Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Blom DJ, Hala T, Bolognese M, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014;370:1809-19. DOI: 10.1056/NEJMoa1316222

A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlipidemia

The Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES)

NCT01516879

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DESCARTES -Independent Data Monitoring Committee

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Felicita Andreotti	Catholic University Medical School	Rome, Italy
Colin Baigent	University of Oxford	Oxford, United Kingdom
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DESCARTES – Clinical Endpoints Committee

Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital (Boston, MA)

Chairman of the CEC: Stephen D. Wiviott

DESCARTES – Central Laboratory for Lipid Analyses

Medpace Reference Laboratories

Laboratory director: Traci Turner

Descartes – Central Laboratory for Safety Analyses

Covance Laboratories

Laboratory director: William E Tarr, Jr.

Study Methods: Additional Details

- **Key eligibility criteria - a full listing of inclusion/exclusion criteria can be found in the protocol**

Inclusion Criteria

4.1.1 Subject has provided informed consent

4.1.2 Male or female ≥ 18 to ≤ 75 years of age at screening

4.1.3 Fasting LDL-C ≥ 75 mg/dL as determined by central laboratory at the initial screening visit

4.1.4 Fasting LDL-C as determined by central laboratory at the end of the lipid stabilization period ≥ 75 mg/dL (2.0 mmol/L) and meeting the following LDL-C values based on risk factor status (NCEP ATPIII risk categories):

• < 100 mg/dL (2.6 mmol/L) for subjects with diagnosed CHD or CHD risk equivalent (includes clinical manifestations of non-coronary forms of atherosclerotic disease [peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease], diabetes, and 2+ risk factors with 10-year risk for hard CHD >20%)

• < 130 mg/dL (3.4 mmol/L) for subjects without diagnosed CHD or CHD risk equivalent

• OR for subjects on maximal background lipid-lowering therapy (defined as atorvastatin 80 mg PO QD and ezetimibe 10 mg PO QD), LDL-C at the end of the lipid stabilization period of ≥75 mg/dL (2.0 mmol/L)

4.1.5 Fasting triglycerides ≤ 400 mg/dL (4.5 mmol/L) by central laboratory at screening and at end of lipid stabilization period

4.2 Exclusion Criteria

4.2.1 Diagnosed with CHD or CHD risk equivalent and not receiving statin therapy, with LDL-C at screening ≤ 99 mg/dL

4.2.2 NYHA class II, III or IV heart failure, or last known left ventricular ejection fraction < 30%

4.2.3 Uncontrolled cardiac arrhythmia defined as recurrent and highly symptomatic ventricular tachycardia, atrial fibrillation with rapid ventricular response, or supraventricular tachycardia that are not controlled by medications, in the past 3 months prior to randomization

4.2.4 Myocardial infarction, unstable angina, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) or stroke within 3 months prior to randomization

4.2.5 Planned cardiac surgery or revascularization

4.2.6 Type 1 diabetes or newly diagnosed type 2 diabetes (within 6 months of randomization or new screening fasting plasma glucose ≥ 126 mg/dL [7.0 mmol/L] or HbA1c ≥ 6.5%), or poorly controlled type 2 diabetes (HbA1c > 8.5%)

4.2.7 Uncontrolled hypertension defined as sitting systolic blood pressure (SBP) > 160 mmHg or diastolic BP (DBP) > 100 mmHg, confirmed with repeat measurement

4.2.8 Subject has taken in the last 6 weeks prior to LDL-C screening red yeast rice, > 200 mg/day niacin, or >1000 mg/day omega-3 fatty acids (eg, DHA and EPA) or prescription lipid-regulating drugs other than statins or ezetimibe, such as fibrates and derivatives, or bile-acid sequestering resins

4.2.9 Treatment in the last 3 months prior to LDL-C screening with any of the following drugs: systemic cyclosporine, systemic steroids (eg IV, intramuscular [IM], or PO), vitamin A derivatives and retinol derivatives for the treatment of dermatologic conditions (eg, Accutane)

4.2.10 Hyperthyroidism or hypothyroidism as defined by thyroid stimulating hormone TSH below the lower limit of normal (LLN) or > 1.5 times the upper limit of normal (ULN), respectively, at screening

4.2.11 Moderate to severe renal dysfunction, defined as an estimated glomerular

filtration rate (eGFR) < 30 ml/min/1.73m2 at screening, confirmed by a repeat measurement at least 1 week apart

4.2.12 Active liver disease or hepatic dysfunction, defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times the ULN as determined by central laboratory analysis at screening or at end of lipid stabilization period, confirmed by a repeat measurement at least 1 week apart

4.2.13 CK > 3 times the ULN at screening or at end of lipid stabilization period, confirmed by a repeat measurement at least 1 week apart

- **Lipid analyses**

All lipid analyses were performed by Medpace Reference Laboratories (MRL). Samples from sites located in the US and Canada were analyzed in Cincinnati, Ohio and those from European, Australian and South African sites in Leuven, Belgium. Both laboratories maintained Part III certification according to the Centers for Disease Control (CDC) Lipid Standardization Program throughout the study.

Low density lipoprotein cholesterol and very-low-density lipoprotein cholesterol were measured after preparative ultracentrifugation (β-quantification). Calculated low density lipoprotein cholesterol was derived using the Friedewald formula.

Triglycerides and cholesterol were measured with enzymatic colorimetric tests (Olympus AU2700 or AU5400 Analyzer, Olympus, Center Valley, PA) with calibration directly traceable to CDC reference procedures. ApoB-containing lipoproteins were precipitated with dextran sulfate, and high density lipoprotein cholesterol was measured in the supernatant. ApoA1 and ApoB were measured with rate immunonephelometry (Dade Behring BNII nephelometer, Siemens Healthcare Diagnostics, Deerfield, IL), and Lp(a) was measured by immunoturbidimetry (Denka Seiken Co. Ltd. Lp(a) assay from Polymedco, Cortlandt Manor, NY on the Olympus Analyzer).

- **Investigator notification of LDL-C not at NCEP ATP III goal during double blind phase**

Patients whose LDL cholesterol at any post randomization study visit exceeded their NCEP-ATP III goal were reminded by clinic staff to adhere to their assigned lipid lowering therapies and diet. To maintain blinding, the same reminder, generated by the central laboratory, was provided to additional patients in each treatment arm.

- **Tertiary endpoint**

Percent change from baseline in apolipoprotein A1 at week 52.

- **Exploratory endpoints**

Exploratory endpoints included the incidence of adjudicated events (see below) and the absolute and percent change from baseline at scheduled visits for lipid parameters. We also assessed absolute values and change from baseline for hemoglobin A1c and PCSK9, and change from baseline for high-sensitivity C-reactive protein.

- **LDL cholesterol endpoint analysis using calculated LDL cholesterol**

All ultracentrifugation LDL cholesterol analyses were repeated using LDL cholesterol calculated by the Friedewald formula.

