Effect of the Proprotein convertase subtilisin/kexin type 9 inhibitor Evolocumab on Glycemia, Body Weight, and new-onset Diabetes Mellitus

Running title: evolocumab, new-onset diabetes and related traits

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Abstract (229 words)

Statin therapy modestly increases new-onset diabetes risk. The effect of PCSK9 inhibition on new-onset diabetes, glycemia and weight remains unclear.We studied the effects of the PCSK9 inhibitor evolocumab on fasting plasma glucose [FPG], glycated hemoglobin (HbA1c), weight and new-onset diabetes mellitus. We pooled 1-year (48-week) data for participants who had completed an evolocumab parent study before entering an open-label extension (OLE) trial. Data were available for 4,802 participants (1,602 on standard of care [SOC]; 3,200 on evolocumab plus SOC) in 2 OLE trials. Evolocumab lowered LDL-cholesterol by approximately 60% compared to SOC alone. Over the first year of the OLE trials, there was no difference in median (Q1, Q3) change in HbA_{1c} (0.1% [–0.1, 0.2] for both SOC and evolocumab plus SOC) and FPG (0.06mmol/L [–0.28, 0.38 mmol/L] for SOC and 0.06mmol/L [–0.28, 0.44 mmol/L] for evolocumab plus SOC). Mean weight change (standard error) at 1 year was –0.1kg (0.2) on SOC compared to 0.3kg (0.1) on evolocumab plus SOC. The exposure-adjusted incidence rate (95% confidence intervals) for new-onset diabetes per 100 patient years was 3.7 (2.9-4.7) on control/SOC alone and 3.9 (3.2-4.6) on evolocumab/evolocumab plus SOC treatment. Glycemic changes observed in 6,430 participants at week 12 in the parent studies were comparable to OLE trial findings. In conclusion, evolocumab therapy has no effect on glucose homeostasis over 1 year of open-label treatment.

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Key words: PCSK9, evolocumab, new-onset diabetes, glucose, HbA1c

Evidence from both randomized clinical trials and studies of genetic polymorphisms demonstrates that lowering LDL-cholesterol lowers the risk of cardiovascular events[1]. While statin therapy is effective and safe, an adverse effect that has emerged in meta-analyses of major trials and studies of genetic polymorphisms is a modest increase in glycated hemoglobin (HbA_{1c}) levels and the risk of developing diabetes[2,3]. It remains unclear whether this effect reflects the specific mechanism of action of a statin or whether other approaches to lowering LDL-cholesterol have the same diabetogenic effect[4,5].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a circulating protein of predominantly hepatic origin that reduces the efficacy of hepatic LDL-receptor recycling [6,7]. Twelve-week clinical trials of the monoclonal antibody PCSK9 inhibitor, evolocumab, have demonstrated reductions in LDL-cholesterol of around 60% [8,9]. Two placebo-controlled clinical trials have also confirmed a reduction in cardiovascular events by PCSK9 inhibition.

Results from a single study of 901 participants suggest that evolocumab has no notable effect on measures of glycemia and beta cell function[12] and, in recently published data from the FOURIER trial, there was no effect of evolocumab on new-onset diabetes compared to placebo over 2.2 years[10]. However, genetic findings indicate that PCSK9 variants associated with lower LDL-cholesterol do increase risk of developing diabetes[14-16]. We therefore examined the effect of evolocumab therapy over 1 year in 2 open-label extension (OLE) studies to determine if this agent has any notable effect on measures of glycemic control, weight, or new-onset diabetes. These 2 OLE studies enrolled participants who had previously completed a qualifying evolocumab parent study.

Methods

Thirteen parent trials[17-28] fed into the 2 ongoing open-label extension (OLE) randomized controlled trials, OSLER-1 and OSLER-2[29] (see **Supplementary Table 1**). Eleven out of the 13 parent studies were randomized trials that compared evolocumab to

placebo or ezetimibe (one was a 52-week trial[21] while the remaining 10 were 12-week trials). In the other 2 parent studies (6 weeks and 12 weeks), participants only received evolocumab.

At the end of the parent trials, participants had the option to continue into an OLE trial. Those who opted to do so were randomized in a 2:1 ratio to evolocumab plus standard of care (SOC) or to SOC alone for the first year of the OLE trial without regard to treatment allocation in the parent trial. Analyses of the OLE trials were limited to the first year; following the first year, all randomized participants were offered open-label evolocumab for the remainder of the study. In these OLE trials, background statin therapy could vary as determined by the treating physician. Participants from the parent trials plus the OLE trials provided written informed consent and the trials were approved by all relevant ethics committees and regulatory bodies. Key eligibility criteria for the parent and OLE trials, including specific exclusion criteria related to diabetes, are provided in **Supplementary Table 1**. For the parent trials, the safety population was defined as all randomized participants who received at least 1 dose of study drug. For the OLE trials, the safety population was defined as all randomized participants. Randomization sequences were generated by computer for the trials by the sponsor, Amgen. In OSLER-1, randomization was stratified by treatment arm in the parent study, while in OSLER 2 it was stratified by parent study and frequency of subcutaneous dosing. Each trial was overseen by an independent data monitoring committee.

The main purpose of this analysis was to investigate the effect of 1-year of open-label evolocumab compared to control therapy on glycemia, body weight, and new-onset diabetes mellitus. Evolocumab was administered by subcutaneous injection either in the clinic or by self-administration at the participant's home. All participants entering an OLE study were randomized to receive either evolocumab plus SOC or SOC alone in a 2:1 ratio. Evolocumab was administered at a dose of 420 mg once a month in OSLER-1 and, based on participant choice, at a dose of either 140 mg every 2 weeks or 420 mg once a month in OSLER-2. The

2 regimens have been shown to be clinically equivalent. Lipid data from biweekly and monthly dosing regimens for evolocumab were similar and were therefore pooled in this analysis. Blood samples were taken at baseline, 12, 24 and 48 weeks to measure fasting (>9 hours) lipids, FPG and HbA1c at a central laboratory (Medpace Reference Laboratories, Cincinnati, USA and Leuven, Belgium). LDL-cholesterol was determined by the Friedewald formula (LDL-cholesterol [mmol/L] = total cholesterol [mmol/L] – HDL-cholesterol [mmol/L] – triglycerides [mmol/L]/2.2). In OSLER-1 weight was measured at baseline and 52 weeks whereas in OSLER-2 weight was measured at baseline and 48 weeks.

