

# **Evaluation of the Efficacy, Safety, and Glycaemic Effects of Evolocumab (AMG 145) in Hypercholesterolaemic Patients Stratified by Glycaemic Status and Metabolic Syndrome**

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## **Abstract**

**Aim:** To examine the lipid and glycaemic effects of 52 weeks of evolocumab treatment.

**Materials and Methods:** DESCARTES was a 52-week placebo-controlled trial of evolocumab.

DESCARTES randomised 905 patients from 88 study centres in nine countries with 901 receiving at least one dose of study drug. For this post-hoc analysis, DESCARTES patients were categorized by baseline glycaemic status – type 2 diabetes, impaired fasting glucose (IFG), metabolic syndrome (MetS), or none of these. Monthly subcutaneous evolocumab (420 mg) or placebo was administered. The main outcomes measured were percentage change in LDL-cholesterol (LDL-C) at week 52 and safety.

**Results:** 413 patients had dysglycaemia (120 type 2 diabetes, 293 IFG), 289 MetS (194 also had IFG), and 393 none of these conditions. At week 52, evolocumab reduced LDL-C by > 50% in all subgroups, with favourable effects on other lipids. No significant differences in fasting plasma glucose, HbA<sub>1c</sub>, insulin, C-peptide or HOMA indices were seen in any subgroup between evolocumab and placebo at week 52. The overall incidence of new-onset diabetes mellitus did not differ between placebo (6.6%) and evolocumab (5.6%); in those with baseline normoglycaemia, the incidences were 1.9% and 2.7%, respectively. Incidences of AEs were similar in evolocumab- and placebo-treated patients.

**Conclusions:** Evolocumab showed encouraging safety and efficacy at 52 weeks in patients with or without dysglycaemia or MetS. Changes in glycaemic parameters did not differ between evolocumab- and placebo-treated patients within the glycaemic subgroups examined.

## Introduction

Diabetes is a major global health concern and in 2013 the estimated worldwide number of adults living with diabetes was 415 million, with type 2 diabetes mellitus (type 2 diabetes) accounting for the vast majority of cases (1). The prevalence of type 2 diabetes is likely to increase to 642 million by 2040 (1). Type 2 diabetes causes considerable morbidity and mortality, with atherosclerotic cardiovascular disease accounting for most of the excess mortality (2). Cardiovascular risk in people with type 2 diabetes is increased approximately two- to three-fold with a greater increase in incident risk in women compared with men (3-6). Type 2 diabetes in a 40-year-old without known vascular disease results in approximately 6.3 and 6.8 years of life lost for men and women, respectively, with 58% of this survival deficit at age 50 due to vascular disease (4).

Statins are effective in primary and secondary prevention of cardiovascular disease in patients with type 2 diabetes and higher doses are more effective than lower doses (7, 8). The IMPROVE-IT study recently confirmed the benefit of more aggressive lipid-lowering in diabetes using combination therapy (9). In this study, the median time-weighted average low-density lipoprotein cholesterol (LDL-C) was 1.4mmol/L (54 mg/dL) in patients allocated to simvastatin 40 mg/day with ezetimibe 10 mg/day compared with 1.8 mmol/L (70 mg/dL) in those receiving simvastatin 40 mg/day alone. The benefit of additional ezetimibe intervention on cardiovascular endpoints was particularly pronounced in patients over 75 years of age and in those with diabetes (27% of the study cohort), suggesting that people with diabetes may derive greater absolute risk reduction from more aggressive LDL-C lowering. Guidelines differ in their approach to

treatment, recommending either a treat to LDL-C target approach or a risk-based statin dose intensity. Many patients however either do not reach their LDL-C target or are unable to tolerate statin therapy of sufficient intensity (10-12). High untreated LDL-C levels may make it more difficult to reach LDL-C targets, while statin-associated muscle symptoms may limit the dose prescribed (13). Ezetimibe can be added to statins or used as monotherapy, but only reduces LDL-C by a further 18-25% (14).

Although statins improve outcomes in diabetes they may negatively impact glucose metabolism. Statin therapy has been associated with an increase in new-onset diabetes (NOD) and glycated haemoglobin (HbA<sub>1c</sub>) levels (15-17). Higher-dose statin therapy and increased adherence are associated with an increased risk of NOD, (15, 18) but the risk of NOD does not appear to be increased with ezetimibe therapy (19, 20). The precise mechanism by which statins cause insulin resistance and increase the risk of diabetes is not known and multiple mechanisms have been proposed (21-24). Of particular relevance in the context of evolocumab therapy is a recent study suggesting that LDL-receptor upregulation and high LDL-receptor mediated transmembrane cholesterol uptake in pancreatic beta cells could be potential mechanisms facilitating NOD in susceptible individuals. In this epidemiological study, type 2 diabetes rates were lower in patients with heterozygous familial hypercholesterolemia (HeFH) than in their unaffected relatives. The potential role of the LDL-receptor was further highlighted by the finding that type 2 diabetes rates were lower in patients with receptor-negative mutations than in those with receptor-defective mutations (25).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzymatically inactive serine protease predominantly secreted by hepatocytes. PCSK9 interrupts LDL-receptor recycling and

high levels of PCSK9 or PCSK9 gain-of-function mutations are associated with increased LDL-C (26, 27). Evolocumab is a fully human monoclonal antibody to PCSK9 that reduced LDL-C by 50-75% in multiple studies (28).

In this post-hoc analysis, we utilized data from the Durable Effect of PCSK9 Antibody Compared with Placebo Study (DESCARTES) (29), the largest and longest double-blind, placebo-controlled randomised study of evolocumab published thus far, to examine the effect of evolocumab on glycaemic parameters as well as its lipid-lowering effects and safety in patients categorized according to their baseline glycaemic status.

## **Materials and Methods**

DESCARTES was a 52-week study of monthly subcutaneous evolocumab (420 mg) vs. matching placebo (2:1) in hypercholesterolemic patients in whom background lipid-lowering therapy had been adjusted to achieve National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) LDL-C targets. Full details of the protocol and outcomes have been published previously(29). The study design diagram is shown in **Supplemental Figure 1**.

