Supplemental Materials

Supplemental Methods

*Trials included in this analysis*

This analysis included data from 10 Phase 3 ODYSSEY double-blind, randomised clinical trials comparing alirocumab with placebo or ezetimibe. Clinicaltrials.gov identifiers were as follows: ALTERNATIVE (NCT01709513);¹ COMBO I (NCT01644175);² COMBO II (NCT01644188);³ FH I (NCT01623115);⁴ FH II (NCT01709500);⁴ HIGH FH (NCT01617655);⁵ LONG TERM (NCT01507831);⁶ MONO (NCT01644474);⁷ OPTIONS I (NCT01730040);⁸ OPTIONS II (NCT01730053).⁹ All studies were performed in accordance with the principles of the Declaration of Helsinki and all applicable amendments by the World Medical Assemblies, and the International Conference on Harmonisation Guidelines for Good Clinical Practice. Trial protocols were reviewed and approved by institutional review boards of participating centres and independent ethics committees, and all study subjects gave written informed consent.

The FH I, FH II and HIGH FH trials exclusively recruited patients with heterozygous familial hypercholesterolaemia (HeFH). ALTERNATIVE recruited patients with statin intolerance; MONO was a monotherapy study in moderate-risk patients not on statins. The other trials recruited patients at high cardiovascular risk (with a history of cardiovascular disease or other risk factors). COMBO I and COMBO II excluded patients with HeFH.

Participants had low-density lipoprotein cholesterol (LDL-C) ≥70 or 100 mg/dL (1.81 or 2.59 mmol/L) depending on cardiovascular risk, except in the LONG TERM
trial (LDL-C ≥70 mg/dL for all participants), the MONO trial (≥100 mg/dL and ≤190 mg/dL [4.91 mmol/L]) and the HIGH FH trial (≥160 mg/dL [4.14 mmol/L]).

Placebo control was used in LONG TERM, HIGH FH, FH I, FH II and COMBO I. The other trials were ezetimibe-controlled.

An alirocumab dose regimen of 150 mg every 2 weeks (Q2W) was used in LONG TERM and HIGH FH. In the other trials, a dose increase strategy was used, whereby the starting dose of alirocumab 75 mg Q2W was increased to 150 mg Q2W at Week 12 if LDL-C at Week 8 was ≥70 mg/dL (in MONO, COMBO I and II, and FH I and II), or ≥70 or ≥100 mg/dL depending on cardiovascular risk (in ALTERNATIVE and OPTIONS I and II).

Patients received study treatment added to background statin therapy with or without other lipid-lowering therapies (LLT), except for ALTERNATIVE and MONO which were conducted without background statins; also, other LLTs were not allowed in COMBO II. Background statin therapy was at maximally tolerated dose (rosuvastatin 20–40 mg, atorvastatin 40–80 mg or simvastatin 80 mg daily, or lower doses with an investigator Documented reason e.g. intolerance) except for OPTIONS I (atorvastatin 20–40 mg) and OPTIONS II (rosuvastatin 10–20 mg).

Randomisation to alirocumab:control was in a 1:2 ratio (except for OPTIONS I, OPTIONS II and ALTERNATIVE, which used a 1:1 ratio).

**Statistical analyses**

Efficacy data were analysed in the intention-to-treat population (including all patients with a baseline and at least one post-baseline LDL-C measurement, regardless of adherence to treatment). Percentage and absolute changes in lipids, with the
exception of triglyceride-rich lipoprotein cholesterol (TRL-C), were analysed using a mixed-effect model with repeated measures (MMRM) to account for missing data. The model includes the fixed categorical effects of treatment group, study, randomisation strata, time point, subgroup, treatment-by-time-point interaction, study-by-time-point interaction, strata-by-time-point interaction, subgroup-by-time-point interaction, and treatment-by-subgroup-by-time-point interaction, as well as the continuous fixed covariates of baseline value and baseline value-by-time-point interaction. Percentage and absolute changes in TRL-C were analysed using multiple imputation followed by robust regression. The robust regression models included the fixed categorical effect of treatment group, study, randomisation strata per IVRS, subgroup and the continuous fixed covariate of baseline value. Rubin’s formulae were used to combine means and standard errors (SEs) of the different imputed data sets. Goal achievement and associated analyses were analysed using last observation carried forward values at Week 24 in case of missing data.

For analysis of goal achievement across baseline triglyceride (TG) quintiles, $P$-values were computed using the Cochran–Armitage test for trend. The Breslow and Day test\textsuperscript{10} was used to test homogeneity of the odds ratios (ORs) measuring the association between goal attainment and treatment (alirocumab versus control) across the quintiles. ORs for LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C) goal attainment associated with a 1 standard deviation increase of log(TG) at baseline were derived by treatment arm from logistic regression model analysis. The logistic regression models were stratified by study and randomization factors including the fixed categorical effect of treatment group, the continuous fixed covariate of log(TG) at baseline, and the interaction between treatment group and log(TG) at baseline.
For analysis of change from baseline in LDL-C, non-HDL-C or HDL-C at Week 24, least-squares means and SEs were taken from an MMRM analysis as previously described. For corresponding analyses of TRL-C, adjusted means and SEs were obtained by combining adjusted means and SEs from robust regression model analyses of the different imputed data sets. The robust regression models included the fixed categorical effect of treatment group, study, randomisation strata, subgroup and the continuous fixed covariate of baseline value. Rubin's formulae were used to combine means and SEs.

