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Individuals with chronic kidney disease are at increased risk of premature cardiovascular disease. Among them, many with elevated low-density lipoprotein cholesterol (LDL-C) are unable to achieve optimal LDL-C on statins and require additional lipid-lowering therapy. To study this, we compared the LDL-C-lowering efficacy and safety of alirocumab in individuals with hypercholesterolemia with impaired renal function, defined as eGFR 30–59 ml/min/1.73 m^2, to those without impaired renal function eGFR ≥60 ml/min/1.73 m^2. A total of 4629 hypercholesterolemic individuals without or with impaired renal function, pooled from eight phase 3 ODYSSEY trials (double-blind treatments of 24–104 weeks), were on alirocumab 150 mg or 75/150 mg every two weeks vs. placebo or ezetimibe. Overall, 10.1% had impaired renal function and over 99% were receiving statin treatment. Baseline LDL-C in alirocumab and control groups was comparable in subgroups analyzed. LDL-C reductions at week 24 ranged from 46.1 to 62.2% or 48.3 to 60.1% with alirocumab among individuals with or without impaired renal function, respectively. Similar reductions were observed for lipoprotein (a), non-high-density lipoprotein cholesterol, apolipoprotein B, and triglycerides. Safety data were similar in both treatment subgroups, regardless of the degree of CKD. Renal function did not change over time in response to alirocumab. This *post hoc* efficacy analysis is limited by evaluation of alirocumab treatment effects on renal and lipid parameters by serum biochemistry. Thus, alirocumab consistently lowered LDL-C regardless of impaired renal function, with safety comparable to control, among individuals with hypercholesterolemia who nearly all were on statin treatment.

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Chronic kidney disease (CKD), characterized by impaired renal function (IRF), is associated with an increased risk of cardiovascular disease (CVD),[1–3] and a mixed dyslipidemia phenotype: elevated levels of triglycerides and remnant lipoproteins, and reduced levels of high-density lipoprotein cholesterol (HDL-C).[1] Individuals with CKD and elevated low-density lipoprotein cholesterol (LDL-C) are categorized as being at very high risk of CVD.[2,4] Statins are widely prescribed to lower LDL-C in those with CKD and have been shown in numerous large trials to reduce LDL-C levels and cardiovascular (CV) events (except in those on dialysis).[1,2,4–11] However, clearance of most statins is affected by renal function, and most individuals with CKD are on multiple drugs to treat other conditions (e.g., hyperglycemia, hypertension), raising the propensity for drug-drug interactions. Recent treatment guidelines for kidney disease recommend lower doses of statins, hence limiting the use of high-dose statins in those with CKD.[1,2,11–13] Therefore, if further LDL-C reduction is required, additional lipid-lowering therapies may be needed. The American College of Cardiology expert consensus decision pathway recommends the addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or ezetimibe to maximally tolerated statin therapy in high-risk patients with atherosclerotic CVD and CKD with <50% LDL-C reduction on statins, including high-intensity statins.[14]

Alirocumab is a monoclonal antibody to PCSK9 that reduces LDL-C levels significantly among high to very high risk individuals, including those with very high baseline LDL-C.[15,16] In the phase 3 ODYSSEY clinical program among individuals with hypercholesterolemia, alirocumab reduced LDL-C levels by up to 61% compared with controls and was

generally well tolerated.[15,17] PCSK9 is expressed transiently in the kidneys and may play a role in kidney development.[18] Increased plasma PCSK9 levels are observed in disorders of the glomerular filtration barrier, such as in individuals with nephrotic syndrome.[19,20] Further, a reduction in PCSK9 levels observed during remission in these individuals correlated with decreased levels of atherogenic lipids, suggesting that reducing PCSK9 may treat dyslipidemia in those with kidney disease.[19] Therefore, it is important to evaluate the safety and efficacy of alirocumab among individuals with IRF. The aim of this analysis was to determine the lipid-lowering efficacy and safety of alirocumab among individuals with or without IRF and to assess the impact of alirocumab on renal function over time.

RESULTS

IRF analysis (pool of 8 trials)

Overall, 10.5% (315/3010) of individuals randomized to alirocumab and 9.4% (152/1619) of those randomized to control were categorized as having IRF. The number of individuals with IRF from each of the 8 trials is shown in Table 1. In the subgroups with and without IRF, baseline characteristics were similar between the alirocumab and control groups (Table 2). Individuals with IRF had a mean estimated glomerular filtration rate (eGFR) of 51 ml/min per 1.73 m^2 in both treatment groups, indicating that, on average, these patients had slightly to moderately decreased renal function, belonging to CKD category G3a per CKD treatment guidelines.[2] Individuals with IRF were slightly older and had a higher incidence of diabetes at baseline compared with those without IRF. Baseline levels of LDL-C, non–HDL-C, and apoB were lower among individuals with versus those without IRF, and there was a lower proportion of individuals with IRF with heterozygous familial hypercholesterolemia (Table 2). Individuals with IRF had higher levels of triglycerides and lipoprotein (a) (Lp[a]) at baseline compared with those who did not have IRF. A lower proportion of individuals with versus without IRF were receiving high-intensity statin treatment (40–80 mg atorvastatin, 20–40 mg rosuvastatin, or 80 mg simvastatin [Table 2]).

Efficacy by IRF status

Efficacy was analyzed among individuals with versus without IRF in 3 pools by alirocumab dose and control. In the placebo-controlled pool with alirocumab at a starting dose of 75 mg every 2 weeks (Q2W), 20% (11/55) of individuals with versus 35.9% (217/605) without IRF had their alirocumab dose increased to 150 mg Q2W. In the ezetimibe-controlled pool with alirocumab starting at 75 mg Q2W, 11.4% (8/70) of individuals with versus 18.5% (104/561) without IRF were increased to the higher dose of 150 mg Q2W.

Table 1 | Trials included in this analysis

Comparison	Study	Duration (wk)	Background therapy	IRF,[a] *N* (%)		Without IRF,[a] *N* (%)	
				Alirocumab	Control[b]	Alirocumab	Control[b]
8 trials included in the IRF analysis				*N* = 315	*N* = 152	*N* = 2695	*N* = 1467
Alirocumab 150 mg Q2W versus placebo	LONG TERM[17] (NCT01507831)	78	Maximally tolerated statin[c] ± other LLT	176 (55.9)	74 (48.7)	1377 (51.1)	714 (48.7)
	HIGH FH[16] (NCT01617655)	78		4 (1.3)	1 (0.7)	68 (2.5)	34 (2.3)
	LONG TERM + HIGH FH			180 (57.1)	75 (49.3)	1445 (53.6)	748 (51.0)
Alirocumab 75/150 mg Q2W versus placebo	FH I[35] (NCT01623115)	78		20 (6.3)	9 (5.9)	303 (11.2)	154 (10.5)
	FH II[35] (NCT01709500)			2 (0.6)	1 (0.7)	165 (6.1)	81 (5.5)
	COMBO I[36] (NCT01644175)	52		37 (11.7)	24 (15.8)	172 (6.4)	83 (5.7)
	FH I + FH II + COMBO I			59 (18.7)	34 (22.4)	640 (23.7)	318 (21.7)
Alirocumab 75/150 mg Q2W versus ezetimibe	COMBO II[37] (NCT01644188)	104	Maximally tolerated statin (no other LLT allowed)	61 (19.4)	23 (15.1)	418 (15.5)	218 (14.9)
	OPTIONS I[38] (NCT01730040)	24	Stable statin dose[d] ± other LLT	7 (2.2)	14 (9.2)	97 (3.6)	88 (6.0)
	OPTIONS II[39] (NCT01730053)	24		8 (2.5)	6 (3.9)	95 (3.5)	95 (6.5)
	COMBO II + OPTIONS I + OPTIONS II			76 (24.1)	43 (28.3)	610 (22.6)	401 (27.3)
Additional 2 trials included in the renal safety analysis (10 trials total)				*N* = 321	*N* = 160	*N* = 2867	*N* = 1635
Alirocumab 75/150 mg Q2W versus ezetimibe	MONO[40] (NCT01644474)[e]	24	No statins ± other LLT	0	0	52 (1.8)	51 (3.1)
	ALTERNATIVE[41] (NCT01709513)[e]	24		6 (1.9)	8 (5.0)	120 (4.2)	117 (7.2)
	MONO + ALTERNATIVE			6 (1.9)	8 (5.0)	172 (6.0)	168 (10.3)