Briefly, patients between the ages of 18 and 75 years with an LDL-C  $\geq 1.9$  mmol/L (75 mg/dL ) and a fasting triglyceride level  $\leq 4.5$  mmol/L (400 mg/dL) following optimization of lipid-lowering therapy in the run-in period were eligible to participate. During the run-in period lipid-lowering therapy was titrated to one of four intensities (diet alone, diet with atorvastatin 10 mg/day, diet with atorvastatin 80 mg/day, or diet with atorvastatin 80 mg/day plus ezetimibe 10 mg/day) until patients had either reached their NCEP ATP III goal or were receiving maximal therapy. Key exclusion criteria included a history of heart failure, recent myocardial infarction,

recent or planned cardiac surgery or revascularization, diagnosis of diabetes (defined as fasting plasma glucose [FPG]  $\geq 7.0$  mmol/L (126 mg/dL) or HbA<sub>1c</sub>  $\geq 6.5\%$  (48 mmol/mol) within 6 months of randomisation, or poorly controlled diabetes (HbA<sub>1c</sub>  $> 8.5\%$  [69 mmol/mol])). Baseline was defined as study day 1 following lipid stabilization.

All lipid analyses were performed in two central laboratories (Medpace Reference Laboratories: Cincinnati, Ohio and Leuven, Belgium) that maintained Part III certification according to the Centers for Disease Control (CDC) Lipid Standardization Program throughout the study. LDL-C was measured after preparative ultracentrifugation. Insulin was measured by Quest Diagnostics (Madison, NJ, USA). HbA<sub>1c</sub> levels were measured by Covance (Princeton, USA) using an ion-exchange high-performance liquid chromatography method, which separates haemoglobin species by differences in charge between HbA<sub>1c</sub> and other haemoglobins. FPG levels were measured by Covance using the hexokinase/glucose-6-phosphate dehydrogenase method.

For this post-hoc analysis, we categorized patients according to their baseline glycaemic status into one of four subgroups: type 2 diabetes, impaired fasting glucose (IFG), metabolic syndrome (MetS) or none of these. Type 2 diabetes and IFG patient groups are collectively referred to as dysglycaemic for selected analyses. We defined type 2 diabetes either by previous diagnosis of diabetes, baseline use of glucose-lowering medication, baseline FPG  $\geq 7.0$  mmol/L (126 mg/dL), or baseline HbA<sub>1c</sub>  $\geq 6.5\%$ . IFG was defined as the absence of type 2 diabetes with a FPG  $\geq 5.6$  mmol/L (100 mg/dL) and  $< 7.0$  mmol/L (126 mg/dL) at baseline. MetS was defined using modified AHA/NHLBI criteria as the absence of type 2 diabetes and the presence of 3 or more of the following components: 1) elevated waist circumference (non-Asian men  $\geq 102$  cm, non-

Asian women  $\geq 88$ cm, Asian men  $\geq 90$  cm, Asian women  $\geq 80$  cm); 2) triglycerides  $\geq 1.7$  mmol/L (150 mg/dL); 3) low HDL cholesterol (HDL-C) (men  $< 1.0$  mmol/L (40 mg/dL); women  $< 1.3$  mmol/L [50 mg/dL]); 4) high blood pressure (systolic  $\geq 130$  mmHg, diastolic  $\geq 85$  mmHg, medical history of hypertension); 5) FPG  $\geq 5.6$  mmol/L (100 mg/dL) (30). IFG and MetS categories could overlap, i.e. patients could have both IFG and MetS, but there was no overlap between type 2 diabetes and the other glycaemic categories.

The primary efficacy end point for DESCARTES was the percentage change from baseline in LDL-C at week 52 in patients receiving evolocumab compared with those receiving placebo. Secondary efficacy endpoints included the percentage change from baseline at week 52 in other lipids, such as lipoprotein (a) (Lp(a)), total cholesterol, HDL-C, triglycerides, and apolipoprotein B (ApoB), among others (29). In this post-hoc analysis, we re-evaluated efficacy and safety endpoints according to patient's baseline glycaemic category. We also evaluated glycaemic changes in all patients, and the incidence of NOD in patients without type 2 diabetes at baseline. NOD was defined as any one of the following post baseline: FPG  $\geq 7.0$  mmol/L (126 mg/dL), HbA<sub>1c</sub>  $\geq 6.5$  %, adverse event report of diabetes mellitus, or initiation of new glucose-lowering therapy. Additionally, we determined baseline characteristics associated with an increased risk of NOD.

We calculated Homeostasis Model Assessment (HOMA) beta-cell function (HOMA\_%B) and insulin resistance (HOMA\_IR) using the HOMA2 calculator.(31)

The study protocol was approved by an independent ethics committee or institutional review board, and all patients provided written consent prior to the initiation of study procedures.



### *Statistical Analyses*

We analysed lipid efficacy parameters for each glycaemic subgroup using a repeated-measures linear-effects model with terms for the treatment group, background-therapy group, scheduled visit, and the interaction between the treatment and the scheduled visit (with the use of an unstructured covariance matrix). We estimated the median treatment differences and SE for glycaemic parameters within each glycaemic subgroup using the Hodges-Lehmann estimate of location shift and calculated p-values using the Wilcoxon Rank Sum test. We generated descriptive statistics for safety parameters and physical measurements without imputation of missing data. For the NOD analysis, *P*-values were calculated using Fisher's exact test. We coded adverse events using version 16.1 of the Medical Dictionary for Regulatory Activities. Missing values were not imputed and all *P*-values reported are nominal. Conversion factors for SI units to conventional units can be found in the **supplementary appendix**.

## Results

Of the 905 patients randomised, 901 received at least one dose of study drug and were included in this post-hoc analysis. At baseline, there were 120 patients with type 2 diabetes, 293 with IFG, 289 with MetS and 393 with neither dysglycaemia (diabetes or IFG) nor MetS. Overall, 194 patients had both IFG and MetS.

