16.9 (5.5)	−5.7 (5.4)	−59.2 (5.5)	−28.4 (5.3)	−4.2 (5.3)	−16.6 (5.3)
LS mean difference (95% CI) vs. comparator	[redacted]			[redacted]			
Interaction *P* value	[redacted]			[redacted]			
Baseline Calculated LDL-C							
< 2.59 mmol/L, n	29	32	29	17	28	23	23
LS means (SE)	−44.1 (6.4)	−19.8 (6.2)	0.0 (6.4)	−41.0 (6.9)	−20.2 (5.2)	3.4 (5.9)	−20.9 (5.8)
LS mean difference (95% CI) vs. comparator	[redacted]			[redacted]			
≥ 2.59 to < 3.37 mmol/L, n	17	12	13	15	11	15	12
LS means (SE)	−38.5 (8.4)	−21.4 (10.2)	−10.6 (9.4)	−66.3 (7.2)	−28.3 (8.3)	−4.6 (7.5)	−22.4 (8.0)
LS mean difference (95% CI) vs. comparator	Versus EZE: −17.1 (−43.3 to 9.0), *P* = 0.1970 Versus ATV: −27.9 (−52.9 to −3.0), *P* = 0.0283			Versus EZE: −38.0 (−59.8 to −16.1), *P* = 0.0008 −61.7 (−82.3 to −41.1), *P* < .0001 Versus ROS: −43.8 (−65.1 to −22.5), *P* < .0001			
≥ 3.37 to < 4.14 mmol/L, n	5	6	9	9	5	4	7
LS means (SE)	−50.0 (16.2)	−26.0 (14.4)	−10.0 (11.4)	−66.0 (9.2)	−25.2 (12.3)	−31.9 (13.8)	−20.1 (10.9)
LS mean difference (95% CI) vs. comparator	Versus EZE: −23.9 (−66.5 to 18.7), *P* = 0.2685 Versus ATV: −39.9 (−78.8 to −1.0), *P* = 0.0444			Versus EZE: −40.8 (−71.1 to −10.4), *P* = 0.0089 −34.0 (−66.8 to −1.2), *P* = 0.0420 Versus ROS: −45.9 (−73.9 to −17.9), *P* = 0.0015			
≥ 4.14 mmol/L, n	4	3	2	5	2	5	3
LS means (SE)	−62.4 (16.9)	−7.5 (21.5)	−19.9 (23.9)	−34.2 (14.5)	30.3 (27.7)	−18.9 (12.3)	−22.6 (16.0)
LS mean difference (95% CI) vs. comparator	Versus EZE: −54.9 (−109 to −1.0) *P* = 0.0461 Versus ATV: −42.5 (−100 to 15.3) *P* = 0.1481			Versus EZE: −64.5 (−126 to −2.9), *P* = 0.0404 −15.3 (−52.9 to 22.2), *P* = 0.4206 Versus ROS: −11.7 (−54.3 to 30.9), *P* = 0.5888			
Interaction *P* value	*P* = 0.8583			*P* = 0.1428			
LMT at Randomization	NR	NR	NR	NR	NR	NR	NR
Statin Treatment as Per IVRS	NR	NR	NR	NR	NR	NR	NR

Aliro = alirocumab; ATV = atorvastatin; CI = confidence interval; EZE = ezetimibe; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; NR = not reported; ROS = rosuvastatin; SE = standard error; vs. = versus.
Source: Clinical Study Report for OPTIONS 1,[13] Bays et al. 2015.[14]

TABLE 41: SUBGROUP DATA FOR OPTIONS 2

	OPTIONS 2					
	Rosuvastatin 10 mg Background			Rosuvastatin 20 mg Background		
Data	Aliro N = 49	Ezetimibe N = 48	ROS 20 N = 48	Aliro N = 54	Ezetimibe N = 53	ROS 40 N = 53
Prior History of MI or Ischemic Stroke						
Yes, n						
LS means (SE)						
LS mean difference (95% CI) vs. ezetimibe						
No, n						
LS means (SE)						
LS mean difference (95% CI) vs. ezetimibe						
Interaction *P* value						
< 2.59 mmol/L, n						
LS means (SE)						
LS mean difference (95% CI) vs. ezetimibe						
≥ 2.59 to < 3.37 mmol/L, n						
LS means (SE)						
LS mean difference (95% CI) vs. ezetimibe						
≥ 3.37 to < 4.14 mmol/L, n						
LS means (SE)						
LS mean difference (95% CI) vs. ezetimibe						
≥ 4.14 mmol/L, n						
LS means (SE)						
LS mean difference (95% CI) vs. ezetimibe						
Interaction *P* value						