eGFR, estimated glomerular filtration rate; IRF, impaired renal function; LLT, lipid-lowering therapy; Q2W, every 2 weeks.
[a]IRF was defined based on medical history: IRF (eGFR: 30–59 ml/min per 1.73 m^2); without IRF included individuals with eGFR: 60–89 ml/min per 1.73 m^2, and normal kidney function (eGFR: ≥90 ml/min per 1.73 m^2).
[b]Control was placebo in 5 trials (LONG TERM, FH I and II, HIGH FH, and COMBO I) and ezetimibe in 3 trials (COMBO II and OPTIONS I and II).
[c]Maximally tolerated statin was defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg daily unless there was an investigator-approved reason for using lower doses (e.g. intolerance).
[d]Atorvastatin 20–40 mg in OPTIONS I and rosuvastatin 10–20 mg in OPTIONS II.
[e]Individuals from MONO and ALTERNATIVE were included only in the analyses of renal function over time.

Table 2 | Baseline characteristics of individuals pooled from eight phase 3 trials by IRF status (randomized population)

Characteristic	IRF[a]		Without IRF[a]	
	Alirocumab (*N* = 315)	Control[b] (*N* = 152)	Alirocumab (*N* = 2695)	Control[b] (*N* = 1467)
Age, yr, mean (SD)	67.3 (9.0)	67.5 (10.1)	58.4 (11.2)	58.9 (10.8)
Males, *N* (%)	178 (56.5)	88 (57.9)	1720 (63.8)	918 (62.6)
Race, white, *N* (%)	290 (92.1)	132 (86.8)	2431 (90.2)	1325 (90.3)
BMI, kg/m^2, mean (SD)	30.8 (6.1)	31.3 (6.1)	30.1 (5.6)	30.3 (5.6)
Individuals on statin, *N* (%)	314 (99.7)	152 (100)	2693 (99.9)	1466 (99.9)
High-intensity statin,[c] *N* (%)	159 (50.5)	77 (50.7)	1600 (59.4)	869 (59.2)
Individuals on additional non-statin LLT, n (%)	76 (24.1)	38 (25.0)	846 (31.4)	466 (31.8)
Ezetimibe, *N* (%)	29 (9.2)	15 (9.9)	508 (18.8)	276 (18.8)
Diabetes, *N* (%)	146 (46.3)	79 (52.0)	793 (29.4)	442 (30.1)
HeFH, *N* (%)	34 (10.8)	18 (11.8)	830 (30.8)	419 (28.6)
Proteinuria, *N* (%)				
Negative	193 (61.3)	89 (58.6)	1667 (61.9)	925 (63.1)
Trace	66 (21.0)	31 (20.4)	545 (20.2)	306 (20.9)
Positive	46 (14.6)	18 (11.8)	229 (8.5)	119 (8.1)
Missing	10 (3.2)	14 (9.2)	254 (9.4)	117 (8.0)
Hs-CRP, mg/dl mean (SD)	0.35 (0.55)	0.41 (0.70)	0.34 (0.66)	0.34 (0.75)
Lipids, mg/dl, mean (SD)				
LDL-C (calculated)	108.1 (33.8)	107.4 (39.3)	124.6 (45.5)	122.2 (43.9)
Non-HDL-C	139.6 (39.2)	138.5 (44.4)	153.4 (48.7)	151.2 (47.8)
HDL-C	49.6 (13.6)	48.6 (13.2)	49.6 (13.3)	49.5 (13.0)
Triglycerides, median (Q1:Q3)	143.0 (103.5:205.0)	148.0 (103.0:201.5)	125.7 (91.0:176.1)	126.5 (93.0:177.0)
Lp(a), median (Q1:Q3)	29.1 (8.1:84.0)	28.4 (10.3:65.0)	24.6 (8.0:69.0)	23.0 (7.3:67.5)
ApoB	93.5 (23.8)	93.1 (26.8)	103.0 (28.3)	101.6 (27.7)
ApoA1	146.6 (25.8)	145.4 (26.2)	144.5 (25.3)	144.6 (26.6)
Renal function at baseline (safety population)				
	N = 313	*N* = 151	*N* = 2691	*N* = 1466
eGFR, ml/min per 1.73 m^2, mean (SD)	51.3 (11.0)	51.2 (11.0)	79.0 (17.0)	79.1 (17.8)
BUN (mmol/l), mean (SD)	7.8 (2.6)	8.5 (3.7)	5.9 (1.7)	5.8 (1.7)
Cr (μmol/l), mean (SE)	114.9 (1.5)	116.6 (2.4)	83.0 (0.4)	82.7 (0.5)

Apo, apolipoprotein; BMI, body mass index; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; hs-CRP, high-sensitivity C-reactive protein; IRF, impaired renal function; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a); lipoprotein (a).

[a]IRF was defined based on medical history: IRF (eGFR: 30–59 ml/min per 1.73 m^2); without IRF included individuals with eGFR: 60–89 ml/min per 1.73 m^2, and normal kidney function (eGFR: ≥90 ml/min per 1.73 m^2).

[b]Control was placebo in 5 trials (LONG TERM, FH I and II, HIGH FH, and COMBO I) and ezetimibe in 3 trials (COMBO II and OPTIONS I and II).

[c]High-intensity statin corresponds to atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg.

Significant reductions in LDL-C were observed with alirocumab versus placebo or ezetimibe treatment at week 24 in all 3 pools analyzed (Figure 1a). In the pools on alirocumab 75/150 mg Q2W, similar reductions in LDL-C were observed among individuals with and without IRF (nonsignificant interaction *P* values; Figure 1a). In the pool with alirocumab 150 mg Q2W versus placebo, the mean change in LDL-C with alirocumab was –62.2% and –60.1% among individuals with and without IRF, respectively (interaction *P* value = 0.016, possibly due to the slight apparent increase from baseline in LDL-C observed in the control-treated group of those with IRF). The mean difference in LDL-C change between alirocumab and control was greater in the placebo-controlled pools compared with the ezetimibe-controlled pools (Figure 1a).

In the placebo-controlled pools, a significant proportion of individuals on alirocumab versus placebo reached prespecified LDL-C goals of <70 mg/dl or <100 mg/dl, depending on CV risk, ranging from 65.4% to 82.7% versus 6.9% to 11.5% in those with IRF, and from 76.1% to 78.5% versus 6.4% to 8.1% in those without IRF (Table 3). In the ezetimibe-controlled pool, the proportion of individuals reaching prespecified LDL-C goals with alirocumab was 82.1% versus 66.1% with ezetimibe in those with IRF and 77.5% versus 50.9% in those without IRF. No significant interaction was observed in the analysis of the proportion of individuals reaching LDL-C goals based on IRF status (Table 3).