Baseline demographic, clinical and anthropometric variables are shown in Table 1. Baseline characteristics were generally well balanced between patients allocated to evolocumab or placebo within each glycaemic subgroup. Lp(a) was higher in patients with type 2 diabetes allocated to evolocumab compared with those allocated placebo (median [Q1, Q3]: 47.0 [8.0, 137.0] vs. 97.0 [30.0, 198.0] nmol/L) and in the MetS subgroup, triglycerides were lower in patients allocated to evolocumab (median [Q1, Q3]: 1.5 [1.1, 2.0] vs. placebo 1.8 [1.2, 2.2] mmol/L, [137 [98, 181] vs. placebo 162 [108, 199] mg/dL]). As expected, baseline characteristics of the subgroups defined by glycaemic status differed in many respects. Patients with type 2 diabetes were on average older than those with no glycaemic abnormality (mean  $\pm$  SD); ( $58.1 \pm 8.7$  vs.  $54.9 \pm 11.4$  years), were more likely to be black or African American (19.2% vs. 6.9%) and had higher background rates of hypertension (79.2% vs. 35.9%), coronary artery disease (25.8% vs. 10.4%) and cerebrovascular disease or peripheral arterial disease (7.5% vs. 3.1%). Patients with type 2 diabetes had the highest statin use at baseline (65.0%). Baseline diabetes medications are listed in **Supplemental Table 1**. Weight, BMI and waist circumference were highest at baseline in patients with type 2 diabetes or MetS. Glycaemic parameters (HbA<sub>1c</sub>, fasting glucose), insulin and C-peptide were lowest in the patients without dysglycaemia or

MetS. Patients with dysglycaemia and those with MetS had higher triglycerides and lower HDL-C at baseline than did those without dysglycaemia or MetS.

In all glycemic subgroups examined, evolocumab reduced LDL-C by > 50% compared to placebo with no loss in efficacy from week 12 to week 52 (**Supplemental Figure 2**). Baseline glycemic category did not influence the achieved LDL-C reduction. At week 52, the placebo-adjusted mean (SE) reduction in LDL-C in the evolocumab treatment groups were 50.8% (6.0%) for type 2 diabetes, 59.4% (3.4%) for IFG, 55.0% (3.5%) for MetS, and 58.1% (3.5%) for no dysglycemia or MetS (**Table 2**). Baseline glycemic category also did not influence the proportion of patients in each group achieving LDL-C < 1.8 mmol/L (70 mg/dL) or < 1.3 mmol/L (50 mg/dL) (**Supplemental Table 2**). Statistically significant reductions were seen in Lp(a) and ApoB for evolocumab- versus placebo-treated patients in all glycaemic subgroups ( $p < 0.05$ ). Beneficial changes were also seen in triglycerides and HDL-C but did not reach statistical significance in all subgroups (**Table 2** and **Supplemental Figure 3**).

At week 52 there were no statistically significant differences between evolocumab- and placebo-treated patients in any glycemic subgroup in median HbA<sub>1c</sub> or FPG levels; FPG and HbA<sub>1c</sub> levels stayed relatively constant throughout the treatment period in all glycaemic subgroups for both evolocumab- and placebo-treated patients (**Figure 1**). The intensity of background lipid-lowering therapy had no discernible effects on the change in FPG and HbA<sub>1c</sub> from baseline to week 52, and percent change over 52 weeks in the most intensively treated group (atorvastatin 80mg/day + ezetimibe 10 mg/day + evolocumab) did not differ notably from the group treated with diet alone

**(Supplemental Figures 4 and 5).** Similar values were seen between evolocumab and placebo within each glycaemic subgroup at week 52 in insulin, C-peptide, HOMA\_%B, and HOMA\_IR.

The overall incidence of NOD did not differ significantly between evolocumab- (5.6%) and placebo- treated (6.6%) patients. Patients with IFG at baseline had a higher rate of NOD – 10.3% and 14.1% for evolocumab and placebo, respectively. NOD was uncommon in patients with a normal FPG (< 5.6 mmol/L [100 mg/dL]) at baseline, occurring in 2.7% of evolocumab and 1.9% of placebo patients (**Table 4**). Patients who developed NOD were older, had higher triglycerides at baseline, were more likely to use statins at baseline, had a higher BMI, higher HbA<sub>1c</sub>, greater waist circumference, higher fasting insulin levels, and consequently higher HOMA\_IR (**Supplemental Table 3**).

Evolocumab treatment was not associated with any notable change in weight or waist circumference from baseline to week 52 across all glycaemic subgroups studied. Numerically, patients with type 2 diabetes had the largest change from baseline in waist circumference (mean (standard error); evolocumab: 1.7 (1.4) cm; placebo: 1.2 (1.5) cm) although the mean weight remained unchanged in both treatment groups. Other week 52 percent changes in clinical variables such as blood pressure and heart rate were for the most part comparable between glycaemic subgroups (**Supplemental Table 4**). There was a small increase in heart rate in all evolocumab-treated subgroups.

The incidence of adverse events was comparable between evolocumab and placebo-treated patients in the dysglycaemia/MetS group, and between evolocumab and placebo in the no

dysglycaemia/MetS group. In patients with baseline dysglycaemia or MetS, adverse events occurred in 73.2% and 69.9% for evolocumab and placebo, respectively (**Table 3**). The corresponding rates of adverse events in patients without dysglycaemia or MetS were 76.6% for evolocumab and 80.7% for placebo. Most adverse events were mild (grades 1 or 2). The most common adverse events were upper respiratory tract infection, influenza, nasopharyngitis, and back pain. Adverse events that led to study drug discontinuation were uncommon and occurred in 2.5% and 1.1% of evolocumab-and placebo-treated patients with dysglycaemia or MetS, respectively. The corresponding rates for patients without dysglycaemia or MetS were 1.8% and 0.8%, respectively. Serious adverse events occurred more frequently in patients with dysglycaemia or MetS (evolocumab vs. placebo: 6.5% vs. 5.5%) than in patients without these conditions (evolocumab vs. placebo: 4.4% vs. 2.5%). Transaminase or creatine kinase elevations were uncommon with no notable differences according to treatment allocation or glycaemic status. Injection site reactions occurred in about 4-6% of patients with no discernible differences between evolocumab-and placebo-treated patients or by glycaemic status. One patient (0.3%) (dysglycaemia or MetS allocated to evolocumab) had a transient post-baseline binding antibody. No neutralizing antibodies were identified.