To determine if there was any confounding due to parent-study effects, changes in glycemia were examined over the parent-study period in the parent trials of evolocumab. We also compared participants who did or did not enrol in an OSLER trial following completion of a parent study to rule out differences and possible confounding. The methodology applied in the parent trials was very similar to the approach taken in the OLE trials (see **Supplementary information**).

T2DM at baseline was defined as medical history of diabetes, baseline HbA_{1c} ≥6.5% (48 mmol/mol), baseline fasting plasma glucose ≥7.0 mmol/L, or use of medication for T2DM. New-onset T2DM during follow-up was defined as any of the following: a diabetes adverse event (AE), at least a single HbA1c ≥6.5% (48 mmol/mol), 2 consecutive fasting plasma glucose values ≥7.0 mmol/L, or newly commenced use of medication for an indication of T2DM. High risk of diabetes was defined as impaired fasting glycemia (i.e. FPG 6.1–6.9mmol/L) or HbA1c ≥6.0% at baseline, and not meeting the criteria for T2DM.

Baseline laboratory values for variables of interest in the OLE trials were taken from the baseline values in the parent trials. Continuous variables are presented as mean (standard deviation) or median (25^{th}, 75^{th} percentiles), as appropriate. Percent change in LDL-cholesterol was calculated for each subject as 100* (week 48 – baseline) / baseline. The mean

percent change in LDL-cholesterol was calculated across trials without modelling. Changes in weight, FPG and HbA_{1c} were compared between those randomized to evolocumab plus SOC and those randomized to SOC alone in the OLE trials. Safety analyses were conducted using descriptive statistics. Descriptive statistics were provided for absolute values as well as changes from baseline in laboratory parameters. Parent studies and the analysis reported here were not powered for safety endpoints; therefore, AEs and safety measures are summarized descriptively without inferential statistical analyses (or corresponding P values). Comparisons were made between all participants in each treatment arm and also for the following subgroups: those with diabetes, those without diabetes and those at high risk of diabetes.

In supportive analyses we compared the effect of evolocumab to control therapy at 12 weeks in the parent studies. Given the possibility that there may have been bias in progression from parent trials to OLE trials based on randomized treatment in the parent trial, we performed a sensitivity analysis to determine whether there were differences between participants who did or did not enrol in an OSLER trial following a parent study.
We also calculated the exposure-adjusted incidence rate per 100 patient years for new onset diabetes, from randomization in the parent trials until the end of year 1 in the OLE trials. Data were analysed using SAS version 9.3. Amgen funded the parent trials and OLE trials, which were designed in collaboration with each trial's investigators. The lead co-authors (N.S., P.P.T. and D.P.) proposed the study and developed the analyses in collaboration with co-authors M.E. and R.S. Amgen was responsible for data collection and analysis.

Results

There were 6,430 participants in the parent trials (4,148 participants randomized to evolocumab and 2,282 to control therapy). Baseline characteristics for participants in the parent trials are provided in **Supplementary Table 2**. Of the 6,430 participants in the parent trials, 4,802 (75% consisting of 1,602 participants randomized to SOC and 3,200 to

evolocumab plus SOC) enrolled in an OLE trial. For these participants at baseline, median HbA1c was 5.6% for SOC and 5.6% for evolocumab; median FPG was 5.4mmol/L for SOC alone and 5.4mmol/L for evolocumab; and 18.0% (SOC) and 17.6% (evolocumab) had diabetes respectively (**Table 1**). Mean LDL-cholesterol was 3.3mmol/L for SOC and 3.3mmol/L for evolocumab plus SOC. Evolocumab plus SOC lowered LDL-cholesterol by 50-60% over 48 weeks (**Table 2** and **Figure 1A**) compared with SOC alone.

Pooled data at 12, 24 and 48 weeks is presented for FPG in **Figure 1B** and for HbA_{1c} in **Figure 1C**. Change in median HbA1c was identical over 48 weeks in both treatment arms, namely 0.1%. Change in median FPG was also very similar between treatment arms over 48 in the analysis of all participants: 0.06mmol/L on evolocumab plus SOC compared to 0.06mmol/L on SOC alone. Subgroup analyses for those with diabetes, without diabetes and at high risk of diabetes were consistent with this lack of effect (**Table 2**). Results at week 12 in a pooled analysis of the 13 parent studies feeding into the OLE trials were consistent with the 1 year OLE results (**Supplementary Table 3).** There was also no difference in change in FPG or HbA1c during the parent trials for those who did (n=4,802) or did not (n=1,628) subsequently proceed from a parent trial into an OLE trial (**Supplementary Table 3**).

Mean weight change during the OLE trials was 0.3kg on evolocumab plus SOC over 48-52 weeks compared with –0.1kg on SOC alone in an analysis of all participants (**Table 2**). In those with diabetes, mean weight change was –0.4kg in participants with evolocumab plus SOC and –0.6kg in participants receiving SOC alone. In participants without diabetes, mean weight change was 0.4kg in participants with evolocumab plus SOC, and was 0.0kg in participants on SOC alone). In participants at high risk for diabetes, mean change in weight was 0.1kg in participants on evolocumab and 0.2kg in participants on SOC alone.

Of those without diabetes at parent-study baseline, the exposure-adjusted incidence of new-onset diabetes per year was 3.85 cases per 100 patient-years on evolocumab/evolocumab plus SOC treatment and 3.69 cases per 100 patient-years on control/SOC alone (**Table 3**).

Discussion

While statins modestly increase the risk of developing diabetes mellitus and recent genetic data suggest a potential link between PCSK9 genes and diabetes risk[14], we demonstrate that 1 year of treatment with evolocumab in an OLE setting does not increase HbA1c, fasting glucose or diabetes risk in comparison to SOC. We also provide novel data for weight change and these results are also broadly reassuring. These results in conjunction with randomized data for evolocumab from the FOURIER[10] and DESCARTES trials[12], for alirocumab from the ODYSSEY program[13], and for bococizumab from the SPIRE trials[11] suggest PCSK9 inhibition is unlikely to have any clinically relevant effect on glycemia.