Significant changes in apoB, non-HDL-C, Lp(a), and HDL-C were observed on alirocumab versus placebo or ezetimibe treatment at week 24 in all 3 pools analyzed and were independent of IRF status in most of the subgroups analyzed by alirocumab dosage and control (nonsignificant interaction *P* values; Figure 1b, c, e, and f). Significant interaction *P* values (from comparing efficacy data based on IRF status) were observed only in the placebo-controlled subgroups with alirocumab 150 mg Q2W for apoB (interaction *P* value = 0.003; Figure 1b) and with alirocumab 75/150 mg Q2W for non–HDL-C (interaction *P* value = 0.028; Figure 1c). In the ezetimibe-controlled subgroups with alirocumab 75/150 mg Q2W, the comparison of percentage of change in HDL-C based on IRF status resulted in an interaction *P* value = 0.049. Similar to the observed changes in LDL-C in the placebo-controlled subgroups with alirocumab 150 mg Q2W, this was possibly due to a

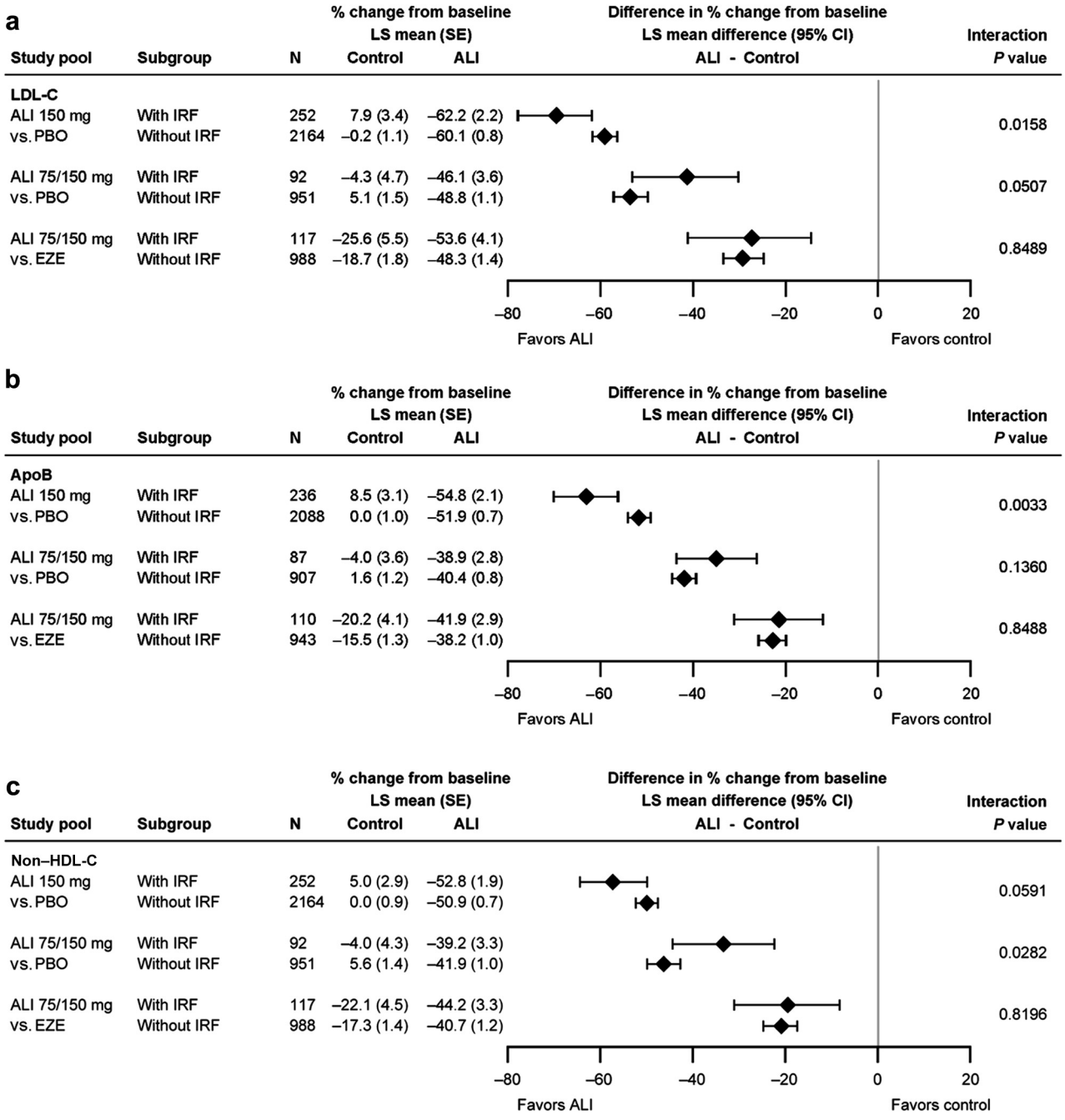

Figure 1 | Percentage of changes from baseline to week 24 in (a) LDL-C, (b) apoB, (c) non–HDL-C, (d) triglycerides, (e) Lp(a), and (f) HDL-C by IRF status (intention-to-treat population; pool of eight phase 3 trials). Pool alirocumab 150 versus placebo (with statins): LONG TERM, HIGH FH. Pool alirocumab 75/150 versus placebo (with statins): COMBO I, FH I, FH II. Pool alirocumab 75/100 versus ezetimibe (with statins): COMBO II, OPTIONS I, OPTIONS II. Adjusted means (SE) taken from multiple imputation followed by robust regression. Interaction *P* values compare the LDL-C percentage of reduction (difference vs. control) for the IRF and without IRF subgroups. IRF were defined based on medical history: with IRF included those with eGFR 30–59 ml/min per 1.73 m^2, without IRF included those with eGFR 60–89 ml/min per 1.73 m^2, and eGFR ≥90 ml/min per 1.73 m^2. ALI, alirocumab; Apo, apolipoprotein; CI, confidence interval; eGFR, estimated glomerular filtration rate; EZE, ezetimibe; IRF, impaired renal function; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LS, least squares; PBO, placebo. (Continued)

percentage increase in these lipids observed in the placebo groups of these pools. No significant interaction was observed based on IRF status in the percentage change from baseline at week 24 in triglycerides and Lp(a) levels with alirocumab versus control treatment in all 3 subgroups analyzed (Figure 1d and e).

Significant reductions from baseline in LDL-C levels with alirocumab versus control treatment were observed at