For the safety analysis, data were pooled into two groups according to the comparator in the individual trials (five trials versus placebo and five trials versus ezetimibe).

Supplemental results

Patient baseline characteristics

As shown in Table 1 in the main text, overall, participants were approximately 60 years of age on average and over half were males. Mean body mass index (BMI) was approximately 30 kg/m\(^2\) and the proportion of patients with type 2 diabetes varied between 18% and 35% depending on the pool. Pool 2 included a higher proportion of patients with HeFH (70%; pool 2 included the FH I and II trials on patients with HeFH) compared with the other pools. Mean baseline LDL-C and non-HDL-C levels ranged from approximately 2.68 to 4.75 mmol/L (103.2–183.7 mg/dL) (similar for calculated and directly measured LDL-C) and 3.57–5.47 mmol/L (137.7–155.5 mg/dL), respectively, among those on background statins (pools 1–3). Among those not on statins (pool 4), mean LDL-C and non-HDL-C levels were higher, as otherwise expected (approximately 4.67 and 5.47 mmol/L [180.6 and 211.5 mg/dL]}
for LDL-C and non-HDL-C, respectively). Median baseline TG levels ranged from 1.48 to 1.55 mmol/L (131.1–137.3 mg/dL), except for pool 2, in which median TG levels were lower: 1.26 mmol/L (111.6 mg/dL) (pool 2 included a high proportion of patients with HeFH, i.e. pure hypercholesterolaemia usually associated with normal TG levels). TG quintiles at baseline are shown in Table 1 in the main text.

**Baseline characteristics by baseline TG levels**

Within each pool, increasing quintiles of baseline TG levels were associated with a higher proportion of patients with hypertension \((p \leq 0.002)\) and, in pools 1 and 2, a higher proportion of smokers \((p \leq 0.003)\). Among those on background statins (pools 1–3), higher TG levels correlated with a lower proportion of patients with HeFH \((p \leq 0.04)\). For any pool considered, increasing quintiles of baseline TGs were associated with a more adverse metabolic profile consisting of higher BMI \((p < 0.0001)\), higher levels of fasting plasma glucose and glycated haemoglobin \((p \leq 0.0004)\), and a larger proportion of patients with diabetes \((p \leq 0.0007)\). Finally, as baseline TG levels increased, there was a significant association with an unfavourable lipid level profile, consisting of increased levels of non-HDL-C \((p < 0.0001)\), LDL-C \((p < 0.04)\), TRL-C \((p < 0.0001)\) and apolipoprotein (apo)B \((p < 0.0001)\), and decreased levels of HDL-C \((p < 0.0001)\) and apoA1 \((p \leq 0.005)\). Among patients who did not receive background statins (pool 4), the increase in non-HDL-C and LDL-C levels with increasing TG quintiles was more marked than in patients on statins (pools 1–3; Figure 1A and Supplementary Material Table 1 online). Lipoprotein (a) levels did not appear to be systematically associated with TG levels. A reduced percentage of patients receiving high-intensity statins with increasing TG levels was observed in pool 1 but not in pools 2 and 3.
Although the trend towards increasing baseline LDL-C and baseline non-HDL-C levels with increasing quintiles of baseline TGs was significant in both cases and for any pool considered, the magnitude was substantially higher for non-HDL-C (approximately a 1.16–1.81 mmol/L [45–70 mg/dL] increase from Q1–Q5 of TG, depending on the pool considered) compared with that of LDL-C (approximately a 0.26–0.52 mmol/L [10–20 mg/dL] increase from Q1–Q5 of TG; Figure 1A and Supplementary Material Table 1 online). There was no meaningful correlation between baseline levels of TGs and LDL-C (correlation coefficients ranged from 0.07 to 0.09 depending on the pool considered; Supplementary Material Table 2 online). On the contrary, correlation coefficients between baseline levels of TGs and non-HDL-C were between 0.37 and 0.45 ($p < 0.0001$ for all). As suggested by Figure 1A, the increases in TRL-C levels, which run in parallel to those in non-HDL-C, would account for a large proportion of the higher increases in non-HDL-C with increasing TG levels (whereas the contribution of LDL-C increases towards non-HDL-C increases would be more limited).

The correlation between baseline levels of TGs, LDL-C and non-HDL-C are shown in Supplementary Table S3. There was no meaningful correlation between LDL-C levels and TGs (correlation coefficients <0.10), and moderate direct correlation between non-HDL-C levels and TGs (correlation coefficients 0.32–0.45 depending on the pool considered, all $p<0.0001$).

**Relationship between baseline TG levels, LDL-C and non-HDL-C goal attainment**

By means of comparison with data presented on TG levels in the main text, the proportion of patients achieving goals at Week 24 for non-HDL-C and LDL-C by
baseline measured TRL-C quintiles is shown in Supplementary Material Figure 6 online.