- **Additional statistical analyses**

Sensitivity analyses were performed on patients who completed study drug and had a week 52 UC LDL cholesterol value, and additionally using reflexive LDL cholesterol (where calculated LDL cholesterol was used, unless it was <40 mg per deciliter or triglycerides were >400 mg per deciliter, in which case UC LDL cholesterol from the same date was used). Furthermore non-parametric analysis (Wilcoxon rank sum test) and an analysis of covariance (ANCOVA) were performed. For ANCOVA last observation carried forward was used to impute missing values.

Supplementary Table S1. Major Lipids and Apolipoproteins at Baseline and Week 52

	Evolocumab									
	Diet only		Diet + Atorvastatin 10 mg/d		Diet + Atorvastatin 80 mg/d		Diet + Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
	P	E	P	E	P	E	P	E	P	E
Calculated LDL-C, n	**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Baseline mg/dL mean (SD)	109.6 (13.5)	108.9 (15.7)	94.0 (13.4)	97.3 (14.7)	92.0 (13.3)	90.1 (12.8)	116.7 (33.1)	113.7 (35.2)	100.2 (21.6)	100.4 (22.3)
Percent change from baseline, n, LS mean % (SE)	**29** 10.8 (3.5)	**63** –53.0 (2.4)	**111** 8.3(2.3)	**217** –56.1 (1.6)	**66** 10.7 (4.7)	**125** –47.2 (3.4)	**52** 2.9 (4.6)	**104** –46.2 (3.2)	**258** 8.7 (1.9)	**509** –50.6 (1.4)
Treatment difference from baseline vs placebo, LS mean % (SE)	–	–63.8 (4.2)	–	–64.4 (2.8)	–	–57.9 (5.9)	–	–49.1 (5.6)	–	–59.3 (2.3)
ApoB, n	**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Baseline mg/dL mean (SD)	91.1 (14.8)	90.0 (12.9)	82.6 (11.0)	84.0 (12.6)	83.3 (12.4)	83.3 (12.5)	100.3 (22.1)	95.5 (23.6)	87.5 (16.3)	87.0 (16.3)
Percent change from baseline, n, LS mean % (SE)	**32** –0.4 (2.9)	**64** –43.3 (2.0)	**117** 2.9 (1.8)	**226** –44.8 (1.3)	**68** 5.4 (3.3)	**131** –39.2 (2.4)	**58** 0.8 (3.5)	**115** -37 (2.5)	**275** 2.9 (1.4)	**536** –41.3 (1.0)
Treatment difference from baseline vs placebo LS mean % (SE)	–	–42.9 (3.5)	–	–47.7 (2.2)	–	–44.5 (4.1)	–	–37.8 (4.3)	–	–44.2 (1.7)

Lipoprotein(a), n	**37**	**74**	**127**	**253**	**72**	**145**	**62**	**125**	**298**	**597**
Baseline nmol/L median (Q1,Q3)	37 (16,62)	20 (7,43)	29 (9,102)	29 (11,80)	52 (20,179)	74 (26,197)	63 (14,226)	67 (24,180)	40 (12,145)	38 (14,137)
Baseline nmol/L, mean (SD)	49 (52.5)	43.6 (57.4)	70.7 (88.7)	61.3 (72.5)	113.3 (132.3)	116.5 (105.7)	123.4 (125.1)	116.2 (129.3)	89.3 (108.6)	84 (98.5)
Percent change from baseline, n, LS mean % (SE)	**32** –12.8 (5.0)	**64** –22.5 (3.6)	**115** –3.6 (2.2)	**226** –32.8 (1.6)	**68** –10.6 (2.9)	**131** –30.1 (2.1)	**57** –1.1 (3.9)	**114** –20.5 (2.8)	**272** –5.4 (1.6)	**535** –27.7 (1.2)
Treatment difference from baseline vs placebo LS mean % (SE)	–	–9.7 (6.1)	–	–29.3 (2.7)	–	–19.5 (3.6)	–	–19.3 (4.8)	–	–22.4 (1.9)
HDL-C, n	**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Baseline mg/dL mean (SD)	54.4 (19.9)	49.2 (14.2)	55.8 (16.4)	55.7 (15.9)	52.6 (14.9)	50.1 (14.2)	49.3 (13.5)	51.3 (15.7)	53.5 (16.1)	52.6 (15.5)
Percent change from baseline, **n**, LS mean % (SE)	**30** –2.1 (3.2)	**63** 9.2 (2.2)	**112** –0.5 (1.3)	**221** 4.8 (0.9)	**67** 1.5 (1.6)	**127** 5.4 (1.2)	**54** 1.0 (2.1)	**104** 5.0 (1.5)	**263** 0.4 (0.9)	**515** 5.8 (0.7)
Treatment difference from baseline vs placebo LS mean % (SE)	–	11.3 (3.9)	–	5.3 (1.6)	–	3.9 (2.0)	–	4.0 (2.6)	–	5.4 (1.1)
ApoA1, n	**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Baseline mg/dL mean (SD)	155.8 (33.6)	146.6 (26.4)	160.1 (26.6)	159.9 (26.4)	153.1 (25.6)	148 (26.1)	147.2 (28.5)	145.5 (27.6)	155.2 (28.0)	152.4 (27.3)
Percent change from baseline, **n**, LS mean % (SE)	**32** –1.7 (2.1)	**64** 3.1 (1.5)	**117** –0.9 (1.0)	**226** 1.5 (0.7)	**68** –0.1 (1.3)	**131** 3.4 (0.9)	**58** –1.7 (1.8)	**115** 0.9 (1.2)	**275** –0.8 (0.7)	**536** 2.2 (0.5)
Total cholesterol, n	37	74	129	254	73	145	63	126	302	599