## Discussion

DESCARTES randomised over 900 patients to evolocumab or placebo for 52 weeks and offers a unique opportunity to examine the efficacy and safety of evolocumab in patients categorized by glycaemic status and to study the effects of evolocumab on glycaemic parameters.

Evolocumab 420 mg given monthly reduced LDL-C at week 52 by more than 50% from baseline in all patients irrespective of baseline glycaemic category. We observed a numerically larger LDL-C reduction from baseline of 58.1% in patients without MetS or dysglycaemia compared with the 50.8% LDL-C reduction seen in patients with type 2 diabetes. However, patients with type 2 diabetes differed from those without MetS or dysglycaemia in multiple important aspects (age, race, baseline statin use, weight and BMI). A recently published meta-analysis examining the efficacy of evolocumab in type 2 diabetes in multiple studies but excluding DESCARTES found similar LDL-C reductions of 60% (95% CI 51-69) and 66% (95% CI 62-70) versus placebo in patients with and without type 2 diabetes (32). In DESCARTES the addition of evolocumab to background lipid-lowering therapy titrated to a target LDL-C of less than 2.6 mmol/L (100 mg/dL) in patients with type 2 diabetes enabled 81.8% of subjects to reach a target of 1.8 mmol/L (70 mg/dL), while 63.6% of patients achieved LDL-C concentrations < 1.3 mmol/L (50 mg/dL). The additional LDL-C reductions achieved by adding evolocumab to statin are consistent with those observed in other evolocumab clinical studies. Adding evolocumab therefore allows more patients to reach very low LDL-C levels that may be associated with improved cardiovascular outcomes (9). Additionally, other lipid-lowering therapies, such as statins and ezetimibe, do not lower Lp(a) significantly, while evolocumab reduced levels by 19-

25% in all glycaemic groups evaluated, consistent with reductions reported in other clinical trials of evolocumab. Mendelian randomisation studies show the Lp(a) is an independent risk factor for atherosclerosis, although there is as yet no cardiovascular outcome evidence for Lp(a) lowering with drug therapy (33-35).

In this study, marked LDL-C lowering achieved by upregulating the LDL-receptor through PCSK9 inhibition was not associated with adverse effects on glycaemic control, beta-cell function or insulin sensitivity. FPG and HbA<sub>1c</sub> levels at week 52 did not differ significantly between patients randomised to placebo or evolocumab in any of the glycaemic subgroups examined (**Figure 1**) and were also not different when patients were stratified by background lipid lowering therapy (**Supplemental Figures 4 and 5**). Additionally there were no significant differences between evolocumab vs. placebo within any glycaemic subgroup at week 52 for insulin resistance and beta-cell function. NOD was identified in 6-7% of all patients without diabetes at baseline and was not more common in evolocumab-treated patients. Our results are in keeping with those of other studies of anti-PCSK9 monoclonal antibodies. OSLER-1 and OSLER-2 were open-label extension studies in which patients that had completed a double-blind, randomised evolocumab trial could enrol. Patients were then randomised to receive either standard of care (SOC) or SOC with evolocumab (420 mg monthly or 140 mg every 2 weeks) for a further year. After 1 year of treatment with evolocumab, NOD was identified in 3% and 3% of patients receiving SOC with evolocumab and SOC alone, respectively, in patients with baseline normoglycaemia from OSLER-1 and -2 (excluding DESCARTES) (36). In the ODYSSEY LONG TERM study patients with high cardiovascular risk at baseline were given alirocumab 150 mg sc once every 2 weeks for 78 weeks. NOD was observed in 1.8% and 2.0% of

alirocumab and placebo treated patients, respectively (37). In two 78-week studies of alicumab (75 mg or 150 mg once every two weeks; dose increased at week 12 if week 8 LDL-C > 1.8 mmol/L (70 mg/dL)) in patients with HeFH (ODYSSEY FH 1 and FH2) the rates of NOD or worsening diabetes were 1.9% and 2.5%, respectively for alicumab and placebo in the FH1 study and 2.4% and 2.5%, respectively in the FH2 study (38).

Strengths of our study include its size and design, which closely mimics clinical practice in most parts of the world with its titration of lipid-lowering therapy to NCEP ATPIII targets. We included patients receiving background therapies ranging from diet alone to the combination of atorvastatin 80 mg/day with ezetimibe 10 mg/day. We measured LDL-C using an ultracentrifugal method as Friedewald estimation of LDL-C is inaccurate in patients with very low LDL-C (secondary to evolocumab) or raised triglycerides (in the setting of type 2 diabetes) (39). We assessed glycaemic status at regular intervals by measuring FPG and HbA<sub>1c</sub>. Our study is also unique in that we measured insulin and C-peptide levels and calculated HOMA indices to assess insulin resistance and beta-cell function. The most important limitation of our study is the relatively short treatment duration of 52 weeks and the possibility that potential effects of evolocumab on insulin sensitivity and pancreatic beta-cell function may have a delayed onset that are not captured in the timeframe of this study. The currently ongoing Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER; NCT01764633) study, with a baseline diabetes prevalence of 33.9% will provide further data on the glycaemic effects of longer term exposure to evolocumab (40). DESCARTES excluded patients with diabetes with HbA<sub>1c</sub> levels > 8.5% at baseline and thus mainly studied patients with type 2 diabetes who had relatively good glycaemic control (median HbA<sub>1c</sub> of



6.5%). We used study baseline lipid values to assign MetS status for this analysis. At baseline most patients were receiving lipid-lowering therapy, which can raise HDLC and lower triglycerides, and we may thus have misclassified some patients as not having MetS who would have met MetS criteria in the untreated state. Our MetS group therefore likely represents a subset of MetS patients that has persistently low HDLC and raised triglycerides despite lipid-lowering therapy.