**Safety**

In the present trials, overall rates of treatment-emergent adverse events (TEAEs), serious TEAEs and discontinuations due to TEAEs were comparable between alirocumab and controls.\textsuperscript{1,7,9} The most common TEAEs were nasopharyngitis, upper respiratory tract infection (both reported at similar rates for alirocumab and controls) and injection-site reactions (reported by a greater proportion of patients treated with alirocumab compared with controls; these events were mostly mild and transient).
Supplemental References

1. 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.

2. 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.

3. 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.

4. 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: 2996-3003.

5. 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.
6. 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.

7. 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.

8. 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.

9. Farnier M, Gaudet D, Valcheva V, Minini P, Miller K, Cariou B. 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.

10. Liu I-M. Breslow–Day Test. In: Armitage P and Conton T, (eds.). *Encyclopedia of Biostatistics*. 2nd ed. Hoboken, NJ: John Wiley and Sons Ltd, 2005.
Supplementary Material Table 1. Correlation coefficients of baseline levels of TGs, LDL-C and non-HDL-C

| Pool   | TGs and LDL-C | p-value | TGs and non-HDL-C | p-value |
|--------|---------------|---------|-------------------|---------|
| Pool 1 | 0.08          | 0.0002  | 0.37              | <0.0001 |
| Pool 2 | 0.07          | 0.0350  | 0.32              | <0.0001 |
| Pool 3 | 0.09          | 0.0041  | 0.45              | <0.0001 |
| Pool 4 | 0.08          | 0.1540  | 0.38              | <0.0001 |

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.
Supplementary Material Table 2. Association between TG quintiles and baseline characteristics – both alirocumab and control arms combined (randomised population).

(A) Pool 1 (LONG TERM + HIGH FH: ALI 150 mg versus PBO with statin)

| n (%), unless otherwise specified | TG quintiles at baseline (mg/dL) | p-value |
|----------------------------------|---------------------------------|---------|
|                                  | Q1 30.97;86.73                  |         |
| Number of patients               | 483                             |         |
|                                  | Q2 86.73;117.70                 |         |
|                                  | 494                             |         |
|                                  | Q3 117.70;150.44                |         |
|                                  | 484                             |         |
|                                  | Q4 150.44;203.54                |         |
|                                  | 496                             |         |
|                                  | Q5 203.54;1422.0                |         |
|                                  | 489                             |         |

| Age, years, mean ± SD           | 59.6 ± 12.3                     | 0.0354  |
| Male                            | 288 (59.6)                      | 0.3879  |
| Race, Caucasian                 | 440 (91.1)                      | 0.0500  |
| Hypertension                    | 294 (60.9)                      | <0.0001 |
| Smoking                         | 75 (15.5)                       | 0.0013  |
| BMI, kg/m², mean ± SD          | 28.11 ± 5.26                    | <0.0001 |
| HeFH                            | 139 (28.8)                      | <0.0001 |
| Diabetes                        | 111 (23.0)                      | <0.0001 |
| Taking high-intensity statin    | 264 (54.7)                      | 0.0180  |
| Patients on LLTs other than statin | 171 (35.4) | 146 (29.6) | 127 (26.2) | 127 (25.6) | 159 (32.5) | 0.0029 |
|-----------------------------------|------------|------------|------------|------------|------------|--------|
| FPG, mmol/L, mean ± SD            | 5.67 ± 1.47| 6.02 ± 1.62| 6.25 ± 1.85| 6.54 ± 2.25| 6.80 ± 2.16| <0.0001|
| HbA1c, %, mean ± SD               | 5.82 ± 0.72| 6.06 ± 0.97| 6.17 ± 1.02| 6.23 ± 1.04| 6.43 ± 1.14| <0.0001|

Baseline lipoprotein levels, mean ± SD unless otherwise specified

| TC, mg/dL                         | 4.98 ± 1.24 | 5.15 ± 1.24 | 5.14 ± 1.10 | 5.33 ± 1.18 | 5.94 ± 1.44 | <0.0001 |
| HDL-C, mmol/L                     | 1.47 ± 0.37 | 1.36 ± 0.31 | 1.27 ± 0.28 | 1.21 ± 0.26 | 1.13 ± 0.24 | <0.0001 |
| LDL-C, mmol/L                     | 3.16 ± 1.18 | 3.26 ± 1.16 | 3.19 ± 1.05 | 3.23 ± 1.13 | 3.41 ± 1.32 | 0.0384  |
| Non-HDL-C, mmol/L                 | 3.52 ± 1.19 | 3.79 ± 1.17 | 3.88 ± 1.05 | 4.12 ± 1.13 | 4.80 ± 1.40 | <0.0001 |
| ApoB, mg/dL                       | 90.85 ± 25.82| 98.10 ± 25.53| 100.10 ± 24.26| 107.55 ± 26.91| 120.43 ± 31.94| <0.0001 |
| Lp(a), median (IQR), mg/dL        | 25.85 (10.00–74.50)| 28.40 (9.89–70.10)| 22.80 (7.02–69.00)| 21.80 (7.05–65.00)| 14.00 (5.02–50.25)| <0.0001 |
| ApoA1, mg/dL                      | 150.26 ± 28.15| 149.36 ± 26.21| 144.62 ± 25.20| 144.86 ± 24.58| 142.66 ± 23.89| <0.0001 |
| TRL-C, median (IQR), mmol/L       | 14.00 (12.00–15.83)| 20.46 (18.92–22.00)| 26.45 (25.00–28.19)| 34.00 (32.00–37.00)| 49.03 (44.02–57.00)| <0.0001 |
| TGs, median (IQR), mmol/L         | 0.80 (0.69–0.89)| 1.16 (1.06–1.24)| 1.50 (1.41–1.59)| 1.93 (1.80–2.08)| 2.83 (2.51–3.41)| <0.0001 |
(B) Pool 2 (COMBO I + FH I/II: ALI 75/150 mg versus PBO with statin)