A recently published analysis that combined information from several PCSK9 polymorphisms suggested a potentially causal link between PCSK9 inhibition and diabetes risk[14]. The same publication also linked polymorphisms in the *NPC1L1* gene (related to ezetimibe therapy) with increased diabetes risk, implying that multiple LDL-cholesterol reducing pathways may enhance diabetes risk, a hypothesis reinforced by genetic analyses of LDL-cholesterol and diabetes risk[5]. Even when causative relationships are identified, extrapolation to what size of effects may be seen with therapeutic interventions (in this case PCSK9 inhibition with monoclonal antibodies) is problematic given that genetic effects are present throughout the lifespan and drug effects may not fully or precisely influence the pathways influenced by genes. This reinforces the need for randomized clinical trials of an intervention to reliably confirm or refute any impact on an outcome of interest. Recently published data from major cardiovascular outcome trials have confirmed that PCSK9 inhibition translates into a reduction in cardiovascular events in high risk patients and that the

benefit is comparable to observations from the major statin trials[10,11]. In addition, these trials have shown no effect of PCSK9 inhibitors on new-onset diabetes, though follow-up was relatively short. The SPIRE trials revealed a small increase in fasting glucose at 1 year but no change in HbA1c. Taken together, data from these trials together with findings in this report are thus reassuring and they effectively rule out any clinically significant medium-term effect of PCSK9 inhibition on measures of glycemia and new-onset diabetes risk. Participants in the evolocumab plus SOC group had a slight increase in weight; however, when we examined subgroups, we found that these changes were driven mostly by participants without diabetes and not at high risk for diabetes. As the OSLER studies were open-label trials where patients and their physicians saw on-label treatment LDL-cholesterol levels, we cannot exclude that a reduction in LDL-C led to more liberal caloric intake by patients receiving evolocumab.

We acknowledge several limitations in our analysis. First, in the OLE trials evolocumab was compared to SOC rather than placebo. Nevertheless, given the potency of LDL-cholesterol reduction with evolocumab along with analysis of objectively measured outcomes, our analyses should be robust. The trials were also relatively short and we therefore acknowledge that we cannot rule out longer-term effects on glycemia. Reassuringly, however, the modest effect of statins on glycemia in patients with diabetes appears most obvious within the first year with little if any deterioration thereafter[30]. Furthermore, length of exposure to evolocumab during the parent-study phase differed between participants, due to both parent-study treatment assignment and parent-study length. We acknowledge that the number of cases of new-onset diabetes was relatively small in our study compared to the FOURIER trial; however, the current results provide detailed information for glycemia and weight for evolocumab not available elsewhere. Finally, our work represents a *post hoc* analysis.

In summary, treatment with evolocumab in a 1-year, OLE setting had no apparent effect on glucose homeostasis.

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Author contributions: D.P., N.S. and P.P.T. conceived the study and, along with R.S. and M.E., contributed to the study design. R.S. obtained funding for the study. M.E. conducted the statistical analyses. D.P., N.S., R.S., M.U., M.E., P.T., D.B., M.K., H.S., and M.C. contributed to interpretation of the data. D.P. wrote the first draft of the manuscript, and all authors contributed to its revision. All authors affirm that they meet ICMJE criteria for publication of this report.

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Figure Legends:

Figure 1. The effect of open-label evolocumab with standard care versus standard care alone on (A) LDL-cholesterol (B) fasting plasma glucose, and (C) HbA1c for up to 48 weeks. Error bars indicate 1 standard error.

Footnote: Abbreviations: EOS: end of study; Evo, evolocumab; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; SE, standard error; SOC, standard of care

Table 1. Baseline demographics for patients entering 48-week OSLER studies*

Variable	SOC Alone (N = 1602)	Evolocumab + SOC (N = 3200)
Age (years), mean (SD)	58.4 ± 10.9	58.0 ± 11.0
Men	831 (51.9%)	1629 (50.9%)
White	1267 (79.1%)	2559 (80.0%)
Asian	236 (14.7%)	455 (14.2%)
Black/African American	72 (4.5%)	135 (4.2%)
Other race	27 (1.7%)	51 (1.6%)
Hypertension	857 (53.5%)	1711 (53.5%)
Type 2 diabetes mellitus†	289 (18.0%)	563 (17.6%)
High risk of diabetes‡	494 (30.8%)	1023 (32.0%)
Current smoker	248 (15.5%)	520 (16.3%)
Coronary artery disease**	319 (19.9%)	610 (19.1%)
Cerebrovascular or peripheral arterial disease	156 (9.7%)	291 (9.1%)
LDL-cholesterol (mmol/L)	3.3 ± 1.2	3.3 ± 1.1
LDL-cholesterol (mg/dL)	127.0 ± 44.9	126.3 ± 44.3
Hemoglobin-A1c (%)§‖	5.6 (5.3, 5.9)	5.6 (5.3, 6.0)
Fasting plasma glucose (mmol/L)§	5.4 (5.1, 5.9)	5.4 (5.1, 5.9)
Fasting plasma glucose (mg/dL)§	98.0 (91.0, 107.0)	98.0 (91.0, 107.0)

SOC: standard of care
Data shown as mean ± SD, or count (%)
* Parent-study baseline
† Defined as previously known T2DM, on glucose-lowering medication, baseline FPG ≥7.0 mmol/L or baseline HbA1c ≥6.5%
**History of angina, myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention
‡ Impaired fasting glucose (i.e. fasting plasma glucose 6.1–6.9mmol/L) or HbA1c ≥6.0% at baseline, and not meeting the criteria for T2DM
§ Median (Q1, Q3)
‖ Available for 1327 participants assigned to SOC alone and 2685 assigned to evolocumab + SOC

Table 2. Changes in Low Density Lipoprotein-cholesterol, fasting plasma glucose, Hemoglobin-A1c and weight over 48-52 weeks in the OSLER-1 and OSLER-2 trials