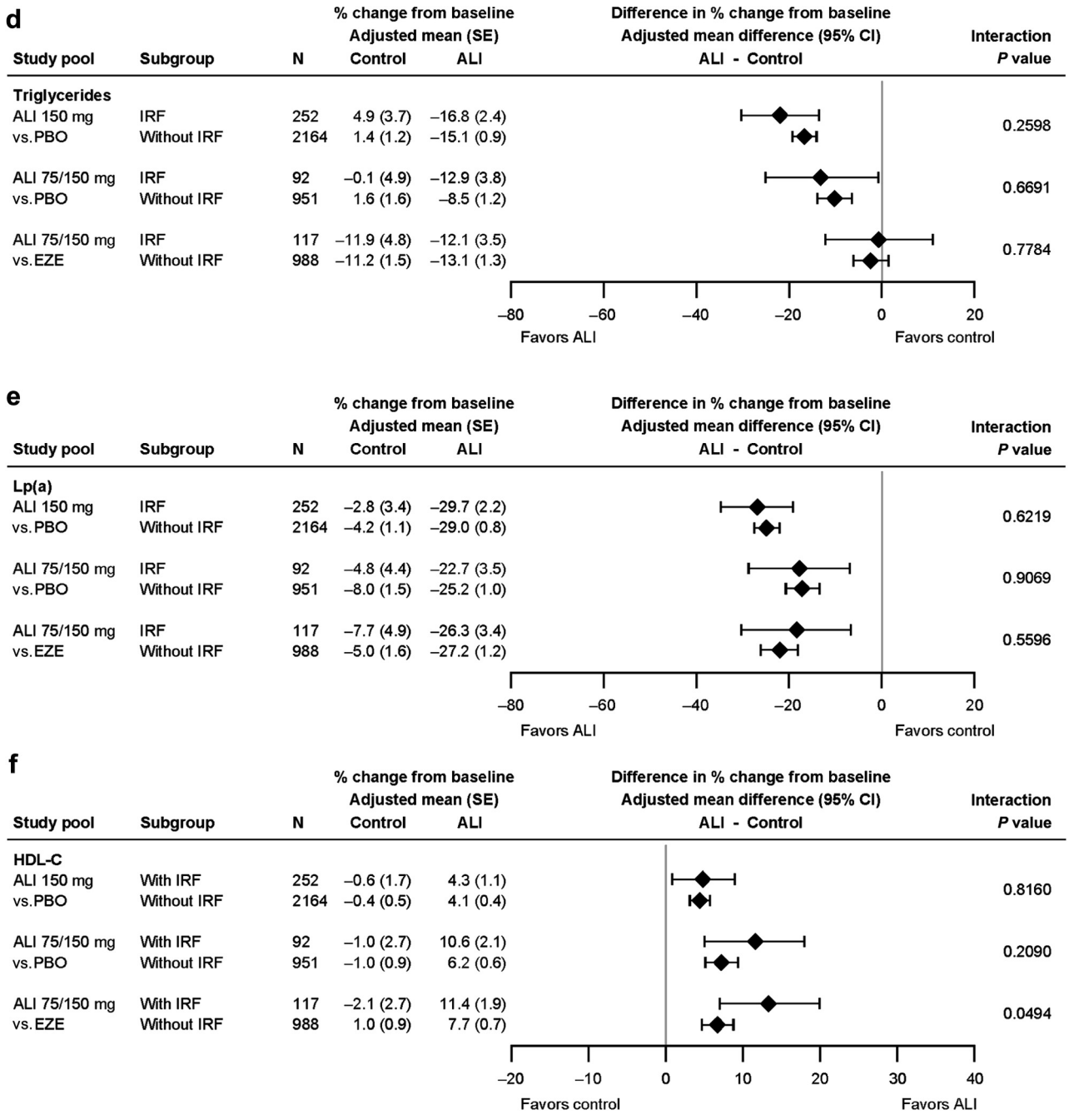

Figure 1 | (Continued)

week 24, regardless of baseline proteinuria status (nonsignificant interaction *P* values; Figure 2). Treatment with alirocumab 150 mg Q2W versus control resulted in sustained reductions in LDL-C, apoB, non-HDL-C, triglycerides, and Lp(a), and increases in HDL-C over time, which were comparable among individuals with and without IRF (Figure 3). Similar results were observed with alirocumab 75/150 mg Q2W versus placebo or ezetimibe for LDL-C, apoB, non-HDL-C, Lp(a) and HDL-C (Supplementary Figures S1 and S2). Absolute LDL-C reductions from baseline among individuals with and without IRF on alirocumab 150 mg Q2W were 74.7 mg/dl (vs. 6.7 mg/dl placebo) and 75.0 mg/dl (vs. 3.8 mg/dl), respectively, at week 24. In the subgroup with alirocumab 75/150 mg Q2W versus placebo, absolute LDL-C reductions from baseline to week 24 among individuals with and without IRF were from 59.1 mg/dl (vs. 12.1 mg/dl placebo) and 65.4 mg/dl (vs. 6.1 mg/dl), respectively. In the subgroup with alirocumab 75/150 mg Q2W versus ezetimibe, absolute LDL-C reductions among individuals with and without IRF were 54.1 mg/dl (vs. 29.5 mg/dl ezetimibe) and 53.8 mg/dl (vs 23.1 mg/dl), respectively, at week 24.

Table 3 | Proportion of individuals reaching LDL-C goals[a] at week 24 pooled from eight phase 3 trials by IRF status (ITT population)

Study pool	IRF		Without IRF	
	Alirocumab	Control	Alirocumab	Control
Percentage of individuals achieving LDL-C goals				
Alirocumab 150 versus placebo	82.7	11.5	78.5	8.1
N	178	74	1423	741
Odds ratio (95% CI)	56.0 (23.3–134.6)		64.3 (46.3–89.5)	
Interaction *P* value	0.7678			
Alirocumab 75/150 versus placebo	65.4	6.9	76.1	6.4
N	58	34	635	316
Odds ratio (95% CI)	25.8 (5.5–121.2)		63.8 (37.1–109.6)	
Interaction *P* value	0.2775			
Alirocumab 75/150 versus ezetimibe	82.1	66.1	77.5	50.9
N	75	42	594	394
Odds ratio (95% CI)	3.0 (1.1–8.2)		5.0 (3.6–6.9)	
Interaction *P* value	0.3555			

CI, confidence interval; IRF, impaired renal function; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol.
Proportions are estimated from multiple imputation. Odds ratios are estimated from logistic regression.
[a]LDL-C goal of <70 mg/dl for individuals at very-high cardiovascular risk and <100 mg/dl for individuals at high cardiovascular risk. Pool alirocumab 150 versus placebo (with statins): LONG TERM, HIGH FH. Pool alirocumab 75/150 versus placebo (with statins): COMBO I, FH I, FH II. Pool alirocumab 75/150 versus ezetimibe (with statins): COMBO II, OPTIONS I, OPTIONS II.

Safety by IRF status

The overall incidence of treatment-emergent adverse effects was similar in the alirocumab and control subgroups with IRF (82.1% and 82.8%, respectively) and in those without IRF (78.4% and 78.2%, respectively; Table 4). Serious adverse events occurred at a higher rate among individuals with IRF compared with those without IRF, although the rate was comparable between the alirocumab and control subgroups (Table 4). Among individuals with IRF, treatment-emergent adverse effects led to discontinuation in 10.5% of the alirocumab-treated group versus 7.3% of the control-treated group ($P = 0.2617$), whereas in those without IRF, 6.2% of the alirocumab-treated group versus 5.9% of the control-treated group experienced treatment-emergent adverse effects leading to discontinuation ($P = 0.7271$, Table 4). Among individuals with IRF, major adverse CV events were seen in 2.6% of alirocumab-treated versus 5.3% of control-treated individuals (hazard ratio: 0.420, 95% confidence interval 0.158–1.121). Among individuals without IRF, major adverse CV events were seen in 2.1% of alirocumab-treated versus 2.1% of control-treated individuals (hazard ratio: 0.938, 95% confidence interval 0.605–1.455). Injection-site reactions were seen in 5.1% of those on alirocumab versus 2.0% of those on control treatment with IRF (hazard ratio: 2.568, 95% confidence interval 0.748–8.816) and in 6.4% of alirocumab versus 4.4% of control group without IRF (hazard ratio: 1.404, 95% confidence interval 1.055–1.869, Table 4). The rates of major adverse CV events and injection site reactions were not dependent on IRF status (nonsignificant interaction *P* values, Table 4). The most common treatment-emergent adverse effects in alirocumab-treated individuals were nasopharyngitis and upper respiratory tract infection among individuals with and without IRF (Table 4).

Effect on renal function over the study period (pool of 10 trials)

In the overall analysis of renal safety involving ten phase 3 trials, 68% of individuals were negative, 22% had trace, and 9% were positive for dipstick proteinuria across all treatment groups. Mean eGFRs from baseline to week 24 were stable in alirocumab and control arms, with or without the presence of proteinuria (Table 5). Mean eGFR was stable from baseline up to 104 weeks in alirocumab and control arms regardless of IRF status in a pooled analysis from eight phase 3 trials based on IRF status (Figure 4). Similar results were observed for mean blood urea nitrogen and creatinine levels in the subgroups analyzed by IRF status (Supplementary Table S1, Supplementary Figure S3). In an overall safety analysis of 4 phase 2 and 5 placebo-controlled phase 3 trials, 1 alirocumab-treated individual (1/2258 [<0.1%]) versus 2 placebo-treated individuals (2/1145 [0.2%]) reached end-stage renal disease

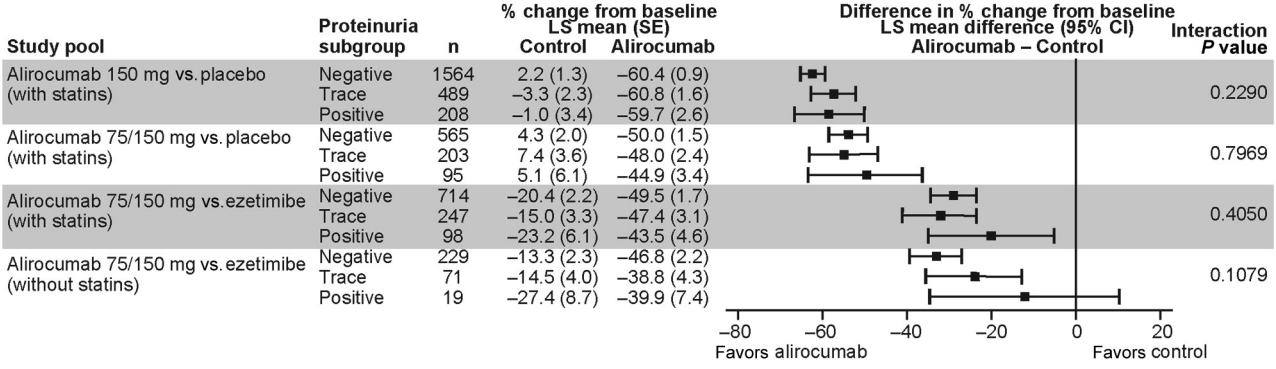

Figure 2 | Percentage of change in low-density lipoprotein cholesterol from baseline to week 24 according to baseline proteinuria status (intention-to-treat population; pool of ten phase 3 trials). LS means and SE taken from mixed-effects model with repeated-measures analysis. CI, confidence interval; LS, least squares.