Baseline, mg/dL, mean (SD)	189.9 (22.4)	183.5 (22.8)	173.1 (20.0)	176.3 (22.0)	169.6 (22.6)	164.9 (21.5)	196.0 (36.6)	187.5 (38.7)	179.1 (27.2)	176.8 (27.5)
Percent change from baseline, n, LS mean % (SE)	30 5.4 (2.3)	63 –30.9 (1.6)	112 5.3 (1.4)	221 –30.1 (1.0)	67 8.1 (2.9)	127 –25.0 (2.1)	54 1.7 (2.9)	104 –27.0 (2.1)	263 5.3 (1.2)	515 –28.2 (0.8)
Treatment difference from baseline vs placebo, % (SE)	–	–36.3 (2.8)	–	–35.5 (1.7)	–	–33.1 (3.6)	–	–28.7 (3.6)	–	–33.5 (1.4)
Non-HDL-C, n	37	74	129	254	73	145	63	126	302	599
Baseline, mg/dL, mean (SD)	135.5 (20.5)	134.3 (21.9)	117.3 (17.2)	120.6 (18.2)	117.0 (19.1)	114.8 (17.8)	146.7 (38.6)	136.2 (38.6)	125.6 (26.9)	124.2 (25.6)
Percent change from baseline, n, LS mean % (SE)	30 9.5 (3.1)	63 –44.9 (2.1)	112 8.5 (2.0)	221 –46.0 (1.4)	67 11.7 (4.3)	127 –37.8 (3.1)	54 2.4 (4.0)	104 –38.9 (2.9)	263 8.4 (1.7)	515 –41.8 (1.2)
Treatment difference from baseline vs placebo, %, (SE)	–	–54.3 (3.8)	–	–54.5 (2.5)	–	–49.5 (5.3)	–	–41.2 (5.0)	–	–50.3 (2.0)
Total cholesterol/HDL-C ratio, n	37	74	129	254	73	145	63	126	302	599
Baseline, mean (SD)	3.8 (1.1)	4.0 (1.2)	3.3 (0.8)	3.3 (0.8)	3.4 (0.9)	3.5 (0.9)	4.3 (1.5)	4.0 (1.4)	3.6 (1.1)	3.6 (1.0)
Percent change from baseline, n, LS mean % (SE)	30 9.7 (3.2)	63 –34.7 (2.2)	112 6.8 (1.8)	221 –32.1 (1.3)	67 8.4 (3.3)	127 -28 (2.4)	54 2.2 (3.3)	104 –28.8 (2.4)	263 6.5 (1.4)	515 –30.7 (1.0)
Treatment difference from baseline vs placebo, % (SE)	–	–44.4 (3.9)	–	–38.9 (2.2)	–	–36.4 (4.0)	–	–31.0 (4.1)	–	–37.1 (1.7)
VLDL-C, n	37	74	129	254	73	145	63	126	302	599
Baseline, mg/dL, mean (SD)	23.1 (16.0)	22.6 (14.7)	18.8 (9.7)	19.4 (10.8)	20.8 (13.3)	20.2 (11.6)	27.0 (16.7)	19.4 (10.0)	21.5 (13.4)	20.0 (11.4)

Percent change from baseline, n, LS mean % (SE)	30 77.2 (18.3)	63 –2.1 (12.5)	112 28.7 (6.9)	219 8.6 (4.9)	65 35.5 (9.4)	125 4.4 (6.8)	54 13.6 (7.8)	104 –3.9 (5.6)	261 31.9 (4.7)	511 2.7 (3.4)
Treatment difference from baseline vs placebo, % (SE)	–	–79.2 (22.2)	–	–20.1 (8.4)	–	–31.1 (11.6)	–	–17.5 (9.6)	–	–29.2 (5.6)
ApoB/ApoA1, n	37	74	129	254	73	145	63	126	302	599
Baseline, mean (SD)	0.6 (0.2)	0.6 (0.2)	0.5 (0.1)	0.5 (0.1)	0.6 (0.1)	0.6 (0.1)	0.7 (0.2)	0.7 (0.2)	0.6 (0.2)	0.6 (0.2)
Percent change from baseline, n, mean % (SE)	32 1.9 (3.2)	64 –44.1 (2.2)	117 4.4 (1.9)	226 –45.1 (1.4)	68 6.1 (3.4)	131 –40.8 (2.4)	58 2.9 (3.9)	115 –36.2 (2.8)	275 4.5 (1.5)	536 –41.8 (1.1)
Treatment difference from baseline vs placebo, % (SE)	–	–45.9 (3.9)	–	–49.5 (2.4)	–	–46.8 (4.2)	–	–39.1 (4.8)	–	–46.2 (1.8)
Triglycerides, n	37	74	129	254	73	145	63	126	302	599
Baseline, mg/dL, median (IQR)	101.5 (85.5-126.5)	108.8 (80.5-147.0)	105.0 (81.5-137.5)	104.5 (82.5-136.5)	110.0 (86.0-152.5)	111.0 (83.5-148.5)	135.5 (95.0-189.0)	96.8 (73.0-133.0)	110.3 (85.0-155.0)	105.0 (80.0-140.0)
Percent change from baseline, n, LS mean % (SE)	30 15.4 (7.1)	63 –7.7 (5.0)	112 10.2 (3.4)	221 –1.0 (2.4)	67 11.5 (4.6)	127 –0.9 (3.4)	54 1.6 (5.6)	104 –2.1 (4.0)	263 9.0 (2.4)	575 –2.6 (1.7)
Treatment difference from baseline vs placebo, % (SE)	–	–23.1 (8.7)	–	–11.2 (4.2)	–	–12.4 (5.7)	–	–3.7 (6.9)	–	–11.5 (2.9)
hsCRP, n	37	74	125	252	73	145	63	125	298	596
Baseline, mg/dL, median (IQR)	0.2 (0.1-0.6)	0.2 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.0-0.2)	0.1 (0.1-0.3)	0.1 (0.1-0.3)
Week 52, mg/dL, n, median (IQR)	32	64	117	226	69	131	58	114	276	535

	0.2	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	(0.1-0.6)	(0.1-0.5)	(0.1-0.4)	(0.1-0.3)	(0.1-0.3)	(0.1-0.3)	(0.1-0.3)	(0.1-0.3)	(0.1-0.3)	(0.1-0.3)
Median % change from baseline at week 52 (IQR)	27.4 (-19 137)	13.1 (-22, 79)	0.7 (-22, 52)	0.0 (-32, 45)	0.9 (-25, 45)	0.0 (-38, 56)	10.2 (-22, 56)	0.0 (-33, 80)	3.2 (-23, 68)	0.0 (-32, 53)

ApoA1=apolipoprotein A1; ApoB=apolipoprotein B; E=evolocumab; HDL-C=high-density lipoprotein-cholesterol; hsCRP=high-sensitivity C-reactive protein; IQR=interquartile range; LDL-C=low-density lipoprotein-cholesterol; Lp(a)=lipoprotein a; P=placebo; PCSK9=proprotein convertase subtilisin/kexin type 9; SD=standard deviation; SE=standard error; IQR=Inter-quartile range; VLDL-C=very low-density lipoprotein-cholesterol.

Supplementary Table S2. Baseline unbound PCSK9 and changes one and four weeks post-administration of study drug

	Evolocumab									
	Diet only		Diet + Atorvastatin 10 mg/d		Diet + Atorvastatin 80 mg/d		Diet + Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
	P	E	P	E	P	E	P	E	P	E
PCSK9 Baseline, n	**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Baseline ng/mL mean (SE)	374.6 (20.4)	319.7 (11.3)	440.7 (11.9)	440.6 (9.2)	553.0 (15.2)	534.3 (13.1)	550.0 (22.6)	578.9 (16.1)	482.6 (9.0)	477.5 (7.0)
PCSK9 1 week post dose										
PCSK9 Week 13, n	**32**	**65**	**121**	**238**	**69**	**132**	**58**	**117**	**280**	**552**
ng/mL mean (SE)	336.7 (21.6)	21.1(7.6)	413.0 (10.7)	24.2 (5.2)	510.5 (16.3)	34.7 (8.4)	528.3 (25.9)	67.4 (14.6)	452.2 (9.3)	35.5 (4.5)
Percent change from baseline, mean % (SE)	–2.1 (6.3)	–91.6 (3.0)	4.5 (5.6)	–94.1 (1.3)	–5.5 (3.3)	–87.6 (6.6)	1.7 (4.9)	–88.7 (2.5)	1.1 (2.9)	–91.1 (1.8)
Absolute change from baseline ng/mL mean (SE)	-33.9 (23.4)	-300.6 (15.1)	-24.8 (13.6)	-419.3 (10.8)	-47.2 (19.0)	-501.1 (15.6)	-14.2 (26.3)	-510.0 (20.2)	-29.2 (9.6)	-444.1 (8.0)
PCSK9 Week 37, n	**32**	**65**	**117**	**234**	**67**	**125**	**55**	**112**	**271**	**536**
ng/mL mean (SE)	339.1 (19.6)	52.0 (15.0)	378.5 (12.0)	52.6 (8.2)	473.3 (15.9)	57.8 (12.9)	502.2 (20.1)	81.0 (15.8)	422.4 (8.8)	59.7 (6.0)
Percent change from baseline, mean % (SE)	-4.1 (5.6)	-84.6 (4.6)	-4.2 (5.1)	-87.1 (2.1)	-11.3 (3.4)	-88.6 (2.5)	-2.8 (4.4)	-86.0 (2.8)	-5.7 (2.6)	-86.9 (1.3)