| n (%), unless otherwise specified | TG quintiles at baseline (mg/dL) | p-value |
|----------------------------------|----------------------------------|---------|
|                                  | Q1 35.0;79.0 | Q2 79.0;102.0 | Q3 102.0;128.0 | Q4 128.0;175.0 | Q5 175.0;999.0 |
| Number of patients               | 205 | 213 | 208 | 213 | 210 |
| Age, years, mean ± SD            | 52.4 ± 13.4 | 55.8 ± 13.3 | 56.1 ± 13.1 | 56.7 ± 11.8 | 56.7 ± 11.8 | 0.0068 |
| Male                             | 107 (52.2) | 129 (60.6) | 118 (56.7) | 132 (62.0) | 125 (59.5) | 0.2762 |
| Race, Caucasian                  | 183 (89.3) | 199 (93.4) | 186 (89.4) | 191 (89.7) | 185 (88.1) | 0.4270 |
| Hypertension                     | 77 (37.6) | 98 (46.0) | 111 (53.4) | 130 (61.0) | 153 (72.9) | <0.0001 |
| Smoking (current)                | 22 (10.7) | 28 (13.1) | 36 (17.3) | 45 (21.1) | 47 (22.4) | 0.0030 |
| BMI, kg/m², mean ± SD            | 28.1 ± 5.6 | 29.1 ± 5.3 | 29.9 ± 5.7 | 31.0 ± 5.4 | 31.9 ± 5.5 | <0.0001 |
| HeFH                             | 165 (80.5) | 150 (70.4) | 152 (73.1) | 149 (70.0) | 119 (56.7) | <0.0001 |
| Diabetes                         | 20 (9.8) | 27 (12.7) | 47 (22.6) | 54 (25.4) | 55 (26.2) | <0.0001 |
| Taking high-intensity statina    | 164 (80.0) | 177 (83.1) | 161 (77.4) | 168 (78.9) | 153 (72.9) | 0.1328 |
| Patients on LLTs other than statin| 117 (57.1) | 138 (64.8) | 128 (61.5) | 116 (54.5) | 112 (53.3) | 0.0869 |
| FPG, mmol/L, mean ± SD           | 5.3 ± 0.7 | 5.5 ± 1.0 | 5.8 ± 1.6 | 5.9 ± 1.3 | 6.2 ± 1.7 | <0.0001 |
|                      | HbA1c, %, mean ± SD | Baseline lipoprotein levels, mean ± SD unless otherwise specified |
|----------------------|---------------------|-------------------------------------------------|
|                      | 5.6 ± 0.5           | TC, mg/dL                                       |
|                      | 5.7 ± 0.6           | 4.97 ± 1.02                                      |
|                      | 5.9 ± 0.7           | 5.01 ± 1.09                                      |
|                      | 5.9 ± 0.7           | 5.36 ± 1.28                                      |
|                      | 6.0 ± 0.7           | 5.46 ± 1.21                                      |
|                      | <0.0001             | 5.81 ± 1.61                                      |
|                      |                     | <0.0001                                         |
|                      |                     | HDL-C, mmol/L                                    |
|                      | 1.47 ± 0.41         | 1.47 ± 0.41                                      |
|                      | 1.37 ± 0.38         | 1.37 ± 0.38                                      |
|                      | 1.36 ± 0.39         | 1.36 ± 0.39                                      |
|                      | 1.20 ± 0.33         | 1.20 ± 0.33                                      |
|                      | 1.10 ± 0.33         | 1.10 ± 0.33                                      |
|                      | <0.0001             | <0.0001                                          |
|                      |                     | LDL-C, mmol/L                                    |
|                      | 3.17 ± 0.96         | 3.17 ± 1.00                                      |
|                      | 3.17 ± 1.00         | 3.17 ± 1.00                                      |
|                      | 3.42 ± 1.21         | 3.42 ± 1.21                                      |
|                      | 3.48 ± 1.16         | 3.48 ± 1.16                                      |
|                      | 3.51 ± 1.56         | 3.51 ± 1.56                                      |
|                      | 0.0269              | 0.0269                                           |
|                      |                     | Non-HDL-C, mmol/L                                |
|                      | 3.50 ± 0.96         | 3.50 ± 0.96                                      |
|                      | 3.64 ± 1.01         | 3.64 ± 1.01                                      |
|                      | 4.00 ± 1.21         | 4.00 ± 1.21                                      |
|                      | 4.25 ± 1.17         | 4.25 ± 1.17                                      |
|                      | 4.71 ± 1.57         | 4.71 ± 1.57                                      |
|                      | <0.0001             | <0.0001                                          |
|                      |                     | Apo B, mg/dL                                     |
|                      | 93.69 ± 21.78       | 93.69 ± 21.78                                   |
|                      | 97.01 ± 22.58       | 97.01 ± 22.58                                   |
|                      | 106.17 ± 26.70      | 106.17 ± 26.70                                   |
|                      | 112.50 ± 26.56      | 112.50 ± 26.56                                   |
|                      | 120.11 ± 35.62      | 120.11 ± 35.62                                   |
|                      | <0.0001             | <0.0001                                          |
|                      |                     | Lp(a), median (IQR), mg/dL                       |
|                      | 26.00 (10.00:67.00) | 26.00 (10.00:68.00)                              |
|                      | 39.00 (10.00:99.00) | 39.00 (10.00:99.00)                              |
|                      | 25.00 (8.00:75.00)  | 25.00 (8.00:75.00)                               |
|                      | 28.00 (8.00:78.00)  | 28.00 (8.00:78.00)                               |
|                      | 0.2399              | 0.2399                                           |
|                      |                     | ApoA1, mg/dL                                     |
|                      | 144.34 ± 26.92      | 144.34 ± 26.92                                   |
|                      | 143.84 ± 25.66      | 143.84 ± 25.66                                   |
|                      | 148.78 ± 27.83      | 148.78 ± 27.83                                   |
|                      | 140.26 ± 27.57      | 140.26 ± 27.57                                   |
|                      | 139.69 ± 27.51      | 139.69 ± 27.51                                   |
|                      | 0.0042              | 0.0042                                           |
|                      |                     | TRL-C, median (IQR), mg/dL                       |
|                      | 13.00 (12.00:15.00) | 13.00 (12.00:15.00)                              |
|                      | 18.00 (17.00:19.00) | 18.00 (17.00:19.00)                              |
|                      | 22.00 (21.00:24.00) | 22.00 (21.00:24.00)                              |
|                      | 30.00 (28.00:32.00) | 30.00 (28.00:32.00)                              |
|                      | 43.00 (38.00:51.00) | 43.00 (38.00:51.00)                              |
|                      | <0.0001             | <0.0001                                          |
|                      |                     | TGs, median (IQR), mmol/L                        |
|                      | 0.753 (0.65:0.82)   | 0.753 (0.65:0.82)                                |
|                      | 1.02 (0.96:1.08)    | 1.02 (0.96:1.08)                                 |
|                      | 1.26 (1.21:1.37)    | 1.26 (1.21:1.37)                                 |
|                      | 1.67 (1.56:1.78)    | 1.67 (1.56:1.78)                                 |
|                      | 2.44 (2.18:2.96)    | 2.44 (2.18:2.96)                                 |
|                      | <0.0001             | <0.0001                                          |
### (C) Pool 3 (COMBO II + OPTIONS I/II: ALI 75/150 mg versus EZE with statin)