## **Conclusions**

In this post-hoc analysis of a phase 3 study comparing evolocumab with placebo in patients with hypercholesterolaemia, treatment with evolocumab monthly for 52 weeks resulted in encouraging lipid efficacy and reduced LDL-C by > 50% in all subgroups. Similar adverse event and serious adverse event rates were seen in patients with and without dysglycaemia or MetS, and between patients treated with evolocumab or placebo. Evolocumab did not result in notable changes in glycaemia, insulin, C-peptide, HOMA\_%B and HOMA\_IR levels, or in the incidence of NOD.

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### **Figure Legends**

**Figure 1.** Impact of Evolocumab on Fasting Plasma Glucose and HbA1c. Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; MetS, metabolic syndrome; SE, standard error; type 2 diabetes, type 2 diabetes mellitus

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**Table 1. Baseline Patient Characteristics**

| Characteristic  | Type 2 Diabetes |                    | IFG             |                     | MetS             |                     | No Dysglycaemia or MetS |                     |
|---|-----------------|--------------------|-----------------|---------------------|------------------|---------------------|-------------------------|---------------------|
|   | Pbo<br>(N = 43) | EvoMab<br>(N = 77) | Pbo<br>(N = 99) | EvoMab<br>(N = 194) | Pbo<br>(N = 107) | EvoMab<br>(N = 182) | Pbo<br>(N = 119)        | EvoMab<br>(N = 274) |
| <b>Demographics</b>                                   |                 |                    |                 |                     |                  |                     |                         |                     |
| Age, years, mean (SD)                                 | 58 (9)          | 58 (9)             | 58 (9)          | 58 (9)              | 57 (10)          | 56 (11)             | 55 (11)                 | 55 (12)             |
| Female sex, n (%)                                     | 27 (62.8%)      | 41 (53.2%)         | 44 (44.4%)      | 88 (45.4%)          | 54 (50.5%)       | 90 (49.5%)          | 65 (54.6%)              | 152 (55.5%)         |
| <b>Race, n (%)</b>                                    |                 |                    |                 |                     |                  |                     |                         |                     |
| White   | 25 (58.1%)      | 46 (59.7%)         | 89 (89.9%)      | 164 (84.5%)         | 94 (87.9%)       | 147 (80.8%)         | 98 (82.4%)              | 227 (82.8%)         |
| Black or African American                             | 8 (18.6%)       | 15 (19.5%)         | 2 (2.0%)        | 12 (6.2%)           | 3 (2.8%)         | 19 (10.4%)          | 11 (9.2%)               | 16 (5.8%)           |
| Other   | 10 (23.3%)      | 16 (20.8%)         | 8 (8.1%)        | 18 (9.3%)           | 10 (9.4%)        | 16 (8.8%)           | 10 (8.4%)               | 31 (11.3%)          |
| Coronary artery disease, n (%)                        | 11 (25.6%)      | 20 (26.0%)         | 12 (12.1%)      | 37 (19.1%)          | 20 (18.7%)       | 28 (15.4%)          | 8 (6.7%)                | 33 (12.0%)          |
| Cerebrovascular or peripheral arterial disease, n (%) | 3 (7.0%)        | 6 (7.8%)           | 4 (4.0%)        | 8 (4.1%)            | 3 (2.8%)         | 8 (4.4%)            | 2 (1.7%)                | 10 (3.6%)           |
| Current cigarette use, n (%)                          | 7 (16.3%)       | 11 (14.3%)         | 15 (15.2%)      | 30 (15.5%)          | 19 (17.8%)       | 32 (17.6%)          | 19 (16.0%)              | 33 (12.0%)          |
| Hypertension, n (%)                                   | 33 (76.7%)      | 62 (80.5%)         | 47 (47.5%)      | 101 (52.1%)         | 64 (59.8%)       | 114 (62.6%)         | 46 (38.7%)              | 95 (34.7%)          |