Absolute change from baseline ng/mL mean (SE)	-38.1 (20.6)	-271.7 (17.3)	-57.8 (15.0)	-385.3 (12.3)	-83.3 (20.7)	-473.8 (18.5)	-47.0 (22.5)	-496.1 (20.9)	-59.6 (9.7)	-415.3 (9.0)
PCSK9 4 weeks post dose										
PCSK9 Week 12, n	**35**	**64**	**115**	**229**	**68**	**127**	**53**	**115**	**271**	**535**
ng/mL mean (SE)	376.1 (21.2)	173.5 (12.9)	425.6 (11.5)	236.1 (6.8)	530.2 (17.3)	304.6 (11.3)	552.3 (26.0)	334.6 (11.4)	470.2 (9.5)	266.1 (5.4)
Percent change from baseline, mean % (SE)	4.6 (4.7)	-45.4 (3.7)	5.3 (5.3)	-42.8 (1.8)	-0.2 (3.3)	-40.9 (2.2)	6.8 (5.5)	-35.9 (3.0)	4.1 (2.7)	-41.2 (1.2)
Absolute change from baseline ng/mL mean (SE)	-1.3 (18.1)	-151.0 (13.8)	-14.1 (13.2)	-209.0 (10.9)	-14.9 (17.3)	-231.2 (14.7)	1.7 (27.2)	-235.1 (17.5)	-9.6 (9.1)	-212.9 (7.2)
PCSK9 Week 24, n	**34**	**67**	**122**	**240**	**70**	**133**	**59**	**116**	**285**	**556**
ng/mL mean (SE)	348.1 (17.7)	166.3 (9.2)	399.3 (11.4)	230.7 (6.6)	482.1 (15.0)	303.9 (8.6)	524.9 (25.4)	365.0 (13.6)	439.5 (9.0)	268.5 (5.4)
Percent change from baseline, mean % (SE)	0.1 (6.0)	-44.4 (4.1)	3.4 (5.6)	-44.1 (1.9)	-10.4 (3.1)	-32.3 (7.7)	-0.8 (4.5)	-30.1 (3.8)	-1.2 (2.8)	-38.4 (2.2)
Absolute change from baseline ng/mL mean (SE)	-27.3 (21.7)	-157.6 (13.5)	-31.0 (15.1)	-214.2 (10.4)	-73.3 (17.6)	-231.4 (15.3)	-26.6 (22.0)	-214.9 (20.0)	-40.1 (9.4)	-211.6 (7.4)
PCSK9 Week 36, n	**27**	**63**	**113**	**219**	**64**	**115**	**53**	**104**	**257**	**501**
ng/mL mean (SE)	304.8 (18.8)	180.1 (14.1)	380.5 (10.8)	231.3 (8.0)	482.7 (19.1)	306 (12.8)	523.6 (26.2)	339.3 (14.1)	427.5 (9.9)	264.4 (6.2)
Percent change from baseline, mean % (SE)	-5.5 (8.3)	-40.0 (4.7)	-0.3 (6.3)	-43.5 (2.3)	-10.8 (3.9)	-33.5 (6.5)	-5.2 (4.2)	-32.0 (5.7)	-4.5 (3.2)	-38.4 (2.2)
Absolute change from baseline ng/mL mean (SE)	-54 (26.9)	-140.8 (18.1)	-48.2 (14.9)	-211.7 (11.8)	-75.5 (21.1)	-226.6 (18.4)	-42.0 (20.9)	-224.5 (18.9)	-54.3 (9.8)	-208.8 (8.1)
PCSK9 Week 52, n	**32**	**64**	**116**	**224**	**68**	**131**	**58**	**114**	**274**	**533**

ng/mL mean (SE)	322.7 (19.0)	169.1 (12.0)	387.5 (11.2)	216.3 (7.8)	483.5 (15.8)	269.9 (7.8)	531.4 (25.7)	357.2 (12.1)	434.2 (9.5)	253.9 (5.5)
Percent change from baseline, mean % (SE)	–5.6 (6.6)	–44.8 (4.1)	–1.2 (5.5)	–47.9 (2.0)	–10.4 (3.5)	–42.2 (5.0)	–0.3 (4.3)	–30.7 (4.3)	–3.8 (2.8)	–42.5 (1.8)
Absolute change from baseline ng/mL mean (SE)	-51.4 (25.9)	-156.8 (16.3)	-42.6 (13.8)	-229.8 (11.4)	-76.6 (20.2)	-264.2 (13.7)	-21.8 (21.9)	-220.0 (18.5)	-47.7 (9.5)	-227.4 (7.4)

*PCSK9 levels measured during these visits could be considered "trough" levels.

†PCSK9 levels measured during these visits could be considered "maximal suppression." Please see text for details.

E=evolocumab; P=placebo; PCSK9=proprotein convertase subtilisin/kexin type 9; SD=standard deviation; SE=standard error.