| n (%), unless otherwise specified | TG quintiles at baseline (mg/dL) |   |   |   | p-value |
|----------------------------------|----------------------------------|---|---|---|---------|
|                                 | Q1 46.00;90.00                  | Q2 90.00;118.00     | Q3 118.00;148.00     | Q4 148.00;201.00     | Q5 201.00;564.00     |   |
| Number of patients              | 221                              | 230                         | 223                         | 230                         | 225                         |   |
| Age, years, mean ± SD           | 62.2 ± 10.4                      | 61.9 ± 10.0                 | 62.9 ± 9.4                  | 61.7 ± 8.7                  | 60.7 ± 9.7                  | 0.0676 |
| Male                            | 150 (67.9)                       | 167 (72.6)                  | 150 (67.3)                  | 158 (68.7)                  | 152 (67.6)                  | 0.7263 |
| Race, Caucasian                 | 189 (85.5)                       | 196 (85.2)                  | 187 (83.9)                  | 199 (86.5)                  | 195 (86.7)                  | 0.9186 |
| Hypertension                    | 158 (71.5)                       | 173 (75.2)                  | 173 (77.6)                  | 193 (83.9)                  | 191 (84.9)                  | 0.0015 |
| Smoking                         | 41 (18.6)                        | 37 (16.1)                   | 51 (22.9)                   | 47 (20.4)                   | 60 (26.7)                   | 0.1043 |
| BMI, kg/m², mean ± SD           | 29.1 ± 5.7                       | 29.5 ± 5.2                  | 30.8 ± 6.4                  | 31.0 ± 5.3                  | 32.1 ± 5.8                  | <0.0001 |
| HeFH                            | 16 (7.2)                         | 9 (3.9)                     | 6 (2.7)                     | 8 (3.5)                     | 4 (1.8)                     | 0.0332 |
| Diabetes                        | 63 (28.5)                        | 66 (28.7)                   | 91 (40.8)                   | 89 (38.7)                   | 101 (44.9)                  | 0.0003 |
| Taking high-intensity statin*   | 146 (66.1)                       | 133 (57.8)                  | 135 (60.5)                  | 147 (63.9)                  | 134 (59.6)                  | 0.3710 |
| Patients on LLTs other than statin | 24 (10.9)                      | 34 (14.8)                   | 27 (12.1)                   | 20 (8.7)                    | 25 (11.1)                   | 0.3533 |
| FPG, mmol/L, mean ± SD          | 5.9 ± 1.2                        | 6.1 ± 1.5                   | 6.2 ± 1.4                   | 6.6 ± 2.1                   | 6.6 ± 1.7                   | <0.0001 |
|                        | 5.9 ± 0.8 | 6.0 ± 0.7 | 6.2 ± 0.8 | 6.2 ± 0.9 | 6.3 ± 0.8 | <0.0001 |
|------------------------|-----------|-----------|-----------|-----------|-----------|---------|
| **Baseline lipoprotein levels, mean ± SD unless otherwise specified** |           |           |           |           |           |         |
| TC, mg/dL              | 4.41 ± 0.91 | 4.66 ± 1.07 | 4.68 ± 0.95 | 4.99 ± 1.11 | 5.28 ± 1.10 | <0.0001 |
| HDL-C, mmol/L          | 1.45 ± 0.37 | 1.33 ± 0.34 | 1.22 ± 0.30 | 1.16 ± 0.27 | 1.07 ± 0.29 | <0.0001 |
| LDL-C, mmol/L          | 2.58 ± 0.83 | 2.79 ± 0.94 | 2.78 ± 0.88 | 2.94 ± 1.03 | 2.83 ± 0.92 | 0.0015  |
| Non-HDL-C, mmol/L      | 2.96 ± 0.82 | 3.33 ± 0.94 | 3.45 ± 0.87 | 3.83 ± 1.03 | 4.21 ± 1.07 | <0.0001 |
| ApoB, mg/dL            | 79.19 ± 17.89 | 88.79 ± 20.08 | 91.89 ± 19.40 | 100.37 ± 23.16 | 106.35 ± 24.25 | <0.0001 |
| Lp(a), median (IQR), mg/dL | 34.00 (11.00:84.00) | 24.00 (8.00:61.00) | 24.00 (8.00:63.00) | 27.00 (10.00:75.00) | 19.00 (8.00:60.00) | 0.0656  |
| ApoA1, mg/dL           | 148.81 ± 25.51 | 144.57 ± 24.95 | 139.64 ± 22.26 | 140.25 ± 22.79 | 138.69 ± 23.88 | <0.0001 |
| TRL-C, median (IQR), mg/dL | 15.00 (13.00:17.00) | 21.00 (19.00:22.00) | 26.00 (25.00:28.00) | 34.00 (32.00:37.00) | 49.00 (44.00:56.50) | <0.0001 |
| TG, median (IQR), mmol/L | 0.86 (0.72:0.94) | 1.16 (1.08:1.24) | 1.48 (1.40:1.58) | 1.94 (1.80:2.09) | 2.83 (2.50:3.36) | <0.0001 |
(D) Pool 4 (ALTERNATIVE + MONO: ALI 75/150 mg versus EZE without statin)