|   |                  |                         |                        |                        |                         |                  |                       |                       |
|---|------------------|-------------------------|------------------------|------------------------|-------------------------|------------------|-----------------------|-----------------------|
| <b>Statin use at study entry, n (%)</b>                 | 31 (72.1%)       | 47 (61.0%)              | 45 (45.5%)             | 88 (45.4%)             | 55 (51.4%)              | 68 (37.4%)       | 35 (29.4%)            | 99 (36.1%)            |
| <b>Other lipid-modifying drug at study entry, n (%)</b> | 4 (9.3%)         | 6 (7.8%)                | 8 (8.1%)               | 25 (12.9%)             | 12 (11.2%)              | 18 (9.9%)        | 10 (8.4%)             | 39 (14.2%)            |
| <b>NCEP risk category at study entry, n (%)</b>         | 43 (100%)        | 67 (87.0%)              | 15 (15.2%)             | 44 (22.7%)             | 21 (19.6%)              | 34 (18.7%)       | 10 (8.4%)             | 40 (14.6%)            |
| High risk   | 0 (0.0%)         | 1 (1.3%)                | 15 (15.2%)             | 30 (15.5%)             | 21 (19.6%)              | 35 (19.2%)       | 7 (5.9%)              | 13 (4.7%)             |
| Moderately high risk                                    | 0 (0.0%)         | 7 (9.1%)                | 36 (36.4%)             | 71 (36.6%)             | 46 (43.0%)              | 75 (41.2%)       | 45 (37.8%)            | 102 (37.2%)           |
| Moderate risk   | 0 (0.0%)         | 2 (2.6%)                | 33 (33.3%)             | 49 (25.3%)             | 19 (17.8%)              | 38 (20.9%)       | 57 (47.9%)            | 119 (43.4%)           |
| Low risk  |                  |                         |                        |                        |                         |                  |                       |                       |
| <b>Weight, mean (SD), kg</b>                            | 92.8 (17.4)      | 90.0 (18.9)             | 87.4 (17.1)            | 86.5 (17.3)            | 92.6 (16.1)             | 93.5 (17.5)      | 80.7 (19.8)           | 79.2 (16.8)           |
| <b>BMI, mean (SD), kg/m<sup>2</sup></b>                 | 33.0 (5.3)       | 32.8 (6.7)              | 30.6 (5.5)             | 30.3 (5.9)             | 32.5 (5.6)              | 32.9 (6.0)       | 28.7 (5.9)            | 28.0 (5.1)            |
| <b>Waist circumference, mean (SD), cm</b>               | 108.8 (13.9)     | 105.2 (11.8)            | 102.1 (13.5)           | 101.3 (13.0)           | 106.3 (13.5)            | 106.9 (11.9)     | 95.4 (13.9)           | 94.1 (12.4)           |
| <b>SBP, mean (SD), mmHg</b>                             | 130.7 (14.5)     | 129.4 (14.5)            | 126.9 (15.4)           | 128.8 (13.8)           | 130.8 (13.7)            | 131.1 (12.8)     | 123.8 (14.2)          | 122.8 (13.6)          |
| <b>DBP, mean (SD), mmHg</b>                             | 79.2 (9.5)       | 79.6 (9.1)              | 78.7 (9.7)             | 78.2 (9.8)             | 82.0 (8.4)              | 80.0 (8.6)       | 76.7 (9.4)            | 76.7 (8.7)            |
| <b>Glycaemic Parameters</b>                             |                  |                         |                        |                        |                         |                  |                       |                       |
| <b>HbA<sub>1c</sub>, median (Q1, Q3), %</b>             | 6.4 (6.0, 7.4)   | 6.5 (6.2, 6.9)          | 5.8 (5.5, 6.0)         | 5.8 (5.6, 6.0)         | 5.7 (5.5, 5.9)          | 5.8 (5.6, 6.0)   | 5.5 (5.3, 5.7)        | 5.5 (5.3, 5.7)        |
| <b>FPG, median (Q1, Q3), mmol/L</b>                     | 6.5 (5.7, 7.9)   | 6.5 (5.8, 7.4)          | 5.8 (5.7, 6.1)         | 5.9 (5.7, 6.1)         | 5.6 (5.2, 6.1)          | 5.7 (5.3, 5.9)   | 5.1 (4.9, 5.3)        | 5.1 (4.8, 5.3)        |
| <b>Insulin, median (Q1, Q3), pmol/L</b>                 | 122.0<br>(107.6, | 143.5 (100.4,<br>200.9) | 122.0 (86.1,<br>179.4) | 122.0 (86.1,<br>147.1) | 122.0 (100.4,<br>172.2) | 129.2<br>(100.4, | 89.7 (64.6,<br>129.2) | 86.1 (64.6,<br>107.6) |

|   |                     |                     |                     |                     |                      |                      |                     |                     |
|---|---------------------|---------------------|---------------------|---------------------|----------------------|----------------------|---------------------|---------------------|
|   | 186.6)              |                     |                     |                     |                      | 172.2)               |                     |                     |
| <b>C-Peptide</b> , median (Q1, Q3), nmol/L  | 1.1 (0.7, 1.4)      | 1.0 (0.8, 1.4)      | 0.9 (0.7, 1.3)      | 0.8 (0.6, 1.1)      | 0.9 (0.8, 1.3)       | 0.9 (0.7, 1.4)       | 0.7 (0.5, 1.0)      | 0.6 (0.5, 0.8)      |
| <b>HOMA_%B</b> , median (Q1, Q3), %   | 104.3 (83.8, 145.5) | 105.3 (72.6, 136.0) | 116.2 (92.8, 142.1) | 106.3 (90.5, 129.0) | 134.2 (111.1, 161.6) | 133.6 (106.4, 167.9) | 121.9 (97.8, 147.8) | 111.1 (91.6, 134.2) |
| <b>HOMA_IR</b> , median (Q1, Q3), %/100   | 2.5 (2.2, 3.9)      | 2.8 (2.0, 3.9)      | 2.3 (1.7, 3.5)      | 2.3 (1.6, 2.8)      | 2.4 (1.8, 3.1)       | 2.5 (1.9, 3.2)       | 1.7 (1.2, 2.4)      | 1.6 (1.2, 2.0)      |
| <b>Lipid Parameters</b>   |                     |                     |                     |                     |                      |                      |                     |                     |
| <b>Low-density lipoprotein cholesterol</b> , mean (SD), mmol/L  | 2.6 (0.6)           | 2.7 (0.7)           | 2.6 (0.5)           | 2.7 (0.5)           | 2.8 (0.6)            | 2.7 (0.6)            | 2.7 (0.5)           | 2.7 (0.6)           |
| <b>Lipoprotein (a)</b> , median (Q1, Q3), nmol/L  | 47.0 (8.0, 137.0)   | 97.0 (30.0, 198.0)  | 28.5 (9.0, 97.0)    | 30.3 (13.0, 117.0)  | 37.0 (12.0, 155.0)   | 30.0 (9.0, 117.0)    | 41.0 (14.0, 140.0)  | 37.0 (13.0, 134.3)  |
| <b>Triglycerides</b> , median (Q1, Q3), mmol/L  | 1.3 (1.0, 1.7)      | 1.3 (1.1, 1.8)      | 1.4 (1.0, 1.9)      | 1.3 (1.0, 1.8)      | 1.8 (1.2, 2.2)       | 1.5 (1.1, 2.0)       | 1.1 (0.9, 1.3)      | 1.0 (0.8, 1.3)      |
| <b>High-density lipoprotein cholesterol</b> , mean (SD), mmol/L   | 1.2 (0.3)           | 1.2 (0.3)           | 1.3 (0.4)           | 1.3 (0.4)           | 1.2 (0.3)            | 1.2 (0.3)            | 1.6 (0.4)           | 1.5 (0.4)           |
| <b>Apolipoprotein B</b> , mean (SD), g/L  | 0.88 (0.19)         | 0.9 (0.19)          | 0.87 (0.13)         | 0.88 (0.17)         | 0.93 (0.18)          | 0.92 (0.18)          | 0.84 (0.14)         | 0.84 (0.14)         |
| <p>To convert variables from SI units (mmol/L) to conventional units (mg/dL) multiply by 18.02 for glucose and 38.61 for cholesterol. Lipoprotein (a) measurements cannot be converted directly from nmol/L to mg/dL due to high variability in apo(a) isoforms, but multiplying by 0.42 will yield an approximate value. To convert apoB values from g/L to mg/dL multiply by 100. To convert insulin from pmol/L to <math>\mu</math>IU/mL multiply by 0.14. To convert C-peptide values from nmol/L to ng/mL multiply by 3.00.</p> <p>Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; EvoMab, evolocumab; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HOMA_%B, homeostasis-model assessment -<math>\beta</math> cell function; HOMA_IR, homeostasis-model assessment insulin resistance; IFG, impaired fasting glucose; n, number</p> |                     |                     |                     |                     |                      |                      |                     |                     |

of patients; MesS, metabolic syndrome; NCEP, national cholesterol education program; Pbo, placebo; Q1, Q3, first and third quartiles; SBP, systolic blood pressure; SD, standard deviation