Supplementary Table S3. Summary of treatment emergent adverse events by treatment group

	Evolocumab									
	Diet only		Diet + Atorvastatin 10 mg/d		Diet + Atorvastatin 80 mg/d		Diet + Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
	P	E	P	E	P	E	P	E	P	E
N	37	74	129	254	73	145	63	126	302	599
Patients with adverse events, n (%)	30 (81.1)	52 (70.3)	101 (78.3)	201 (79.1)	54 (74.0)	111 (76.6)	39 (61.9)	84 (66.7)	224 (74.2)	448 (74.8)
Any										
Serious, n (%)	3 (8.1)	1 (1.4)	1 (0.8)	13 (5.1)	3 (4.1)	11 (7.6)	6 (9.5)	8 (6.3)	13 (4.3)	33 (5.5)
Leading to discontinuation of study drug, n (%)	0 (0.0)	1 (1.4)	1 (0.8)	8 (3.1)	1 (1.4)	3 (2.1)	1 (1.6)	1 (0.8)	3 (1.0)	13 (2.2)
Adjudicated events	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	2 (1.4)	2 (3.2)	2 (1.6)	2 (0.7)	6 (1.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Common adverse events[+], n (%)										
Nasopharyngitis	3 (8.1)	11 (14.9)	9 (7.0)	29 (11.4)	10 (13.7)	13 (9.0)	7 (11.1)	10 (7.9)	29 (9.6)	63 (10.5)
Upper respiratory tract infection	4 (10.8)	6 (8.1)	7 (5.4)	22 (8.7)	2 (2.7)	15 (10.3)	6 (9.5)	13 (10.3)	19 (6.3)	56 (9.3)
Influenza	2 (5.4)	5 (6.8)	8 (6.2)	18 (7.1)	2 (2.7)	8 (5.5)	7 (11.1)	14 (11.1)	19 (6.3)	45 (7.5)

Back pain	2 (5.4)	2 (2.7)	8 (6.2)	17 (6.7)	5 (6.8)	7 (4.8)	2 (3.2)	11 (8.7)	17 (5.6)	37 (6.2)
Liver function tests										
ALT or AST > 3 × ULN*	1 (2.7)	0 (0.0)	0 (0.0)	1 (0.4)	2 (2.7)	1 (0.7)	0 (0.0)	3 (2.4)	3 (1.0)	5 (0.8)
ALT or AST > 5 × ULN*	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.6)	1 (0.3)	3 (0.5)
Muscle										
Myalgia	1 (2.7)	1 (1.4)	3 (2.3)	14 (5.5)	5 (6.8)	3 (2.1)	0 (0.0)	6 (4.8)	9 (3.0)	24 (4.0)
CK > 5 × ULN*	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	1 (1.4)	1 (0.7)	0 (0.0)	4 (3.2)	1 (0.3)	7 (1.2)
CK > 10 × ULN*	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.4)	1 (0.7)	0 (0.0)	1 (0.8)	1 (0.3)	3 (0.5)
Injection site reactions**	2 (5.4)	4 (5.4)	9 (7.0)	20 (7.9)	3 (4.1)	5 (3.4)	1 (1.6)	5 (4.0)	15 (5.0)	34 (5.7)
Glycemia										
Glucose, change from baseline at week 52 (mmol/L); n mean (SE)	31 0.05 (0.08)	63 –0.03 (0.08)	117 0.06 (0.07)	225 0.09 (0.07)	68 –0.10 (0.09)	131 0.01 (0.06)	57 0.08 (0.16)	114 0.14 (0.11)	273 0.02 (0.05)	533 0.07 (0.04)
HbA1C, change from baseline at week 52 (%); n, mean (SE)	30 –0.06 (0.05)	64 –0.09 (0.04)	117 0.04 (003)	227 0.04 (0.02)	68 –0.10 (0.06)	129 -0.02 (0.03)	58 0.05 (0.07)	115 0.09 (0.04)	273 0.00 (0.03)	535 0.02 (0.02)

*At any post-baseline visit

** Potential Events identified Using Broad Search Strategy. Event categories are defined using preferred terms (PT) from MedDRA and either Standard MedDRA Queries (SMQ) or internal groupings

+ preferred term reported in ≥5% patients in either group.

$Preferred Terms for the 2 Treatment Emergent deaths were Cardiac failure and Myocardial infarction

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CK=creatine kinase; E=Evolocumab; HbA1C=hemoglobin A1c; P=Placebo;

SD=standard deviation; ULN=upper limit of normal; SE=standard error

Supplementary Table S4. Summary of all treatment-emergent serious adverse events*

Preferred Term	Diet only		Diet + Atorvastatin 10 mg/		Diet + Atorvastatin 80 mg/d		Diet + Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
	P	**E**	**P**	**E**	**P**	**E**	**P**	**E**	**P**	**E**
n	**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Number of subjects reporting TE serious AEs	3 (8.1)	1 (1.4)	1 (0.8)	13 (5.1)	3 (4.1)	11 (7.6)	6 (9.5)	8 (6.3)	13 (4.3)	33 (5.5)
Angina pectoris	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	2 (3.2)	1 (0.8)	2 (0.7)	2 (0.3)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.3)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Atrial fibrillation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)
Sinus bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Vertigo positional	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Exotosis of external	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

ear										
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Hemorrhoids	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Device breakage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Chest pain	0 (0.0	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Biliary tract disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cholelithiasis	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Skin infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Joint injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)
Multiple fractures	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Overdose	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Road traffic accident	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Skull fracture	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Aspartate aminotransferase	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

increased										
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic enzyme increased	1 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hypomagnesemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.3)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Spinal osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Ovarian cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Renal neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Uterine cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Migraine with aura	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Convulsion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)
Peripheral sensory neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)
Ovarian cyst	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	2 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)	2 (0.3)
Asthma	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Pleurisy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Breast prosthesis implantation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)

*Serious adverse events reported in 13 (4.3%) patients in the combined placebo group and 33 (5.5%) patients in the combined evolocumab groups

patients could experience >1 serious adverse event

E=evolocumab; P=placebo; TE=Treatment Emergent; AE=Adverse Events

Supplementary Table S5. Summary of treatment-emergent adverse events leading to discontinuation of study drug*

Preferred Term	Diet only		Diet + Atorvastatin 10 mg/		Diet + Atorvastatin 80 mg/d		Diet + Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
	P	E	P	E	P	E	P	E	P	E
n	37	74	129	254	73	145	63	126	302	599
Number of subjects reporting TEAEs leading to discontinutation	0 (0.0)	1 (1.4)	1 (0.8)	8 (3.1)	1 (1.4)	3 (2.1)	1 (1.6)	1 (0.8)	3 (1.0)	13 (2.2)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site erythema	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site pruritus	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Injection site Swelling	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Injection site Urticaria	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Polymyalgia rheumatica	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Clear cell renal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Ovarian cancer metastatic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.2)
Migraine	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Transient ischemic attack	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Skin odor abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (0.3)	0 (0.0)

*Adverse events leading to discontinuation of study drug reported in 3 (1.0%) patients in the combined placebo group and 13 (2.2%) patients in the combined evolocumab groups

patients could experience >1 event leading to discontinuation

E=evolocumab; P=placebo. TEAE=Treatment Emergent Adverse Events

Supplementary Table S6. Summary of patients with at least one potential injection-site reaction and type of reaction