| n (%) | TG quintiles at baseline (mg/dL) | p-value |
|-------|-------------------------------|---------|
|       | Q1 36.0;89.0 | Q2 89.0;121.0 | Q3 121.0;158.0 | Q4 158.0;228.0 | Q5 228.0;727.0 |       |
| Number of patients | 69 | 71 | 70 | 73 | 70 |        |
| Age, years, mean ± SD | 60.7 ± 10.0 | 63.1 ± 8.9 | 63.2 ± 7.6 | 62.8 ± 8.4 | 62.7 ± 8.2 | 0.4718 |
| Male | 35 (50.7) | 39 (54.9) | 39 (55.7) | 35 (47.9) | 44 (62.9) | 0.4515 |
| Race, Caucasian | 63 (91.3) | 63 (88.7) | 64 (91.4) | 66 (90.4) | 69 (98.6) | 0.2393 |
| Hypertension | 28 (40.6) | 29 (40.8) | 39 (55.7) | 50 (68.5) | 47 (67.1) | 0.0003 |
| Smoking | 7 (10.1) | 5 (7.0) | 6 (8.6) | 7 (9.6) | 2 (2.9) | 0.4941 |
| BMI, kg/m², mean ± SD | 26.27 ± 5.61 | 29.00 ± 6.14 | 29.76 ± 6.55 | 29.71 ± 6.30 | 30.46 ± 4.40 | <0.0001 |
| HeFH | 8 (11.6) | 9 (12.7) | 4 (5.7) | 11 (15.1) | 7 (10.0) | 0.4752 |
| Diabetes | 5 (7.2) | 6 (8.5) | 15 (21.4) | 15 (20.5) | 22 (31.4) | 0.0007 |
| Taking high-intensity statin | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | N/A |
| Patients on LLTs other than statin | 10 (14.5) | 21 (29.6) | 21 (30.0) | 25 (34.2) | 29 (41.4) | 0.0119 |
| FPG, mmol/L, mean ± SD | 5.3 ± 0.9 | 5.5 ± 0.8 | 5.8 ± 1.2 | 5.8 ± 1.1 | 6.3 ± 1.3 | <0.0001 |
### Baseline lipoprotein levels, mean ± SD unless otherwise specified