	Visit	LDL-C in mmol/L (baseline: mean (SD) [n]; wk 48 and change: mean (SE) [n])		Fasting plasma glucose in mmol/L (median (Q1, Q3) [n])		HbA1c in % (median (Q1, Q3) [n])		Weight in kg (baseline: mean (SD) [n]; wk 48 and change: mean (SE) [n])	
		SOC	**EvoMab + SOC**	**SOC**	**EvoMab + SOC**	**SOC**	**EvoMab + SOC**	**SOC**	**EvoMab + SOC**
All	Baseline	3.3 ± 1.2 [1602]	3.3 ± 1.1 [3200]	5.4 (5.1, 5.9) [1602]	5.4 (5.1, 5.9) [3200]	5.6 (5.3, 5.9) [1327]	5.6 (5.3, 6.0) [2685]	83.1 ± 18.3 [1274]	83.0 ± 17.8 [2521]
	Week 48*	3.4 ± 0 [1219]	1.5 ± 0 [2508]	5.5 (5.1, 6.0) [1261]	5.5 (5.1, 6.0) [2561]	5.6 (5.4, 5.9) [1260]	5.6 (5.4, 5.9) [2555]	83.0 ± 0.5 [1274]	83.3 ± 0.4 [2521]
	Change to Week 48*	0 ± 0 [1219]	-1.8 ± 0 [2508]	0.1 (-0.3, 0.4) [1261]	0.1 (-0.3, 0.4) [2561]	0.1 (-0.1, 0.2) [1017]	0.1 (-0.1, 0.2) [2079]	-0.1 ± 0.2 [1274]	0.3 ± 0.1 [2521]
Diabetes	Baseline	3.0 ± 1.0 [289]	3.0 ± 0.9 [563]	6.9 (6.0, 8.2) [289]	6.9 (5.9, 7.9) [563]	6.5 (6.1, 7.1) [278]	6.5 (6.1, 7.1) [542]	89.3 ± 21.1 [198]	88.3 ± 20.4 [367[
	Week 48*	3.1 ± 0.1 [183]	1.3 ± 0 [352]	6.9 (5.9, 8.2) [194]	6.8 (6.0, 7.9) [363]	6.5 (6.0, 7.2) [194]	6.5 (6.1, 7.1) [364]	88.7 ± 1.5 [198]	87.8 ± 1.1 [367]
	Change to Week 48*	0 ± 0.1 [183]	-1.8 ± 0.1 [352]	0.1 (-0.6, 0.9) [194]	0.2 (-0.7, 1.0) [363]	0.1 (-0.1, 0.4) [183]	0.1 (-0.2, 0.5) [344]	-0.6 ± 0.4 [198]	-0.4 ± 0.3 [367]
No Diabetes	Baseline	3.4 ± 1.2 [1313]	3.3 ± 1.2 [2637]	5.3 (5.0, 5.7) [1313]	5.3 (5.0, 5.7) [2637]	5.5 (5.3, 5.7) [1049]	5.5 (5.3, 5.7) [2143]	81.9 ± 17.5 [1076]	82.1 ± 17.2 [2154]
	Week 48*	3.4 ± 0 [1036]	1.5 ± 0 [2156]	5.4 (5.1, 5.8) [1067]	5.4 (5.0, 5.8) [2198]	5.6 (5.3, 5.8) [1066]	5.5 (5.3, 5.8) [2191]	82.0 ± 0.5 [1076]	82.5 ± 0.4 [2154]
	Change to Week 48*	0 ± 0 [1036]	-1.8 ± 0 [2156]	0.1 (-0.2, 0.4) [1067]	0.1 (-0.2, 0.4) [2198]	0.1 (-0.1, 0.2) [834]	0.1 (-0.1, 0.2) [1735]	0.0 ± 0.2 [1076]	0.4 ± (0.1 [2154]

High risk of diabetes	Baseline	3.3 ± 1.1 [494]	3.2 ± 1.1 [1023]	5.8 (5.6, 6.1) [494]	5.8 (5.7, 6.1) [1023]	5.7 (5.4, 6.0) [410]	5.7 (5.4, 6.0) [843]	84.1 ± 17.6 [403]	86.0 ± 17.0 [827]
	Week 48*†	3.3 ± 0.1 [386]	1.4 ± 0 [828]	5.8 (5.4, 6.2) [400]	5.8 (5.4, 6.2) [844]	5.7 (5.5, 6.0) [400]	5.7 (5.5, 6.0) [842]	84.2 ± 0.9 [403]	86.1 ± 0.6 [827]
	Change to Week 48*†	0 ± 0 [386]	-1.8 ± 0 [828]	-0.1 (-0.4, 0.3) [400]	-0.1 (-0.4, 0.3) [844]	0.0 (-0.1, 0.2) [325]	0.0 (-0.1, 0.2) [672]	0.2 ± 0.2 [403]	0.1 ± 0.2 [827]

SOC: standard of care; EvoMab: evolocumab; SD: standard deviation; SE: standard error; wk: week

* For columns reporting weight data, data are taken from week 48 in OSLER-2 and week 52 in OSLER-1

† Subset of those with no diabetes, defined as: impaired fasting glucose (i.e. FPG 6.1–6.9 mmol/L) or HbA1c ≥6.0% at baseline, and not meeting the criteria for T2DM

To convert glucose to mg/dL, multiply by 18; to convert LDL-cholesterol to mg/dL, multiply by 38.6

Table 3. Exposure-Adjusted Annual Event Rate for New-Onset Diabetes Mellitus*

	Control/Standard of care (n = 1359)	**Evolocumab/Evolocumab (n = 2591)**
New-onset diabetes from start of parent study through year one of OSLER		
Total Patient Years	1682.2	3297.8
Total Events	62	127
Exposure-adjusted incidence rate per 100 patient years (95% confidence intervals)	3.7 (2.9-4.7)	3.9 (3.2-4.6)

*Defined as post-baseline commencement of glucose-lowering therapy, a diabetes adverse event, HbA1c $\geq$ 6.5%, or two consecutive fasting plasma glucose values $\geq$ 7.0mmol/L