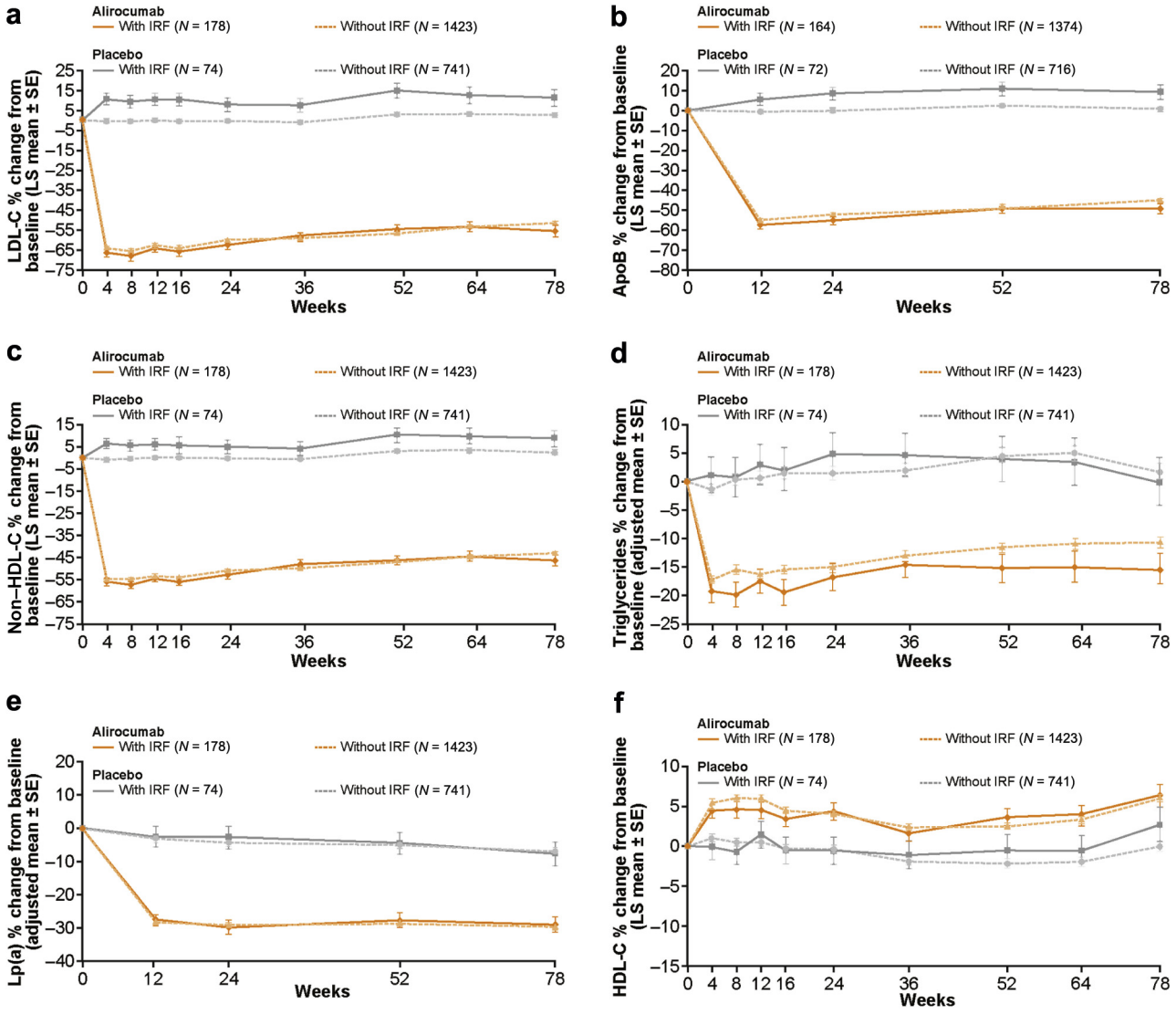

Figure 3 | Percentage of change from baseline of lipoproteins over time by IRF status in 2 trials using alirocumab 150 mg Q2W versus placebo (a) LDL-C, (b) apoB, (c) non–HDL-C, (d) triglycerides, (e) Lp(a), and (f) HDL-C (intention-to-treat population). Alirocumab 150 mg Q2W: LONG TERM, HIGH FH. ApoB, apolipoprotein B; HDL-C, high-density lipoprotein cholesterol; IRF, impaired renal function; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LS, least squares.

(ESRD). There were no cases of ESRD in the pooled analysis of the 5 ezetimibe-controlled trials.

There was no significant difference in the percentage of change from baseline in high-sensitivity C-reactive protein (hs-CRP) at week 24 with alirocumab and control treatment in all groups analyzed with the exception of individuals without IRF treated with alirocumab 75/150 mg Q2W versus ezetimibe (−0.5 vs. −15.6%; Supplementary Figure S4). Percentages of change in hs-CRP levels from baseline to week 24 analyzed by alirocumab doses and control treatments were similar in those with and without IRF (nonsignificant interaction *P* values; Supplementary Figure S4). Furthermore, hs-CRP levels were similar up to week 78 in the alirocumab 150 mg Q2W versus placebo treatment groups regardless of IRF status (Supplementary Figure S5).

Results similar to the overall IRF analysis were obtained in a separate subanalysis of individuals with type 2 diabetes mellitus with and without IRF (Supplementary Tables S2–S5 and Supplementary Figures S6 and S7).

DISCUSSION

Individuals with IRF are at high risk of future CV events. The more intensive lipid-lowering resulting from alirocumab treatment compared with statins might provide an important new tool for CVD prevention in this population. In an analysis of 4629 individuals from 8 ODYSSEY phase 3 trials treated with alirocumab or control (placebo or ezetimibe), mostly on background statin with or without other LLT, alirocumab substantially lowered LDL-C levels regardless of the presence or absence of IRF. Absolute LDL-C reductions observed with

Table 4 | Safety data pooled from eight phase 3 trials by IRF status (safety population)