| Lipoprotein | Baseline Levels | P-value |
|-------------|-----------------|---------|
| HbA1c, % | 5.6 ± 0.4 | 5.7 ± 0.5 | 5.8 ± 0.7 | 5.8 ± 0.5 | 5.9 ± 0.6 | 0.0004 |
| TC, mg/dL | 6.46 ± 2.09 | 6.44 ± 1.89 | 6.45 ± 1.75 | 6.96 ± 1.43 | 7.68 ± 2.23 | <0.0001 |
| HDL-C, mmol/L | 1.67 ± 0.51 | 1.41 ± 0.31 | 1.37 ± 0.41 | 1.24 ± 0.26 | 1.04 ± 0.25 | <0.0001 |
| LDL-C, mmol/L | 4.42 ± 2.07 | 4.49 ± 1.88 | 4.37 ± 1.67 | 4.74 ± 1.38 | 4.89 ± 1.47 | 0.0016 |
| Non-HDL-C, mmol/L | 4.79 ± 2.07 | 5.03 ± 1.89 | 5.09 ± 1.66 | 5.72 ± 1.39 | 6.64 ± 2.21 | <0.0001 |
| ApoB, mg/dL | 112.95 ± 36.75 | 119.97 ± 36.54 | 123.21 ± 33.66 | 138.51 ± 28.80 | 153.44 ± 38.43 | <0.0001 |
| Lp(a), median (IQR), mg/dL | 19.00 (7.00:42.00) | 15.00 (6.00:42.00) | 15.00 (5.00:43.00) | 18.00 (6.00:43.00) | 19.00 (7.00:38.00) | 0.8790 |
| ApoA1, mg/dL | 160.62 ± 33.12 | 155.10 ± 27.08 | 153.79 ± 26.27 | 149.61 ± 21.01 | 142.10 ± 23.92 | 0.0020 |
| TRL-C, median (IQR), mg/dL | 15.00 (13.00:16.00) | 21.00 (19.00:23.00) | 27.00 (26.00:30.00) | 38.00 (34.00:42.00) | 53.00 (48.00:60.00) | <0.0001 |
| TGs, median (IQR), mmol/L | 0.84 (0.73:0.91) | 1.21 (1.06:1.30) | 1.52 (1.45:1.68) | 2.12 (1.92:2.37) | 3.12 (2.71:3.85) | <0.0001 |

*aHigh-intensity statin corresponds to atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily.*

*p-values for continuous variables are derived from Kruskal-Wallis tests. P-values for categorical variables are derived from the Chi-Square test.*

*ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.*
ALI: alirocumab; apo: apolipoprotein; BMI: body mass index; EZE: ezetimibe; FPG: fasting plasma glucose; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol; HeFH: heterozygous familial hypercholesterolaemia; IQR: interquartile range; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; Lp(a): lipoprotein (a); PBO: placebo; SD: standard deviation; TC: total cholesterol; TG: triglyceride; TRL-C: triglyceride-rich lipoprotein cholesterol.
Supplementary Material Table 3. Percent and absolute changes from baseline in lipid parameters at Week 24 by study pool (ITT population)

|                  | Pool 1               | Pool 2               | Pool 3               | Pool 4               |
|------------------|----------------------|----------------------|----------------------|----------------------|
|                  | LONG TERM + HIGH FH  | COMBO I + FH I/II    | COMBO II + OPTIONS I/II | ALTERNATIVE + MONO |
|                  | PBO-controlled trials | EZE-controlled trials |                       |                      |
| ALI 150 mg       | ALI 75/150 mg        | ALI 75/150 mg        | ALI 75/150 mg        | EZE 10 mg           | ALI 75/150 mg        | EZE 10 mg           |
| with statin      | with statin          | with statin          | with statin          | with statin         | without statin       | without statin      |
| (n=1601)         | (n=693)              | (n=350)              | (n=669)              | (n=436)             | (n=178)              | (n=173)              |
| **LS mean (SE) % change from baseline** |                      |                      |                      |                      |
| LDL-C            | –60.4 (0.7)*         | –48.6 (1.0)*         | +4.2 (1.5)           | –48.9 (1.4)*        | –19.3 (1.7)          | –45.6 (1.8)*        | –14.8 (1.8)         |
| Non-HDL-C        | –51.1 (0.6)*         | –41.7 (1.0)*         | +4.7 (1.3)           | –41.1 (1.1)*        | –17.8 (1.4)          | –40.4 (1.5)*        | –14.7 (1.5)         |
| ApoB             | –52.2 (0.7)*         | –40.2 (0.8)*         | +1.0 (1.1)           | –38.6 (1.0)*        | –15.9 (1.2)          | –36.5 (1.4)*        | –11.2 (1.4)         |
| HDL-C            | +4.1 (0.4)*          | +6.6 (0.6)*          | –1.0 (0.8)           | +8.1 (0.7)*         | +0.8 (0.8)           | +7.2 (1.3)          | +5.3 (1.3)          |
| TGs*             | –15.3 (0.8)*         | –8.9 (1.1)*          | +1.4 (1.5)           | –13.0 (1.2)         | –11.2 (1.5)          | –10.3 (2.2)         | –6.0 (2.3)          |
| TRL-C*           | –15.5 (0.8)*         | –8.6 (1.1)*          | +1.6 (1.6)           | –13.1 (1.2)         | –11.4 (1.5)          | –9.8 (2.2)          | –6.5 (2.3)          |
| **LS mean (SE) absolute change from baseline** |                      |                      |                      |                      |
| Calculated LDL-C, mmol/L | –1.94 (0.02)*      | –1.68 (0.04)*        | +0.11 (0.05)         | –1.39 (0.03)*       | –0.61 (0.04)         | –2.05 (0.08)*       | –0.77 (0.08)       |
|                     | Non-HDL-C, mmol/L | ApoB, mg/dL | HDL-C, mmol/L | TGs,† mmol/L |
|---------------------|-------------------|-------------|---------------|--------------|
|                     | –2.06 (0.03)*     | –53.4 (0.6)*| +0.04 (<0.01)*| –0.36 (0.01)*|
|                     | –0.09 (0.04)      | –1.8 (0.9)  | –0.02 (0.01)  | –0.10 (0.02)  |
|                     | –1.74 (0.04)*     | –44.2 (0.9)*| +0.06 (0.01)* | –0.21 (0.01)*|
|                     | +0.16 (0.06)      | +0.2 (1.2)  | –0.03 (0.01)  | –0.08 (0.02)  |
|                     | –1.51 (0.04)*     | –37.0 (0.9)*| +0.08 (0.01)* | –0.33 (0.02)  |
|                     | –0.70 (0.05)      | –16.3 (1.1) | –0.01 (0.01)  | –0.28 (0.02)  |
|                     | +0.89 (0.08)*     | –47.8 (1.8)*| 0.08 (0.02)   | –0.28 (0.04)  |
|                     | –2.19 (0.08)      | –16.0 (1.8) | 0.05 (0.02)   | –0.23 (0.04)  |