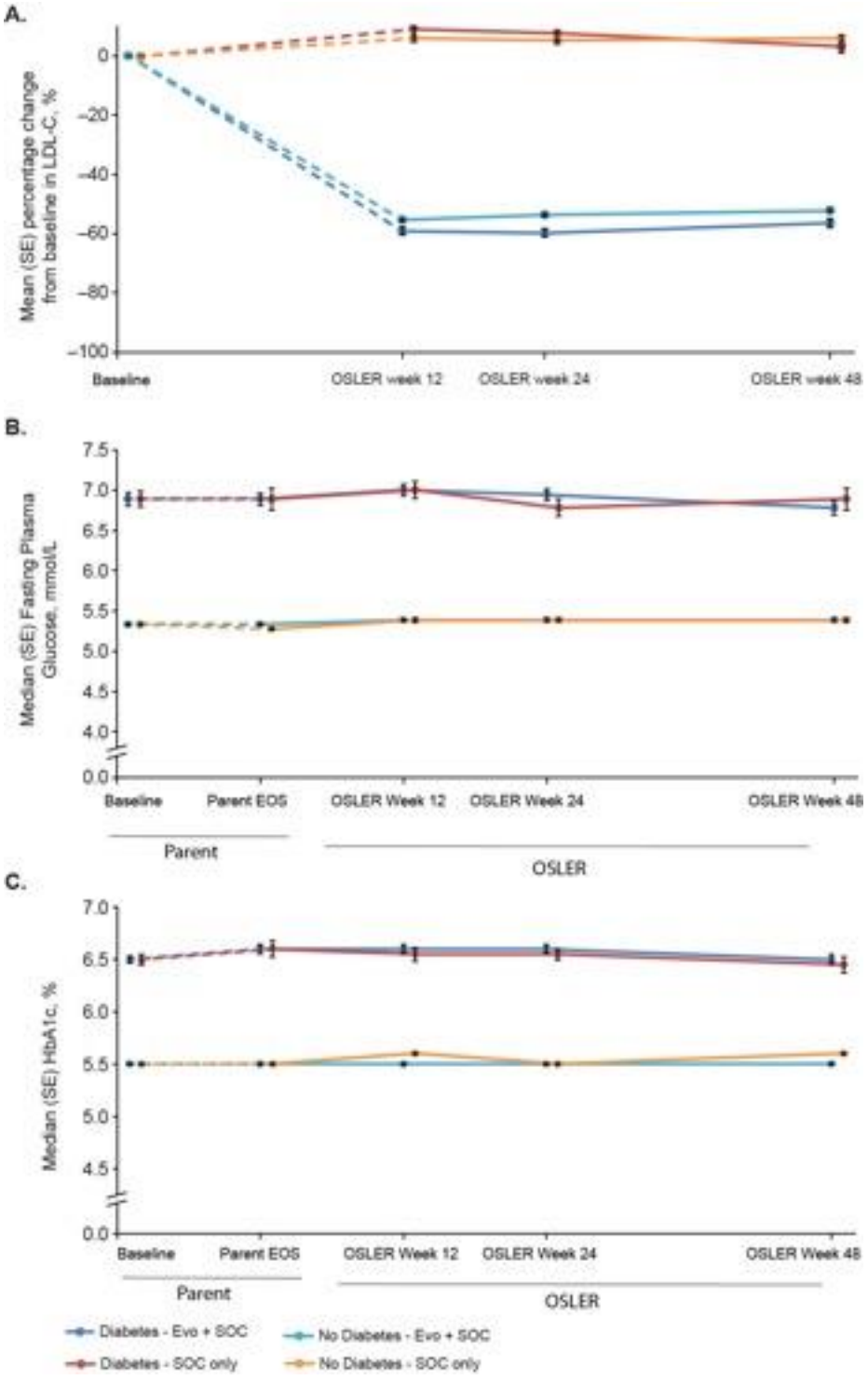
A.
Mean (SE) percentage change from baseline in LDL-C, %
0
−20
−40
−60
−80
−100
Baseline
OSLER week 12
OSLER week 24
OSLER week 48
B.
Median (SE) Fasting Plasma Glucose, mmol/L
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
0.0
Baseline
Parent EOS
OSLER Week 12
OSLER Week 24
OSLER Week 48
Parent
OSLER
C.
Median (SE) HbA1c, %
7.0
6.5
6.0
5.5
5.0
4.5
0.0
Baseline
Parent EOS
OSLER Week 12
OSLER Week 24
OSLER Week 48
Parent
OSLER
Diabetes - Evo + SOC
No Diabetes - Evo + SOC
Diabetes - SOC only
No Diabetes - SOC only

Figure 1.

SUPPLEMENTARY INFORMATION

METHODS

Parent trial analysis

Data were pooled from 13 parent studies (**Supplementary Table 1**). Patients, study personnel, investigators, and Amgen study staff were blinded to treatment assignment within dose frequency groups of the parent trials. Blood samples were taken at baseline and week 12.

Data from the 12-week parent trials were pooled and analysed together. Exposure to Evolocumab or control during the parent study was included in the exposure-adjusted new-onset diabetes analysis. Changes in FPG and HbA1c in the parent study were compared between those receiving evolocumab and those receiving control. For change in LDL-cholesterol in the parent trials, the control group was further divided into those allocated placebo and ezetimibe respectively.

SUPPLEMENTARY RESULTS

Parent trial results

Baseline data for parent-study patients is provided in **Supplementary Table 2**. Over 12 weeks, evolocumab lowered LDL-C by about 40% compared to ezetimibe and by about 60% compared to placebo (**Supplementary Table 3**). There was no difference in change in FPG or HbA1c over this time period in the analysis of all participants. Median change in HbA1c was 0.0% (interquartile range [IQR] –0.1, 0.2) on control and 0.0% (IQR –0.1, 0.1) on evolocumab while median change in FPG was 0.00mmol/L (IQR –0.02, 0.02) on control and 0.06mmol/L (IQR –0.3, 0.4) on evolocumab. Results in the subgroups with diabetes, without diabetes and at high

risk of diabetes were entirely consistent with this null overall effect (**Supplementary Table 3**). Maximal change in FPG was 0.06mmol/L and in HbA1c was 0.1% in any of these subgroups. Similarly, there was no difference in change in FPG or HbA1c for those who did (n=4,802) or did not (n=1,628) proceed from a parent trial to an OLE trial (**Supplementary Table 3**).