	IRF[a]		Without IRF[a]	
n (%)	Alirocumab ($N = 313$)	Control ($N = 151$)	Alirocumab ($N = 2691$)	Control ($N = 1466$)
TEAEs	257 (82.1)	125 (82.8)	2111 (78.4)	1146 (78.2)
Treatment-emergent SAEs	72 (23.0)	39 (25.8)	447 (16.6)	238 (16.2)
TEAEs leading to death	2 (0.6)	4 (2.6)	20 (0.7)	18 (1.2)
P value[b] (vs. control)	0.0911		0.1167	
TEAEs leading to discontinuations	33 (10.5)	11 (7.3)	167 (6.2)	87 (5.9)
P value[b] (vs. control)	0.2617		0.7271	
Safety events of special interest				
Adjudicated CV event[c]	21 (6.7)	9 (6.0)	105 (3.9)	53 (3.6)
HR (95% CI)	1.032 (0.472–2.254)		1.033 (0.742–1.438)	
Interaction *P* value[d]	0.9973			
Major adverse CV events[e]	8 (2.6)	8 (5.3)	56 (2.1)	31 (2.1)
HR (95% CI)	0.420 (0.158–1.121)		0.938 (0.605–1.455)	
Interaction *P* value[d]	0.1433			
Injection-site reaction (HLT)	16 (5.1)	3 (2.0)	171 (6.4)	65 (4.4)
HR (95% CI)	2.568 (0.748–8.816)		1.404 (1.055–1.869)	
Interaction *P* value[d]	0.3500			
General allergic TEAE (CMQ)	25 (8.0)	16 (10.6)	250 (9.3)	113 (7.7)
HR (95% CI)	0.706 (0.376–1.322)		1.177 (0.942–1.470)	
Interaction *P* value[d]	0.1324			
Pruritus (PT)[f]	4 (1.3)	1 (0.7)	32 (1.2)	5 (0.3)
General allergic serious TEAE (CMQ)[f]	3 (1.0)	0	11 (0.4)	6 (0.4)
Neurocognitive disorders (CMQ)	5 (1.6)	3 (2.0)	23 (0.9)	12 (0.8)
HR (95% CI)	0.692 (0.165–2.901)		1.021 (0.507–2.054)	
Interaction *P* value[d]	0.6332			
ALT >3 x ULN (PCSA)[f]	3 (1.0)	2 (1.3)	53 (2.0)	21 (1.4)
TEAEs by preferred term in ≥5% of individuals in any group				
Nasopharyngitis	31 (9.9)	10 (6.6)	292 (10.9)	155 (10.6)
Urinary tract infection	28 (8.9)	16 (10.6)	117 (4.3)	68 (4.6)
Upper respiratory tract infection	24 (7.7)	17 (11.3)	191 (7.1)	107 (7.3)
Fall	23 (7.3)	5 (3.3)	60 (2.2)	49 (3.3)
Hypertension	20 (6.4)	9 (6.0)	104 (3.9)	60 (4.1)
Injection-site reaction	16 (5.1)	3 (2.0)	169 (6.3)	64 (4.4)
Influenza	10 (3.2)	3 (2.0)	166 (6.2)	78 (5.3)
Dizziness	18 (5.8)	5 (3.3)	96 (3.6)	68 (4.6)
Headache	17 (5.4)	5 (3.3)	136 (5.1)	75 (5.1)
Back pain	16 (5.1)	8 (5.3)	134 (5.0)	78 (5.3)
Arthralgia	13 (4.2)	7 (4.6)	137 (5.1)	84 (5.7)
Myalgia	9 (2.9)	6 (4.0)	131 (4.9)	58 (4.0)
Diarrhea	15 (4.8)	12 (7.9)	126 (4.7)	58 (4.0)
Bronchitis	13 (4.2)	9 (6.0)	120 (4.5)	62 (4.2)
Osteoarthritis	13 (4.2)	10 (6.6)	63 (2.3)	37 (2.5)

ALT, alanine aminotransferase; CI, confidence interval; CKD, chronic kidney disease; CMQ, custom MedDRA query; CV, cardiovascular; eGFR, estimated glomerular filtration rate; IRF, impaired renal function; HLT, high-level group term; HR, hazard ratio; PCSA, Potentially Clinically Significant Abnormalities; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event defined as any adverse event that developed, worsened, or became serious during the period from first to last injection +70 days (or to the first injection in the open-label extension, whichever came first); ULN, upper limit of normal.

Values shown are *N* (%).

[a]IRF was defined based on medical history: IRF (eGFR: 30–59 ml/min per 1.73 m^2); without IRF included individuals with mild CKD (eGFR: 60–89 ml/min per 1.73 m^2), and normal kidney function (eGFR: ≥90 ml/min per 1.73 m^2).

[b]The *P* value was calculated from a χ^2 test if all expected counts were >5. Otherwise, the Fisher exact test was used.

[c]Includes coronary heart disease death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization procedure.

[d]Interaction *P* value was type 3 *P* value calculated from Cox regression model with treatment, impaired renal status, and treatment-by-impaired renal status interaction as covariates, stratified by study.

[e]Excludes congestive heart failure requiring hospitalization and ischemia-driven coronary revascularization procedure.

[f]Hazard ratio and *P* value are not calculated for these parameters due to a lack of derived data in the time-to-event analysis dataset.

alirocumab at week 24 were comparable to those with versus without IRF among the subgroups analyzed by alirocumab dosage and control, suggesting a similar potential effect on CV risk reduction.[21] Reduction of LDL-C by ~30 mg/dl in patients with moderate to severe CKD on statin therapy plus ezetimibe versus placebo has been shown to reduce the incidence of major atherosclerotic events by 17%.[8] The alirocumab safety profile was consistent regardless of IRF status and comparable to that of control treatment. Although in our analysis we did not observe an increased risk of ESRD with alirocumab versus control treatment, the total number of events was too small to draw a meaningful conclusion.

Alirocumab also consistently reduced apoB, non–HDL-C, and Lp(a), independent of IRF status. Moderate reductions in

Table 5 | Mean change in eGFR from baseline to week 24 according to baseline proteinuria status (safety population; pool of ten phase 3 trials)

	Placebo controlled		Ezetimibe controlled	
Baseline proteinuria	Placebo	Alirocumab	Ezetimibe	Alirocumab
eGFR, ml/min per 1.73 m^2, mean (SD)				
Negative	−0.1 (10.9)	0.5 (10.4)	0.1 (9.6)	0.3 (10.7)
N	660	1252	311	485
Trace	−1.0 (9.7)	−0.2 (10.9)	−0.6 (11.7)	0.9 (10.1)
N	194	426	126	141
Positive	1.6 (9.4)	1.1 (12.7)	−0.3 (10.2)	−3.4 (13.5)
N	79	177	35	61

eGFR, estimated glomerular filtration rate.
Data are mean and SD, taken from a mixed-effects model with repeated-measures analysis.

triglycerides and moderate increases in HDL-C were also observed with alirocumab treatment, irrespective of IRF status. These data are consistent with previous reports in the overall patient population and subgroup analyses.[15,17,22] Non–HDL-C and apoB may correlate more closely with CVD risk than LDL-C in individuals with IRF and has been proposed as an alternative treatment target.[1,23] Elevated Lp(a) levels among individuals with IRF have been shown to predict eGFR decline prospectively and are associated with increased CV risk.[24,25] Data on Lp(a) reduction with statins or other LDL-C–lowering therapies have not been consistent.[25] As elevated Lp(a) levels are generally observed in individuals with IRF, potentially mediating atherosclerotic CVD, the substantial reduction in Lp(a) seen with alirocumab versus control in our analysis suggests that alirocumab may reduce CVD in those individuals with IRF compared with that of other lipid-lowering therapies. Different apo(a) isoforms were not assessed in these trials; however, an independent study did not find an association between apo(a) isoforms and the reduction of Lp(a) with alirocumab.[26]

In our analysis, alirocumab was generally well tolerated and had no effect on renal function over the study period compared with control, regardless of baseline renal function status. Individuals with diabetes often develop CKD and are at high risk of CVD.[27,28] Alirocumab did not affect eGFR levels over the study period in an analysis of individuals with diabetes with or without IRF. We found no evidence of an adverse impact on renal function in these individuals with IRF treated with alirocumab versus control. The metabolism of alirocumab, as a monoclonal antibody, is not expected to be affected by the glomerular filtration rate. However, because PCSK9 is expressed in the kidney,[18] the assessment of safety and efficacy among individuals with IRF was important. To the best of our knowledge, the impact of PCSK9 inhibitors among individuals with IRF has not been previously reported. Individuals with IRF at high or very high CV risk who are not able to reach optimal LDL-C values on statins or other lipid-lowering therapies may benefit from treatment with PCSK9 inhibitors. Our results indicate that alirocumab could be an effective option for reducing LDL-C, apoB, non–HDL-C, and Lp(a) in individuals with IRF.