* p<0.0001 versus comparator.

*Adjusted means (SE).

Calculated LDL-C determined by Friedewald equation. Calculated TRL-C determined by subtracting calculated LDL-C from non-HDL-C.

ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; apo: apolipoprotein; EZE: ezetimibe; ITT: intention-to-treat; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; LS: least squares; PBO: placebo; SE: standard error; TG: triglyceride; TRL-C: triglyceride-rich lipoprotein cholesterol.
Supplementary Material Figure 1. Absolute changes in ApoB by baseline TG quintile

ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; Apo: apolipoprotein; EZE: ezetimibe; LS: least squares; PBO: placebo; SE: standard error; TG: triglyceride.
Supplementary Material Figure 2. Percent changes in (A) calculated LDL-C, non-HDL-C, HDL-C and calculated TRL-C, and (B) ApoB by baseline TG quintiles
ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; apo: apolipoprotein; EZE: ezetimibe; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PBO: placebo; LS: least squares; SE: standard error; TG: triglyceride; TRL-C: triglyceride-rich lipoprotein cholesterol.
Supplementary Material Figure 3. Absolute changes in measured LDL-C by baseline TG quintiles

ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; EZE: ezetimibe; LDL-C: low-density lipoprotein cholesterol; PBO: placebo; LS: least squares; SE: standard error; TG: triglyceride.
Measured TRL-C = non-HDL-C – measured LDL-C (i.e. LDL-C determined by beta-quantification). Pool 1 does not include the HIGH FH study and pool 4 does not include the MONO study, as LDL-C was not routinely assessed by beta-quantification in those trials.

ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; EZE: ezetimibe; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PBO: placebo; LS: least squares; SE: standard error; TG: triglyceride; TRL-C: triglyceride-rich lipoprotein cholesterol.
Supplementary Material Figure 5. Proportion of patients achieving goals at Week 24 for non-HDL-C and measured (beta-quantification) LDL-C by baseline TG quintile

*p < 0.05 for trend test. Measured LDL-C was determined by beta-quantification). Pool 1 does not include the HIGH FH study and pool 4 does not include the MONO study, as LDL-C was not routinely assessed by beta-quantification in those trials.

ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; EZE: ezetimibe; HDL-C: high-density lipoprotein cholesterol; ITT: intent-to-treat; LDL-C: low-density lipoprotein cholesterol; LOCF: last observation carried forward; PBO: placebo; TG: triglyceride.
Supplementary Material Figure 6. Proportion of patients achieving goals at Week 24 for non-HDL-C and measured (beta-quantification) LDL-C by baseline measured TRL-C quintile

*p < 0.05 for trend tests across the quintiles. Measured LDL-C was determined by beta-quantification; measured TRL-C was derived by non-HDL-C minus measured LDL-C. Measured LDL-C was not available for the HIGH FH study (in pool 1) or the MONO study (in pool 4), so N-values are lower for measured compared with calculated LDL-C in those pools.

ALI 75/150 denotes that the dose could be increased from 75 to 150 mg at Week 12 depending on Week 8 LDL-C levels.

ALI: alirocumab; EZE: ezetimibe; HDL-C: high-density lipoprotein cholesterol; ITT: intent-to-treat; LDL-C: low-density lipoprotein cholesterol; PBO: placebo; TRL-C: triglyceride-rich lipoprotein cholesterol.