	Diet only		Atorvastatin 10 mg/		Atorvastatin 80 mg/d		Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
	P	**E**	**P**	**E**	**P**	**E**	**P**	**E**	**P**	**E**
n	37	74	129	254	73	145	63	126	302	599
Injection-site reaction*	2 (5.4)	4 (5.4)	9 (7.0)	20 (7.9)	3 (4.1)	5 (3.4)	1 (1.6)	5 (4.0)	15 (5.0)	34 (5.7)
Erythema	1 (2.7)	4 (5.4)	4 (3.1)	9 (3.5)	1 (1.4)	1 (0.7)	0 (0.0)	2 (1.6)	6 (2.0)	16 (2.7)
Pain	1 (2.7)	0 (0.0)	2 (1.6)	5 (2.0)	1 (1.4)	2 (1.4)	0 (0.0)	1 (0.8)	4 (1.3)	8 (1.3)
Bruising	0 (0.0)	0 (0.0)	5 (3.9)	3 (1.2)	1 (1.4)	2 (1.4)	0 (0.0)	2 (1.6)	6 (2.0)	7 (1.2)
Swelling	0 (0.0)	1 (1.4)	2 (1.6)	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	6 (1.0)
Induration	0 (0.0)	1 (1.4)	0 (0.0)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	5 (0.8)
Pruritus	1 (2.7)	1 (1.4)	1 (0.8)	2 (0.8)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	3 (0.5)
Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Nodule	1 (2.7)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.2)
Urticaria	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

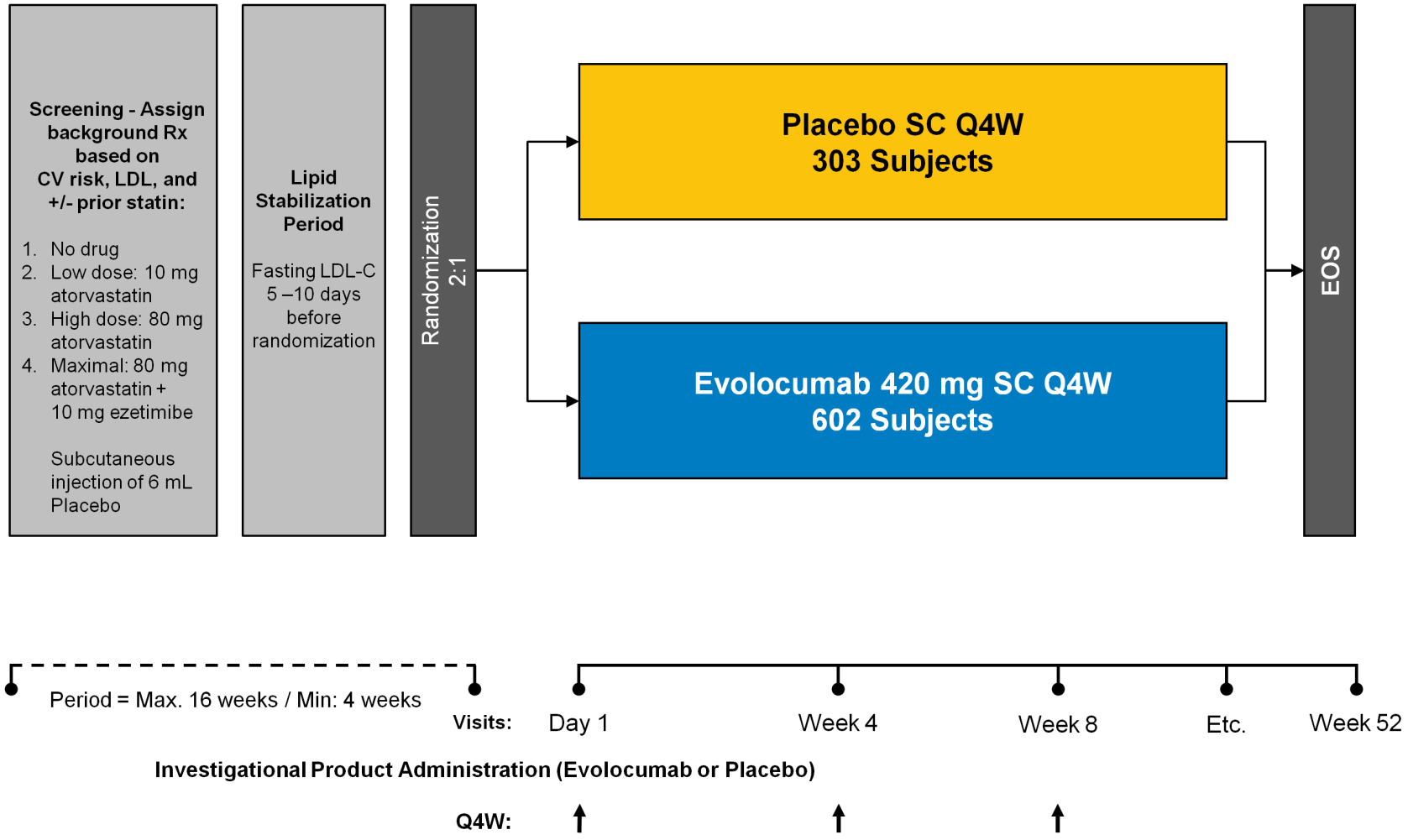
*Patients can experience multiple injection-site reactions. E=evolocumab; P=placebo.

Supplementary Table S7. Anti-evolocumab antibodies

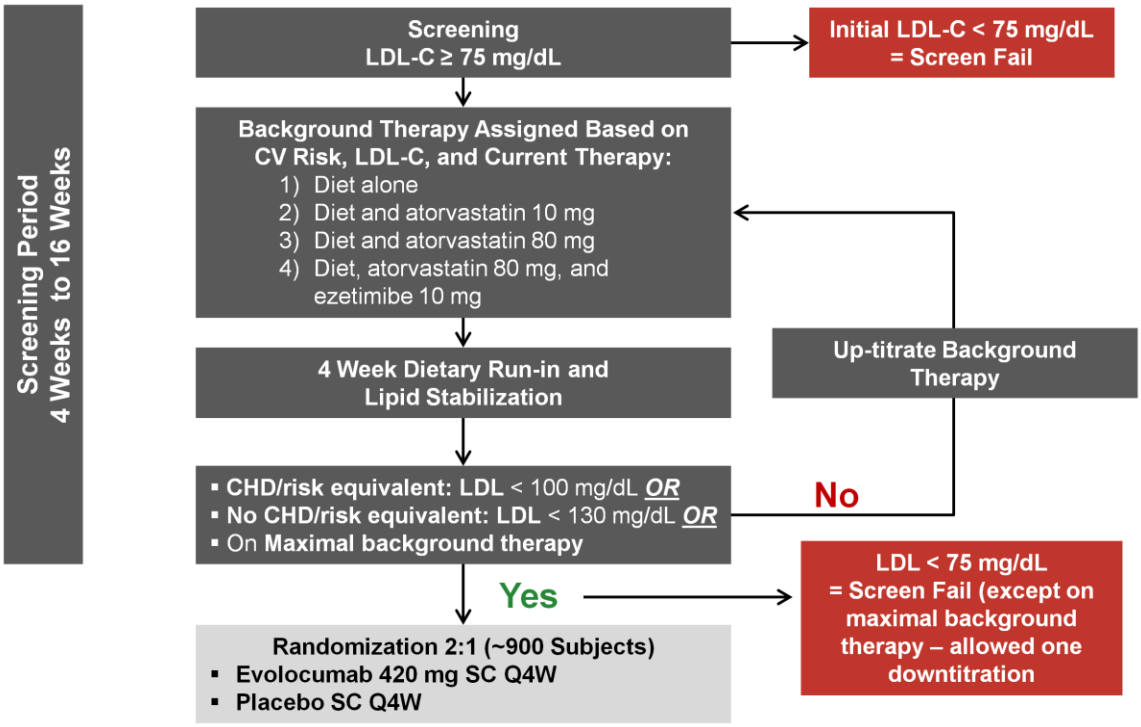
		Diet only		Atorvastatin 10 mg/d		Atorvastatin 80 mg/d		Atorvastatin 80 mg/d + Ezetimibe 10 mg/d		All	
		P	**E**	**P**	**E**	**P**	**E**	**P**	**E**	**P**	**E**
n		**37**	**74**	**129**	**254**	**73**	**145**	**63**	**126**	**302**	**599**
Binding Antibodies, n (%)	Subjects with baseline result	37	74	128	251	73	143	63	125	301	593
	Detectable antibody at or before baseline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.3)
	Subjects with newly detectable post-baseline result	35	71	127	252	73	138	62	124	297	585
	Antibody newly detected during treatment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
	Transient antibody during treatment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Neutralizing antibodies, n (%)	Subjects with baseline result	37	74	128	251	73	143	63	125	301	593
	Detectable antibody at or before baseline	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Subjects with newly detectable post-baseline result	35	71	127	252	73	138	62	124	297	585
	Antibody newly detected during treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Transient antibody during treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