Supplementary Table 1. Parent studies enrolling into OSLER-1 or OSLER-2

	Study	Acronym	Eligibility Criteria	Duration	Treatment Arms	Background Statin	N	Associated Publication
1	Reduction of LDL-C with PCSK9 inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study	RUTHERFORD	Heterozygous FH with LDL-C ≥2.6mmol/L [Patients with type 1 diabetes or newly diagnosed or poorly controlled (HbA1c >8.5%) type 2 diabetes excluded]	12 weeks	3 treatment groups: Evolocumab 350 mg, 420 mg, or placebo QM	Statin ± ezetimibe	167	Raal et al. 2012 Circulation
2	Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects	GAUSS	Statin-intolerant patients, LDL-C ≥2.6mmol/L [Patients with type 1 diabetes or poorly controlled or recently diagnosed type 2 diabetes excluded]	12 weeks	5 treatment groups: Evolocumab 280 mg, 350 mg, or 420 mg QM, OR Ezetimibe 10 mg plus SC placebo QM OR Ezetimibe 10 mg plus evolocumab 420 mg QM	No/low-dose statin	157	Sullivan et al. 2012 JAMA
3	Monoclonal antibody against PCSK9 to reduce Elevated LDL-C in subjects currently Not receiving Drug therapy for Easing Lipid levels	MENDEL	LDL-C ≥2.6 and < 4.9mmol/L; Patients with CAD were excluded. [Diabetes mellitus or fasting plasma glucose at screening ≥7.0mmol/L or HbA1c ≥6.5% excluded]	12 weeks	9 treatment groups:Evolocumab 70 mg, 105 mg, or 140 mg or placebo Q2W OR Evolocumab 280 mg, 350 mg, or 420 mg or placebo QM OR Daily ezetimibe 10 mg	None	406	Koren et al. 2012 Lancet
4	LAPLACE-TIMI 57: LDL-C Assessment wtih PCSK9 monoclonaL Antibody inhibition Combined with statin thErapy	LAPLACE-TIMI 57	LDL-C ≥2.2 mmol/L [Patients with type 1 diabetes or newly diagnosed or poorly controlled (HbA1c >8.5%) type 2 diabetes excluded]	12 weeks	8 treatment groups: Evolocumab 70 mg, 105 mg, 140 mg, or placebo Q2W OR Evolocumab 280 mg, 350 mg, 420 mg, or placebo QM	Statin ± ezetimibee	629	Giugliano et al. 2012 Lancet
5	Durable Effect of PCSK9 antibody CompARed wiTh placEbo Study	DESCARTES	LDL-C ≥1.9mmol/L Excluded: LDL-C ≤2.6mmol/L with CAD or risk equivalent and not receiving a statin [Patients with type 1 diabetes or newly diagnosed type 2 diabetes (within 6 months of randomization or new screening fasting plasma glucose ≥7.0mmol/L] or HbA1c ≥6.5%), or poorly controlled type 2 diabetes (HbA1c >8.5%) were excluded]	52 weeks	Background lipid-lowering therapy stabilized; patients then randomized to one of 5 treatment groups: evolocumab 420 mg every month, or diet alone, or diet + atorvastatin 10 mg per day, or diet + atorvastatin 80 mg per day, or diet + atorvastatin 80 mg + ezetimibe 10 mg per day	Lipid-lowering therapy, ranging from diet alone to atorvastatin 80 mg plus ezetimibe, was optimized to reach NCEP ATP III LDL-C treatment goals	901	Blom et al. 2014 NEJM
6	Monoclonal antibody against PCSK9 to reduce elevated LDL-C in subjects currently not receiving drug therapy for easing lipid levels-2	MENDEL-2	LDL-C ≥2.6 and <4.9mmol/L [Patients with diabetes were excluded]	12 weeks	6 treatment groups: evolocumab 140 mg Q2W + oral placebo, evolocumab 420 mg QM + oral placebo, oral ezetimibe + SC placebo Q2W, ezetimibe + SC placebo QM, or oral placebo + SC placebo Q2W, or oral placebo + SC placebo QM	None	614	Koren et al. 2014 JACC

7	LDL-C assessment w/ PCSK9 monoclonal antibody inhibition combined with statin therapy-2	LAPLACE-2	≥4.0mmol/L and on no statin ≥2.6mmol/L and on non-intensive statin ≥2.1mmol/L and on intensive statin [Patients with type 1 diabetes or newly diagnosed or poorly controlled (HbA1c >8.5%) type 2 diabetes excluded]	12 weeks	24 treatment groups: Background atorvastatin 80 mg plus one of the following: • evolocumab 140 mg Q2W + placebo QD PO or • ezetimibe QD PO + placebo SC Q2W or • placebo PO + placebo SC Q2W or • evolocumab 420 mg QM + placebo QD PO or • ezetimibe QD PO + placebo SC QM or • placebo PO + placebo SC QM or OR Background rosuvastatin 40 mg plus one of the following: • evolocumab 140 mg Q2W + placebo QD PO or • ezetimibe QD PO + placebo SC Q2W or • placebo PO + placebo SC Q2W or • evolocumab 420 mg QM + placebo QD PO or • ezetimibe QD PO + placebo SC QM or • placebo PO + placebo SC QM or OR Background atorvastatin 10 mg plus one of the following: • evolocumab 140 mg Q2W + placebo QD PO or • placebo PO + placebo SC Q2W or • evolocumab 420 mg QM + placebo QD PO or • placebo PO + placebo SC QM or OR Background rosuvastatin 5 mg plus one of the following: • evolocumab 140 mg Q2W + placebo QD PO or • placebo PO + placebo SC Q2W or • evolocumab 420 mg QM + placebo	5 background statin regimens: atorvastatin 80mg, atorvastatin 10 mg, rosuvastatin 40 mg, rosuvastatin 5 mg, or simvastatin 40 mg	1896	Robinson et al. 2014 JAMA