Elevated hs-CRP levels are associated with increased CVD risk and have been used as an inflammatory marker in several statin trials.[29–31] In our pooled analysis of eight phase 3 trials, hs-CRP levels were unchanged with alirocumab treatment, regardless of IRF status, indicating that this inflammatory marker of CVD risk is unaffected by alirocumab treatment among individuals with or without IRF. A recent meta-analysis of randomized, controlled trials assessing changes in hs-CRP concentrations during treatment with PCSK9 inhibitors found no significant effect of various doses and types of PCSK9 inhibitors on hs-CRP levels.[32]

There are some limitations to this study as individuals with severe CKD (eGFR <30 ml/min per 1.73 m^2) or ESRD were not recruited for the trials that were analyzed. Calculation of eGFR in our analysis was performed by the Modification of Diet in Renal Disease (MDRD) equation and not by the CKD-Epidemiology Collaboration (CKD-EPI) equation, which is considered to have a small improvement in precision and greater accuracy, especially at higher eGFR values.[2] As eGFR

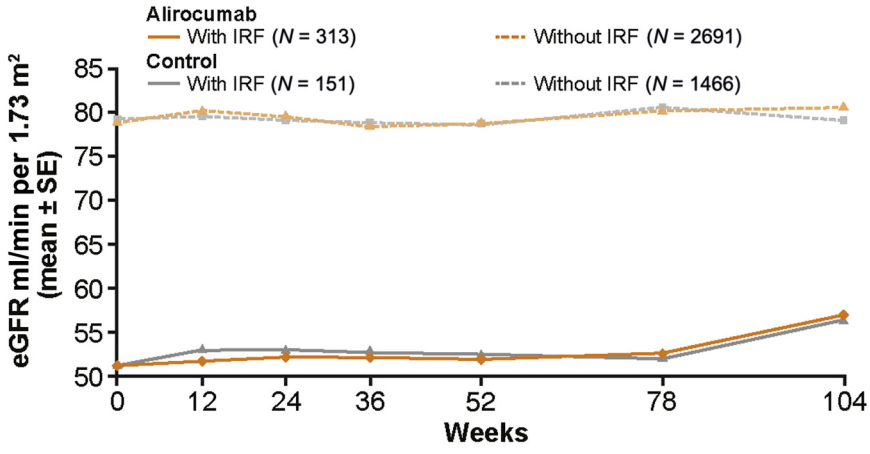

Figure 4 | Mean estimated glomerular filtration rate (eGFR) values over time by impaired renal function (IRF) status (safety population, pool of eight phase 3 trials).

values were constant during the course of our analysis in groups analyzed by IRF status (eGFR = 30–59 ml/min per 1.73 m^2 for ≥3 months), this limitation most likely had a minimal impact on our results. Whether the significant reductions seen in LDL-C and other atherogenic lipids in individuals with IRF will lower CV risk will need to be determined. The ongoing ODYSSEY OUTCOMES study in ~18,000 individuals with recent acute coronary syndrome randomized to receive alirocumab or placebo has an expected follow-up period of at least 2 years and will provide an evaluation of the effect of alirocumab on major adverse CV events.[33]

METHODS

This analysis was performed in 2 parts from ten phase 3 randomized, controlled ODYSSEY trials. For all efficacy and safety analyses in subgroups by IRF status, individuals were pooled from eight phase 3 trials based on impairment of renal function. Individuals were pooled by alirocumab dosage and control treatment used, with a threshold of 10 individuals with IRF in each treatment group considered to be included in the efficacy analysis (i.e., alirocumab 150 mg Q2W vs. placebo, alirocumab 75/150 mg Q2W vs. placebo, and alirocumab 75/150 mg Q2W vs. ezetimibe) (all on background statins [Table 1]). The other 2 trials, MONO and ALTERNATIVE, comprising the pool of individuals who were treated with alirocumab 75/150 mg Q2W versus ezetimibe (without any background statins) were not included in the efficacy analysis because <10 individuals in each treatment group had IRF (Table 1). An overall safety analysis was performed in all individuals pooled by control (placebo or ezetimibe) from all ten phase 3 trials (Table 1).

Table 1 summarizes the key design criteria of the trials included in this pooled analysis. All trials had similar designs, with double-blind treatment periods of 24 to 104 weeks, and enrolled individuals with hypercholesterolemia. Individuals were randomized to either alirocumab or control in a 2:1 ratio in LONG TERM, FH I, FH II, HIGH FH, COMBO I, and COMBO II trials (1:1 in the other trials). Two trials (LONG TERM and HIGH FH, $N = 2448$) compared alirocumab 150 mg Q2W with placebo. The other 8 trials (COMBO I, FH I, FH II, COMBO II, OPTIONS I, OPTIONS II, MONO, and ALTERNATIVE, $N = 2598$) used a dose adjustment strategy whereby the alirocumab starting dose of 75 mg Q2W was increased to 150 mg Q2W at study week 12 if prespecified LDL-C levels were not attained by week 8 (indicated as alirocumab 75/150 mg in the text). Control was placebo in the LONG TERM, FH I, FH II, HIGH FH, and COMBO I trials and ezetimibe in the others. Most individuals were receiving background maximally tolerated statin therapy with or without other lipid-lowering therapies; there was no background statin therapy in the MONO and ALTERNATIVE studies.

IRF, as measured by the 4-variable MDRD equation,[2,34] was defined as eGFR = 30–59 ml/min per 1.73 m^2 for ≥3 months (including screening visit and as reported by the investigator). This corresponds to eGFR categories used to define "mild-to-moderate" and "moderate-to-severe" CKD in treatment guidelines.[2] Individuals with eGFR ≥60 ml/min per 1.73 m^2 or otherwise not meeting the definition of IRF were included in the "without IRF" subgroups. All studies excluded individuals with an eGFR <30 ml/min per 1.73 m^2.

LDL-C percentage changes from baseline were assessed in pools of studies based on alirocumab dosage (75/150 mg Q2W or 150 mg Q2W) and control (placebo or ezetimibe, Table 1). The percentage of change from baseline in calculated LDL-C, apo B, non–HDL-C, and HDL-C was analyzed using an intent-to-treat analysis (including all lipid data irrespective of adherence to study treatment) and a mixed-effects model with a repeated-measures approach to obtain least-squares means and SEs. The models included the fixed categorical effects of treatment group, randomization, time point, IRF status, treatment-by-time point interaction, strata-by-time point interaction, IRF status-by-time point interaction, IRF status-by-treatment interaction, and IRF status-by-treatment-by-time point interaction, as well as the continuous fixed covariates of the baseline LDL-C value and baseline value-by-time point interaction. Adjusted mean and SE for triglycerides, Lp(a), and hs-CRP (endpoints anticipated to have a nonnormal distribution) were estimated by multiple imputation and robust regressions using M-estimation. The robust regression models included the following covariates: treatment group, randomization strata, IRF status, treatment group by IRF status interaction, and baseline value(s). The homogeneity of treatment effect across individuals with or without IRF was assessed using an interaction test. An interaction P value >0.05 was considered as insignificant interaction between groups assessed. The percentage of change from baseline over the duration of each study was also assessed for each lipid parameter.