E=evolocumab; P=placebo.

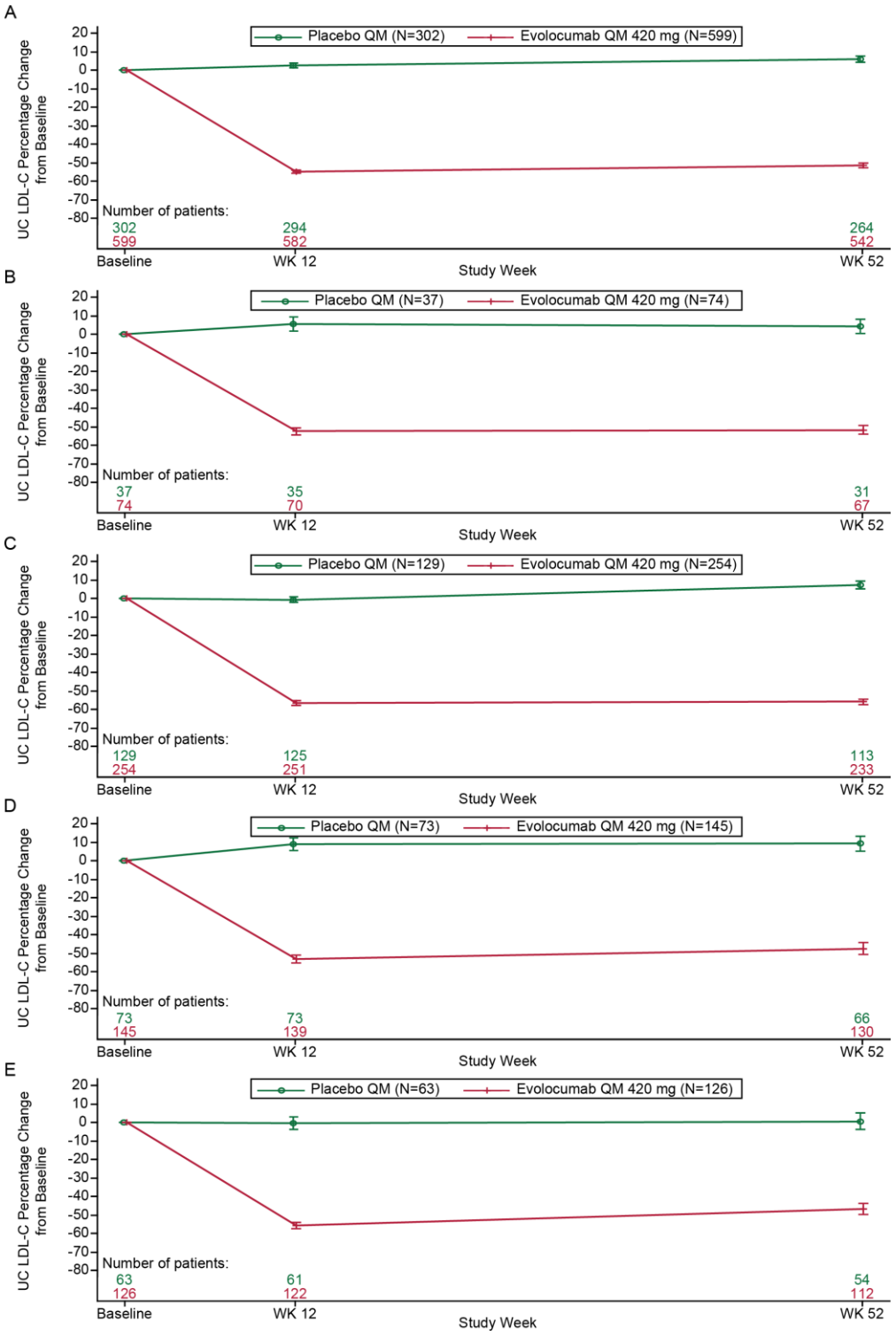
Supplementary Figure S1. Study Design and Treatment Schema.



Supplementary Figure S2. Flow diagram: Lipid stabilization and Titration Phase.