					QD PO or • placebo PO + placebo SC QM or OR Background simvastatin 40 mg plus one of the following: • evolocumab 140 mg Q2W + placebo QD PO or • placebo PO + placebo SC Q2W or • evolocumab 420 mg QM + placebo QD PO or • placebo PO + placebo SC QM or			
8	Goal achievement after utilizing an anti-PCSK9 antibody in statin intolerant subjects -2	GAUSS-2	Not at LDL-C goal per NCEP ATP III risk categories for fasting LDL-C, statin intolerant [Patients with type 1 diabetes or newly diagnosed type 2 diabetes (within 6 months of randomization or new screening fasting plasma glucose ≥7.0mmol/L] or HbA1c ≥6.5%), or poorly controlled type 2 diabetes (HbA1c >8.5%) were excluded]	12 weeks	4 treatment groups: placebo SC Q2W or QM, evolocumab 140 mg Q2W or 420 mg QM	None	307	Stroes et al. 2014 JACC
9	Reduction of LDL-C with PCSK9 inhibition in heterozygous familial hypercholesterolemia disorder study-2	RUTHERFORD-2	LDL-C ≥2.6mmol/L, FH [no diabetes-based exclusion criteria]	12 weeks	4 treatment groups: Evolocumab 140 mg or placebo Q2W, or evolocumab 420 mg or placebo QM,	On stable background lipid-lowering therapy for at least 4 weeks	329	Raal et al. 2015 Lancet
10	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Tolerability and Efficacy of Evolocumab (AMG 145) in Japanese Subjects	YUKAWA	LDL-C ≥3.0mmol/L [Patients with recently diagnosed (i.e. less than 3 months) or poorly controlled type 2 diabetes mellitus	12 weeks	6 treatment groups: Placebo SC Q2W, evolocumab 70 mg SC Q2W, evolocumab 140 mg SC Q2W, placebo SC QM, evolocumab 280 mg SC QM, evolocumab 420 mg SC QM	On stable statin therapy (with or without ezetimibe) for ≥ 4 weeks prior to LDL-C screening	307	Hirayama et al. 2014 Circ J
11	A Double-blind, Randomized, Placebo-controlled, Multicenter Study to Evaluate Safety, Tolerability and Efficacy of AMG 145 on LDL-C in Combination With Statin Therapy in Japanese Subjects With Cardiovascular Risk and With Hyperlipidemia or Mixed Dyslipidemia	YUKAWA-2	LDL-C ≥2.6mmol/L [Patients with type 1 diabetes, newly diagnosed (within 3 months prior to randomization) type 2 diabetes or poorly controlled type 2 diabetes were excluded]	12 weeks	8 treatment groups: Background atorvastatin 5 or 20 mg/day for 4 weeks, followed by evolocumab 140 mg SC Q2W, 420 mg SC QM, placebo SC Q2W, or placebo SC QM	On stable statin for ≥4 weeks before LDL-C screening, without need for uptitration	404	Kiyosue et al. 2016 Am J Cardiol
12	Study to Assess In-home Use of Evolocumab	THOMAS-1	LDL-C ≥2.2mmol/L [Patients with type 1 diabetes,	6 weeks	Evolocumab 140 mg SC Q2W	On stable statin for ≥4 weeks before	149	Dent et al. 2016

	(AMG 145) Using a Prefilled Syringe or a Prefilled Autoinjector/Pen		uncontrolled or recently-diagnosed type 2 diabetes were excluded]			LDL-C screening		SpringerPlus
13	A randomized, multi-center clinical study in subjects with hypercholesterolemia or mixed dyslipidemia	THOMAS-2	LDL-C ≥2.2mmol/L [Patients with type 1 diabetes, uncontrolled or recently-diagnosed type 2 diabetes were excluded]	12 weeks	Evoocumab 420 mg SC QM	On stable statin for ≥4 weeks before LDL-C screening	164	See above. Published with THOMAS-1

CAD: coronary artery disease; LDL: low density lipoprotein; FH: familial hypercholesterolemia; PCSK9: proprotein convertase subtilisin/kexin type 9; NCEP ATP III: National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood. Cholesterol in Adults; Q2W: every two weeks; QM: monthly ; SC: subcutaneous

Supplementary Table 2. Baseline demographics for parent trials of evolocumab

Characteristic		**Any control (n = 2282)**	**Any EvoMab (n = 4148)**
Age		57.6 ± 11.1	57.9 ± 11.3
Male		1122 (49.2%)	2104 (50.7%)
Race*	White	1753 (76.8%)	3270 (78.8%)
	Asian	386 (16.9%)	557 (13.4%)
	Black / African American	106 (4.6%)	248 (6.0%)
	Other race	37 (1.6%)	72 (1.8%)
Hypertension		1156 (50.7%)	2241 (54.0%)
Type 2 diabetes†		387 (17.0%)	720 (17.4%)
High risk of diabetes‡		686 (30.1%)	1328 (32.0%)
Current smoker		371 (16.3%)	636 (15.3%)
Coronary artery disease		372 (16.3%)	821 (19.8%)
Cerebrovascular disease or peripheral arterial disease		182 (8.0%)	381 (9.2%)
LDL-cholesterol (mmol/L)		3.2 ± 1.1	3.3 ± 1.1
LDL-cholesterol (mg/dL)		124.2 ± 42.0	126.2 ± 44.0
Hemoglobin-A1c (%)§‖		5.6 (5.3, 5.9)	5.6 (5.3, 5.9)
Fasting plasma glucose (mmol/L) §		5.4 (5.0, 5.9)	5.4 (5.0, 5.9)
Fasting plasma glucose (mg/dL) §		97.0 (90.0 106.0)	97.0 (90.0, 107.0)

Data shown as mean ± SD or count (%)

* Race not specified for 1 participant

† Defined as previously known T2DM, on glucose-lowering medication, baseline FPG ≥ 7.0 mmol/L or baseline HbA1c ≥6.5%

‡ Impaired fasting glucose (i.e. fasting plasma glucose 6.1–6.9mmol/L) or HbA1c ≥6.0% at baseline, and not meeting the criteria for T2DM

§ Median (Q1, Q3)

‖ Available for 1991 participants assigned to control and 3149 assigned to evolocumab

Supplementary Table 3. Changes in Low Density Lipoprotein-cholesterol, fasting plasma glucose and Hemoglobin-A1c over 12 weeks in parent trials of evolocumab