A χ^2 test (if expected count was >5) or the Fisher exact test was used to calculate the P value for significance between treatment groups in overall safety. For significance between treatment groups in the rates of adverse events of special interest, the P values were calculated from a Cox regression model including treatment, IRF status, and treatment-by-IRF status interaction as covariates, stratified by study. The interaction P values for comparing adverse events of special interest between patients with and without IRF was a type 3 P value calculated from a Cox regression model with treatment, IRF status, and treatment-by-IRF status interaction as covariates, stratified by study. ESRD was defined as eGFR values <15 ml/min per 1.73 m^2 and was analyzed in the overall pool of placebo-controlled and ezetimibe-controlled trials. Hs-CRP, a biomarker associated with increased CVD, was also evaluated and individuals with hs-CRP values ≥10 mg/l were excluded from these analyses, as this suggests concurrent infection.[29]

In the assessment of overall renal safety, renal function was analyzed in all individuals (pool of 10 trials, Table 1) assessed by analyzing changes in eGFR, serum creatinine and blood urea nitrogen with or without the presence of proteinuria over the study period. Proteinuria status was assessed by dipstick urinalysis. In addition, an analysis of renal safety was performed in the subgroup of individuals with type 2 diabetes (defined based on medical history) and IRF pooled from the same eight phase 3 trials as for the analysis comparing those with and without IRF.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Table S1. Mean change in renal function descriptors from baseline to week 24 according to baseline proteinuria status (safety population; pool of ten phase 3 trials).

Table S2. Baseline characteristics of randomized individuals with type 2 diabetes mellitus pooled from eight phase 3 trials by impaired renal function status.

Table S3. Proportion of individuals with type 2 diabetes mellitus reaching low-density lipoprotein cholesterol goals† at week 24 by impaired renal function status (intention-to-treat population; pool of eight phase 3 trials).

Table S4. Mean change in estimated glomerular filtration rate from baseline to week 24 according to baseline proteinuria status among individuals with type 2 diabetes mellitus (safety population; pool of ten phase 3 trials).

Table S5. Safety data among individuals with type 2 diabetes mellitus by impaired renal function status (safety population; pool of eight phase 3 trials).

Figure S1. Percentage of change from baseline of lipoproteins over time by impaired renal function status in 3 trials using alirocumab 75/150 mg every 2 weeks versus placebo†: (**A**) LDL-C, (**B**) apoB, (**C**) non–HDL-C, (**D**) triglycerides, (**E**) Lp(a), and (**F**) HDL-C (ITT population).

Figure S2. Percentage of change from baseline of lipoproteins over time by impaired renal function status in 3 trials using alirocumab 75/150 mg Q2W versus ezetimibe:† (**A**) LDL-C, (**B**) apoB, (**C**) non–HDL-C, (**D**) triglycerides, (**E**) Lp(a), and (**F**) HDL-C (ITT population).

Figure S3. Mean (**A**) creatinine and (**B**) blood urea nitrogen values over time by impaired renal function status (safety population; pool of eight phase 3 trials).

Figure S4. Percentage of change from baseline in hs-CRP at week 24: subgroup analysis by impaired renal function status, excluding hs-CRP values ≥10 mg/l (ITT population; pool of eight phase 3 trials).

Figure S5. Percentage of change in hs-CRP over time excluding individuals with hs-CRP ≥10 mg/l by impaired renal function status in two trials using alirocumab 150 mg Q2W versus placebo (ITT population).

Figure S6. Percentage of change from baseline to week 24 among individuals with type 2 diabetes mellitus by impaired renal function status in (**A**) LDL-C, (**B**) non–HDL-C, and (**C**) Lp(a) (ITT populations; pool of eight phase 3 trials).

Figure S7. Mean estimated glomerular filtration rate values over time among individuals with type 2 diabetes mellitus by impaired renal function status (safety population; pool of eight phase 3 trials).

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

REFERENCES

1. Harper CR, Jacobson TA. Managing dyslipidemia in chronic kidney disease. *J Am Coll Cardiol*. 2008;51:2375–2384.
2. KDIGO. Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease: summary of recommendation statements and clinical approach to the patient. *Kidney Int Suppl*. 2013:3.
3. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–1305.
4. Barylski M, Nikfar S, Mikhailidis DP, et al. Statins decrease all-cause mortality only in CKD patients not requiring dialysis therapy–a meta-analysis of 11 randomized controlled trials involving 21,295 participants. *Pharmacol Res*. 2013;72:35–44.
5. Hobbs FD, Banach M, Mikhailidis DP, et al. Is statin-modified reduction in lipids the most important preventive therapy for cardiovascular disease? A pro/con debate. *BMC Med*. 2016;14:4.
6. Cholesterol Treatment Trialists' (CCC) Collaboration, Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
7. Nikolic D, Nikfar S, Salari P, et al. Effects of statins on lipid profile in chronic kidney disease patients: a meta-analysis of randomized controlled trials. *Curr Med Res Opin*. 2013;29:435–451.
8. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181–2192.
9. Palmer SC, Craig JC, Navaneethan SD, et al. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:263–275.
10. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012;33:1635–1701.
11. Tonelli M, Wanner C, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. Lipid management in chronic kidney disease: synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. *Ann Intern Med*. 2014;160:182.
12. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci*. 2015;11:1–23.
13. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008;51:1448–1454.
14. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of

Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017;70:1785–1822.
15. Farnier M, Gaudet D, Valcheva V, et al. Efficacy of alirocumab in high cardiovascular risk populations with or without heterozygous familial hypercholesterolemia: Pooled analysis of eight ODYSSEY Phase 3 clinical program trials. *Int J Cardiol*. 2016;223:750–757.
16. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. *Cardiovasc Drugs Ther*. 2016;30:473–483.
17. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.
18. Seidah NG, Benjannet S, Wickham L, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. *Proc Natl Acad Sci U S A*. 2003;100:928–933.
19. Haas ME, Levenson AE, Sun X, et al. The role of proprotein convertase subtilisin/kexin type 9 in nephrotic syndrome-associated hypercholesterolemia. *Circulation*. 2016;134:61–72.
20. Pavlakou P, Liberopoulos E, Dounousi E, et al. PCSK9 in chronic kidney disease. *Int Urol Nephrol*. 2017;49:1015–1024.
21. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722.
22. Leiter LA, Muller-Wieland D, Baccara-Dinet MT, et al. Efficacy and safety of alirocumab in people with prediabetes vs those with normoglycaemia at baseline: a pooled analysis of 10 phase III ODYSSEY clinical trials. *Diabet Med*. 2018;35:121–130.
23. Jacobson TA, Maki KC, Orringer CE, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 2. *J Clin Lipidol*. 2015;9:S1–122.e121.
24. Konishi H, Miyauchi K, Tsuboi S, et al. Plasma lipoprotein(a) predicts major cardiovascular events in patients with chronic kidney disease who undergo percutaneous coronary intervention. *Int J Cardiol*. 2016;205:50–53.
25. Kronenberg F, Konig P, Neyer U, et al. Multicenter study of lipoprotein(a) and apolipoprotein(a) phenotypes in patients with end-stage renal disease treated by hemodialysis or continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol*. 1995;6:110–120.
26. Enkhmaa B, Anuurad E, Zhang W, et al. The roles of apo(a) size, phenotype, and dominance pattern in PCSK9-inhibition-induced reduction in Lp(a) with alirocumab. *J Lipid Res*. 2017;58:2008–2016.
27. Suckling R, Gallagher H. Chronic kidney disease, diabetes mellitus and cardiovascular disease: risks and commonalities. *J Ren Care*. 2012;38(Suppl 1):4–11.
28. Cavanaugh KL. Diabetes management issues for patients with chronic kidney disease. *Clin Diabet*. 2007;25:90–97.
29. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
30. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836–843.
31. Ridker PM, Rifai N, Pfeffer MA, et al. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation*. 1999;100:230–235.
32. Sahebkar A, Di Giosia P, Stamerra CA, et al. Effect of monoclonal antibodies to PCSK9 on high-sensitivity C-reactive protein levels: a meta-analysis of 16 randomized controlled treatment arms. *Br J Clin Pharmacol*. 2016;81:1175–1190.
33. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168:682–689.
34. Levey AS, Bosch JP, Lewis J, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. *Ann Intern Med*. 1999;130:461–470.
35. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36:299–3003.
36. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. *Am Heart J*. 2015;169:906–915.e913.
37. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186–1194.
38. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab*. 2015;100:3140–3148.
39. Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. *Atherosclerosis*. 2016;244:138–146.
40. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. *Int J Cardiol*. 2014;176:55–61.
41. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769.