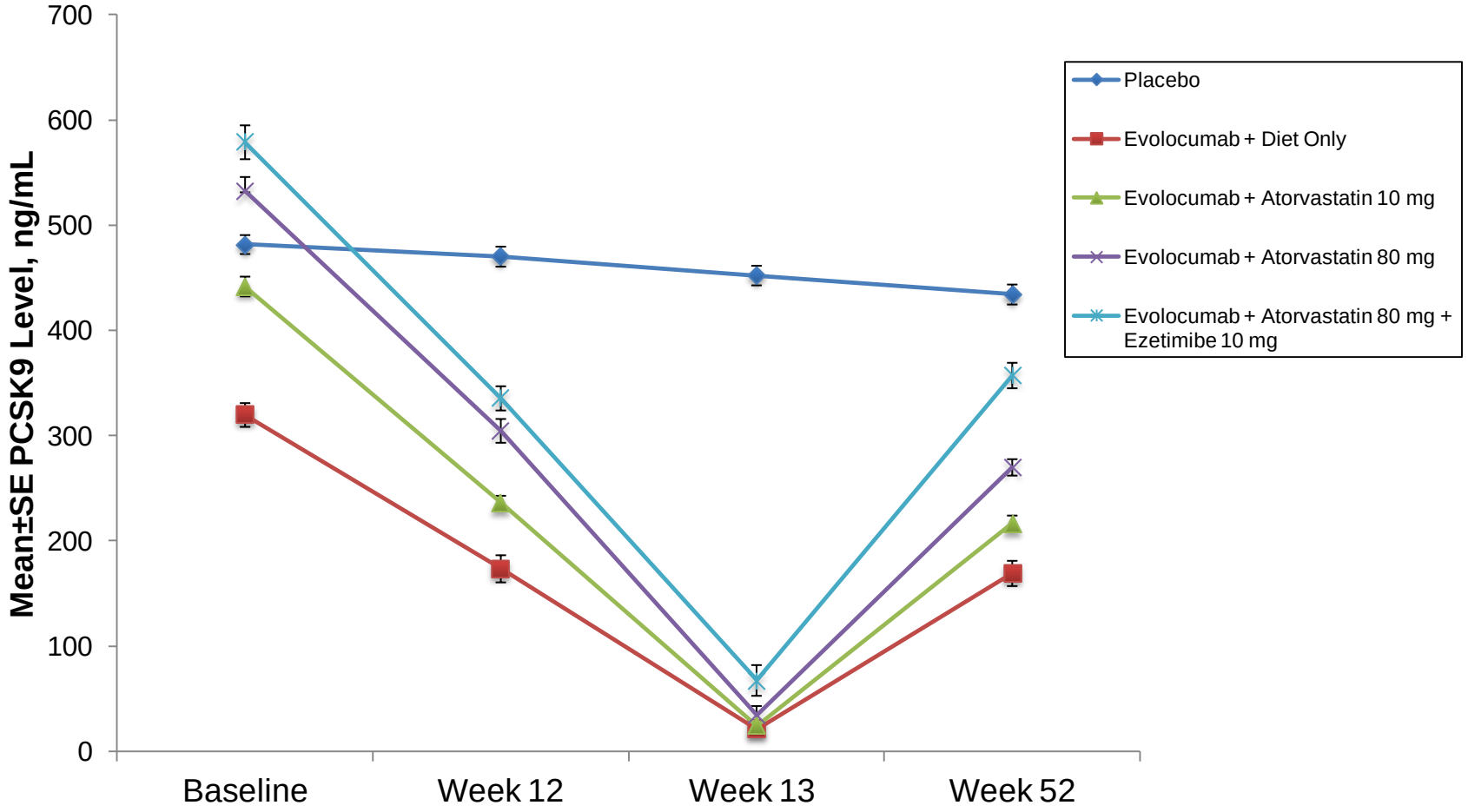


Supplementary Figure S3. Mean percent change (±SE) for evolocumab and placebo groups from baseline in ultracentrifugation LDL cholesterol by scheduled visit



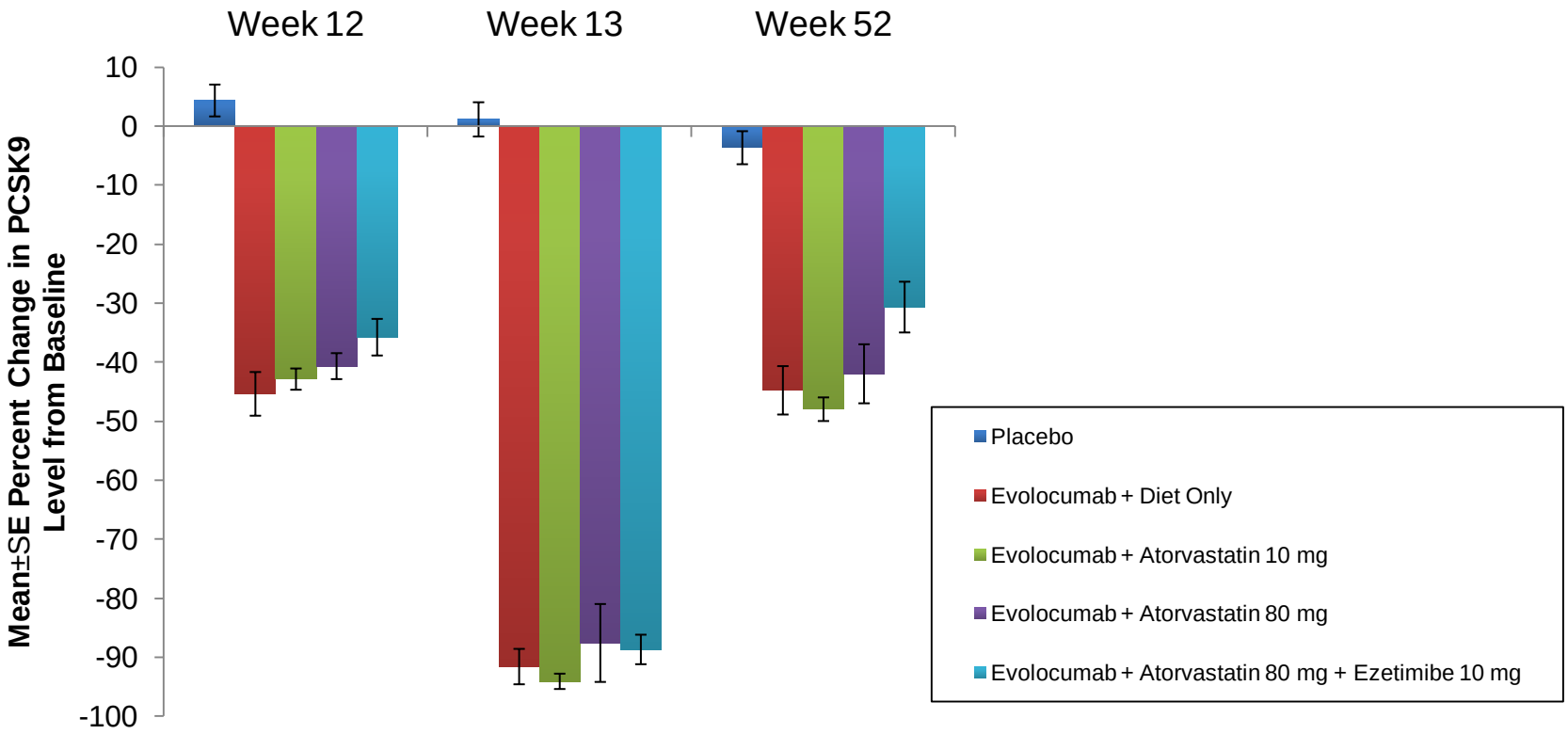
Panel A: All patients
Panel B: Diet-only
Panel C: Atorvastatin 10 mg
Panel D: Atorvastatin 80 mg
Panel E: Atorvastatin 80 mg plus ezetimibe 10 mg s
LDL-C=Low-density lipoprotein cholesterol; UC= ultracentrifugation

Supplementary Figure S4. Mean PCSK9 levels at baseline and at weeks 12, 13, and 52 by treatment group



Week 12 and 52=4 weeks post last injection of study drug; week 13= 1 week post last injection of study drug
PCSK9=proprotein convertase subtilisin/kexin type 9

Supplementary Figure S5. Mean percent change in PCSK9 levels from baseline at weeks 12, 13, and 52 by treatment group



Week 12 and 52=4 weeks post last injection of study drug; week 13= 1 week post last injection of study drug
PCSK9=proprotein convertase subtilisin/kexin type 9