	OPTIONS 2					
	Rosuvastatin 10 mg Background			Rosuvastatin 20 mg Background		
Data	Aliro N = 49	Ezetimibe N = 48	ROS 20 N = 48	Aliro N = 54	Ezetimibe N = 53	ROS 40 N = 53
LMT at Randomization						
Statin with other LMT at random, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS means (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI) vs. ezetimibe	[redacted]			[redacted]		
Statin without other LMT at random, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS means (SE)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LS mean difference (95% CI) vs. ezetimibe	[redacted]			[redacted]		
Interaction *P* value	[redacted]			[redacted]		
Statin Treatment as Per IVRS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Aliro = alirocumab; CI = confidence interval; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; ROS = rosuvastatin; SE = standard error; vs. = versus.
Source: Clinical Study Report for OPTIONS 2,[15] Farnier et al. 2016.[16]

TABLE 42: SUBGROUP DATA FOR ALTERNATIVE AND MONO

	ALTERNATIVE		MONO	
Data	**Aliro N = 126**	**Ezetimibe N = 124**	**Alirocumab N = 52**	**Ezetimibe N = 51**
Prior History of MI or Ischemic Stroke				
Yes, n	26	23	NR	NR
LS means (SE)	−51.2 (4.8)	−15.5 (5.1)	NR	NR
LS mean difference (95% CI) vs. ezetimibe	−35.7 (−49.5 to −22.0), *P* < .0001		NR	
No , n	100	99	NR	NR
LS means (SE)	−43.4 (2.5)	−14.3 (2.5)	NR	NR
LS mean difference (SE) vs. ezetimibe	−29.1 (−36.0 to −22.2), *P* < .0001		NR	
Interaction *P* value	*P* = 0.3971		NR	
Baseline Calculated LDL-C				
< 3.37 mmol/L	[redacted]	[redacted]	16	14
LS means (SE)	[redacted]	[redacted]	−43.4 (5.5)	−6.7 (5.8)
LS mean difference (SE) vs. ezetimibe	[redacted]		−36.7 (−52.6 to −20.7)	
≥ 3.37 to < 4.14 mmol/L	[redacted]	[redacted]	21	29
LS means (SE)	[redacted]	[redacted]	−51.6 (4.7)	−19.7 (4.2)
LS mean difference (SE) vs. ezetimibe	[redacted]		−31.9 (−44.4 to −19.4)	
≥ 4.14 mmol/L	[redacted]	[redacted]	15	8
LS means (SE)	[redacted]	[redacted]	−45.6 (5.6)	−15.7 (7.6)
LS mean difference (SE) vs. ezetimibe	[redacted]		−29.8 (−48.6 to −11.1)	
Interaction *P* value	[redacted]		*P* = 0.8390	
LMT at Randomization				
Statin with other LMT at random				
LS means (SE)	[redacted]	[redacted]	NR	NR
LS mean difference (SE) vs. ezetimibe	[redacted]		NR	
Statin without other LMT at random				
LS means (SE)	[redacted]	[redacted]	NR	NR
LS mean difference (SE) vs. ezetimibe	[redacted]		NR	
Interaction *P* value	[redacted]		NR	
Statin Treatment as Per IVRS	[redacted]	[redacted]	[redacted]	[redacted]

Aliro = alirocumab; CI = confidence interval; IVRS = interactive voice response system; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; LS = least squares; MI = myocardial infarction; NR = not reported; SE = standard error; vs. = versus.
Source: Clinical Study Report for ALTERNATIVE[17] and MONO,[18] Roth 2014,[19] Roth 2015,[20] Moriarty 2015.[21]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the EuroQol 5-Dimensions Questionnaire (EQ-5D) outcome measure.

European Quality-of-Life Scale–5 Dimensions

The European Quality-of-Life Scale (EQ-5D) is a generic health-related quality of life instrument that may be applied to a wide range of health conditions and treatments.[29,30] The first of the two parts of the EQ-5D is a descriptive system that classifies respondents (aged ≥ 12 years) based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing "no problems", "some problems", and "extreme problems", respectively. Respondents are asked to choose the level that reflects their health state for each of the five dimensions, corresponding with 243 different health states. A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[29,30] The second part is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state". Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS which best represents their health on that day. Hence, the EQ-5D produces three types of data for each respondent:

- a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- a population preference-weighted health index score based on the descriptive system
- a self-reported assessment of health status based on the EQ-VAS.

The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the 3L version (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the UK algorithm and −0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health", respectively. Reported minimal clinically important differences for the 3L version of the scale have ranged from 0.033 to 0.074.[31]

Conclusion

The generic EQ-5D instrument has been widely used, but its psychometric properties have not been fully evaluated in hypercholesterolemia. No information regarding the minimal clinically important difference for the EQ-5D among patients suffering from hypercholesterolemia was found; however, general minimal clinically important differences have ranged from 0.033 to 0.074.

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