**Table 2. Week 52 Results**

| Parameter   | Type 2 Diabetes                   | IFG                                  | MetS                                 | No Dysglycemia or MetS                |
|---|-----------------------------------|--------------------------------------|--------------------------------------|---------------------------------------|
|   | Pbo (N = 43) vs.<br>EvoMab (N=77) | Pbo (N = 99) vs.<br>EvoMab (N = 194) | Pbo (N = 107) vs.<br>EvoMab(N = 182) | Pbo (N = 119) vs.<br>EvoMab (N = 274) |
| <b>Glycaemic Parameters</b>   |                                   |                                      |                                      |                                       |
| <b>HbA<sub>1c</sub></b><br>Tx difference vs. Pbo, median change from baseline (SE)* | 0.10 (0.10)                       | 0.00 (0.05)                          | 0.00 (0.03)                          | 0.00 (0.03)                           |
| <b>FPG</b><br>Tx difference vs. Pbo, median change from baseline (SE)*              | -0.11 (0.21)                      | 0.00 (0.07)                          | -0.06 (0.06)                         | 0.06 (0.06)                           |
| <b>Insulin</b><br>Tx difference vs. Pbo, median change from baseline (SE)*          | -7.2 (14.6)                       | 0.0 (7.3)                            | 0.0 (5.5)                            | -7.2 (5.5)                            |
| <b>C-Peptide</b><br>Tx difference vs. Pbo, median change from baseline (SE)*        | 0.1 (0.1)                         | 0.0 (0.04)                           | 0.0 (0.04)                           | 0.0 (0.03)                            |
| <b>HOMA_%B</b><br>Tx difference vs. Pbo, median change from baseline (SE)*          | 5.5 (5.7)                         | -1.3 (3.5)                           | -1.7 (3.9)                           | -2.3 (4.2)                            |
| <b>HOMA_IR</b><br>Tx difference vs. Pbo, median change from baseline (SE)*          | -0.2 (0.3)                        | 0.0 (0.1)                            | -0.1 (0.1)                           | -0.1 (0.1)                            |
| <b>Lipid Parameters</b>   |                                   |                                      |                                      |                                       |
| <b>Low-density lipoprotein cholesterol</b>  | -50.8 (6.0)†                      | -59.4 (3.4)†                         | -55.0 (3.5)†                         | -58.1 (3.5)†                          |

|   |                          |                          |                          |                          |
|---|--------------------------|--------------------------|--------------------------|--------------------------|
| Tx difference vs. Pbo, LS mean % change from baseline (SE)  |                          |                          |                          |                          |
| <b>Lipoprotein (a)</b>  |                          |                          |                          |                          |
| Tx difference vs. Pbo, LS mean % change from baseline (SE)  | -18.5 (4.8) <sup>†</sup> | -23.6 (3.5) <sup>†</sup> | -21.9 (3.5) <sup>†</sup> | -24.6 (3.0) <sup>†</sup> |
| <b>Triglycerides</b>  |                          |                          |                          |                          |
| Tx difference vs. Pbo, LS mean % change from baseline (SE)  | -8.8 (9.0)               | -9.4 (5.2)               | -17.2 (5.2) <sup>‡</sup> | -10.9 (4.3) <sup>‡</sup> |
| <b>High-density lipoprotein cholesterol</b>   |                          |                          |                          |                          |
| Tx difference vs. Pbo, LS mean % change from baseline (SE)  | 2.0 (2.3)                | 4.6 (2.0) <sup>‡</sup>   | 5.5 (2.1) <sup>‡</sup>   | 8.1 (1.7) <sup>†</sup>   |
| <b>Apolipoprotein B</b>   |                          |                          |                          |                          |
| Tx difference vs. Pbo, LS mean % change from baseline (SE)  | -38.0 (5.2) <sup>†</sup> | -46.1 (2.8) <sup>†</sup> | -43.3 (2.8) <sup>†</sup> | -45.0 (2.8) <sup>†</sup> |
| <p>To convert variables from SI units (mmol/L) to conventional units (mg/dL) multiply by 18.02 for glucose and 38.61 for cholesterol. Lipoprotein (a) measurements cannot be converted directly from nmol/L to mg/dL due to high variability in apo(a) isoforms, but multiplying by 0.42 will yield an approximate value. To convert apoB values from g/L to mg/dL multiply by 100. To convert insulin from pmol/L to <math>\mu</math>IU/mL multiply by 0.14. To convert C-peptide values from nmol/L to ng/mL multiply by 3.00.</p> <p>Abbreviations: EvoMab, evolocumab; FPG, fasting plasma glucose; HbA<sub>1c</sub>, glycated haemoglobin; HOMA_%B (<math>\beta</math> cell function) &amp; HOMA_IR (insulin resistance) calculated using the HOMA2 model; IFG, impaired fasting glucose; LS, least squares; MetS, metabolic syndrome; Pbo, placebo; SE, standard error; tx, treatment; LDL-C, ultracentrifugation low-density lipoprotein cholesterol.</p> <p>*Difference in median and SE calculated using Hodges-Lehmann method. <i>P</i> values were calculated using the Wilcoxon Rank Sum test. All p-values for all glycaemic parameters were non-significant (<math>P &gt; .05</math>).</p> <p><sup>†</sup><math>P \leq .001</math> vs. placebo</p> <p><sup>‡</sup><math>P \leq .05</math> vs. placebo</p> |                          |                          |                          |                          |