		LDL-C in mmol/L (mean ± SD for baseline [n]; mean ± SE for week 12 [n])			Fasting plasma glucose in mmol/L (median (Q1, Q3) [n])		HbA1c in % (median (Q1, Q3) [n])	
		Any placebo	**Ezetimibe**	**EvoMab**	**Control**	**EvoMab**	**Control**	**EvoMab**
All subjects	Baseline	3.1 ± 1.0 [1728]	3.7 ± 1.3 [554]	3.3 ± 1.1 [4148]	5.4 (5, 5.9) [2282	5.4 (5, 5.9) [4148]	5.6 (5.3, 5.9) [1991]	5.6 (5.3, 5.9) [3149]
	Week 12	3.1 ± 0.03 [1577]	3.0 ± 0.06 [501]	1.4 ± 0.02 [3692]	5.4 (5.1, 5.9) [2193]	5.4 (5.1, 6) [3846]	5.6 (5.3, 5.9) [2174]	5.6 (5.3, 5.9) [3586]
	Change to Week 12	0 ± 0.02 [1577]	-0.7 ± 0.03 [501]	-1.9 ± 0.01 [3692]	0 (-0.3, 0.3) [2193]	0.1 (-0.3, 0.4) [3846]	0.0 (-0.1, 0.2) [1932]	0.0 (-0.1, 0.1) [3035]
Diabetes	Baseline	2.8 ± 0.8 [309]	3.2 ± 1.2 [78]	3.0 ± 1.0 [720]	6.9 (5.9 7.9) [387]	6.8 (5.9, 7.9) [720]	6.6 (6.1, 7.2) [381]	6.5 (6.0, 7.1) [614]
	Week 12	2.7 ± 0.05 [289]	2.5 ± 0.13 [66]	1.2 ± 0.03 [636]	6.9 (5.9 8.2) [374]	6.9 (6, 8.1) [660]	6.6 (6.1, 7.2) [377]	6.6 (6.0, 7.2) [616]
	Change to Week 12	0 ± 0.04 [289]	-0.7 ± 0.09 [66]	-1.8 ± 0.03 [636]	0.1 (-0.4, 0.7) [374]	0.1 (-0.6, 0.7) [660]	0.1 (-0.1,0.3) [372]	0.0 (-0.2, 0.3) [595]
No Diabetes	Baseline	3.1 ± 1.0 [1419]	3.7 ± 1.3 [476]	3.3 ± 1.2 [3428]	5.3 (4.9, 5.7) [1895]	5.3 (5, 5.7) [3428]	5.5 (5.3, 5.7) [1610]	5.5 (5.3, 5.7) [2535]
	Week 12	3.2 ± 0.03 [1288]	3.0 ± 0.06 [435]	1.4 ± 0.02 [3056]	5.3 (4.9, 5.7) [1819]	5.3 (5, 5.7) [3186]	5.5 (5.3, 5.8) [1797]	5.5 (5.3, 5.8) [2970]
	Change to Week 12	0.1 ± 0.02 [1288]	-0.7 ± 0.04 [435]	-1.9 ± 0.02 [3056]	0 (-0.3, 0.3) [1819]	0.1 (-0.2, 0.3) [3186]	0.0 (-0.1, 0.2) [1560]	0.0 (-0.1, 0.1) [2440]
High risk for	Baseline	3.0 ± 1.0 [531]	3.6 ± 1.3 [155]	3.2 ± 1.1 [1328]	5.8 (5.6, 6.1) [686]	5.8 (5.6, 6.1) [1328]	5.7 (5.5, 6.0) [593]	5.7 (5.5, 6.0) [1008]

diabetes*	Week 12	3.1 ± 0.05 [492]	2.9 ± 0.09 [142]	1.3 ± 0.02 [1174]	5.7 (5.4, 6.1) [667]	5.7 (5.4, 6.1) [1232]	5.7 (5.5, 6.0) [660]	5.7 (5.4, 6.0) [1161]
	Change to Week 12	0.1 ± 0.03 [492]	-0.7 ± 0.05 [142]	-1.9 ± 0.03 [1174]	-0.1 (-0.4, 0.2) [667]	-0.1 (-0.4, 0.2) [1232]	0.0 (-0.1, 0.2) [581]	0.0 (-0.1, 0.1) [970]
Enrolled into Osler	Baseline	3.1 ± 1.0 [1278]	3.7 ± 1.3 [376]	3.3 ± 1.2 [3148]	5.4 (5, 5.9) [1654]	5.4 (5.1, 5.9) [3148]	5.6 (5.3, 6.0) [1435]	5.6 (5.3, 6.0) [2357]
	Week 12	3.1 ± 0.03 [1204]	2.9 ± 0.07 [353]	1.4 ± 0.02 [2895]	5.4 (5.1, 5.9) [1631]	5.4 (5.1, 6) [2995]	5.6 (5.3, 6.0) [1600]	5.6 (5.3, 5.9) [2772]
	Change to Week 12	0 ± 0.02 [1204]	-0.7 ± 0.04 [353]	-2.0 ± 0.02 [2895]	0 (-0.3, 0.3) [1631]	0.1 (-0.3, 0.3) [2995]	0.0 (-0.1, 0.2) [1413]	0.0 (-0.1, 0.1) [2313]
Did not enrol into Osler	Baseline	3.1 ± 0.9 [450]	3.6 ± 1.3 [178]	3.1 ± 1.0 [1000]	5.3 (5, 5.8) [628]	5.4 (5, 5.9) [1000]	5.5 (5.3, 5.9) [556]	5.6 (5.3,5.9) [792]
	Week 12	3.2 ± 0.06 [373]	3.0 ± 0.10 [148]	1.4 ± 0.03 [797]	5.4 (5, 5.9) [562]	5.4 (5.1, 5.9) [851]	5.6 (5.3, 5.9) [574]	5.6 (5.3, 5.9) [814]
	Change to Week 12	0.1 ± 0.04 [373]	-0.6 ± 0.06 [148]	-1.8 ± 0.03 [797]	0.1 (-0.2, 0.4) [562]	0.1 (-0.2, 0.4) [851]	0.0 (-0.1, 0.2) [519]	0.0 (-0.1, 0.2) [722]

* Subset of those with no diabetes, defined as impaired fasting glycemia or HbA1c ≥ 6.0% at baseline

SOC: standard of care; EvoMab: evolocumab; SD: standard deviation; SE: standard error

To convert glucose to mg/dL, multiply by 18; to convert LDL-cholesterol to mg/dL, multiply by 38.6