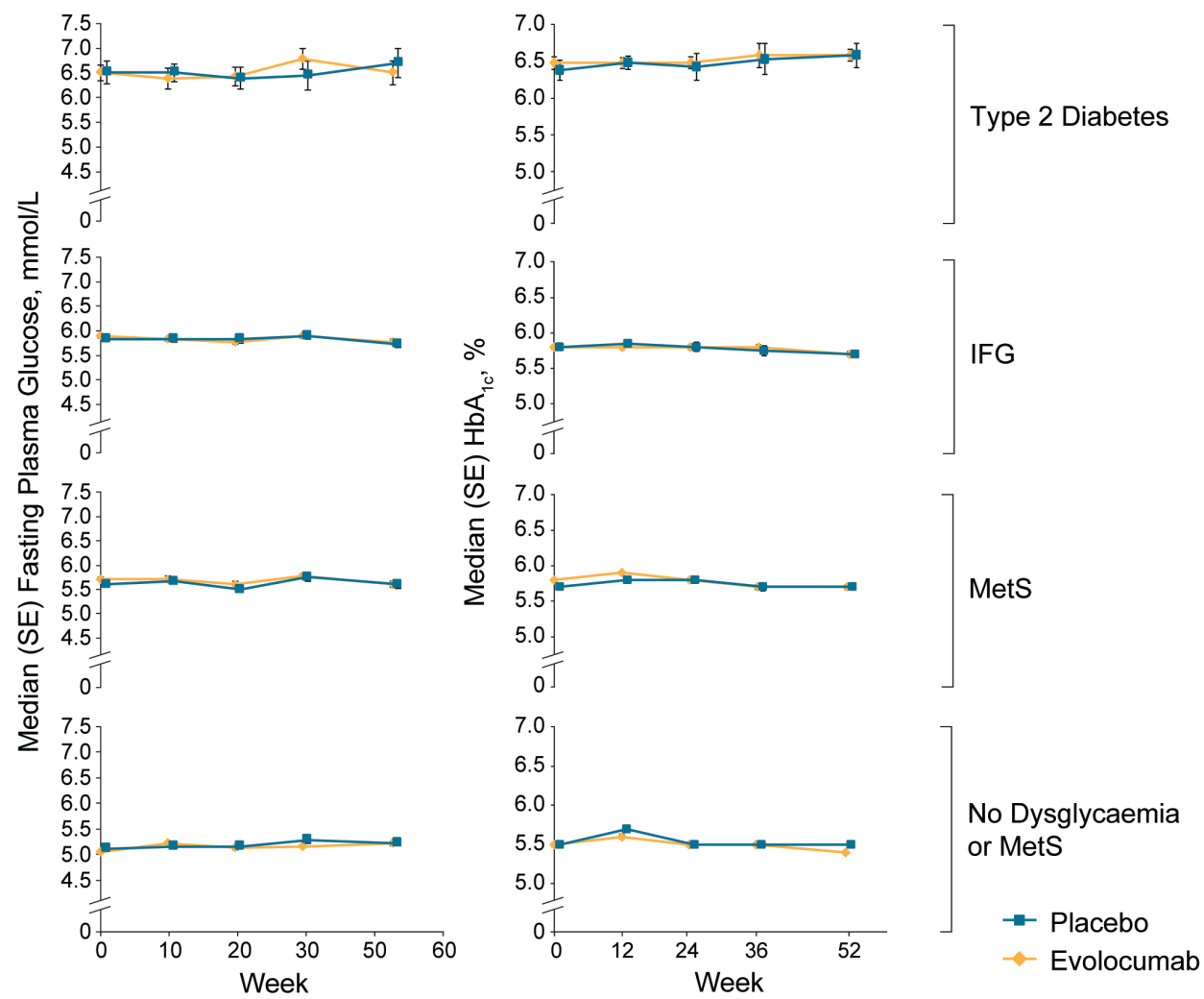
**Table 3. Safety**

| Safety, %   | Dysglycaemia or MetS |                     | No Dysglycaemia or MetS |                     |
|---|----------------------|---------------------|-------------------------|---------------------|
|   | Pbo<br>(N = 183)     | EvoMab<br>(N = 325) | Pbo<br>(N = 119)        | EvoMab<br>(N = 274) |
| Any Adverse Event (AE)  | 69.9                 | 73.2                | 80.7                    | 76.6                |
| Most common AEs in any group  |                      |                     |                         |                     |
| Nasopharyngitis   | 8.7                  | 8.6                 | 10.9                    | 12.8                |
| Upper respiratory tract infection   | 6.6                  | 10.2                | 5.9                     | 8.4                 |
| Influenza   | 6.6                  | 9.2                 | 5.9                     | 5.5                 |
| Back Pain   | 5.5                  | 5.5                 | 5.9                     | 6.9                 |
| Grade $\geq 2$  | 46.4                 | 44.9                | 47.1                    | 44.9                |
| Grade $\geq 3$  | 4.9                  | 10.5                | 5.0                     | 4.7                 |
| Grade $\geq 4$  | 0.0                  | 0.9                 | 0.0                     | 1.1                 |
| Serious   | 5.5                  | 6.5                 | 2.5                     | 4.4                 |
| Leading to discontinuation  | 1.1                  | 2.5                 | 0.8                     | 1.8                 |
| CK > 5 x ULN*   | 0.5                  | 1.2                 | 0.0                     | 1.1                 |
| CK > 10 x ULN*  | 0.5                  | 0.6                 | 0.0                     | 0.4                 |
| ALT or AST > 3 x ULN*   | 0.5                  | 0.6                 | 1.7                     | 1.1                 |
| ALT or AST > 5 x ULN*   | 0.0                  | 0.3                 | 0.8                     | 0.7                 |
| Total bilirubin > 2 x ULN*  | 0.5                  | 0.3                 | 0.0                     | 1.5                 |
| Potential injection site reactions  | 4.4                  | 6.2                 | 5.9                     | 5.1                 |
| Postbaseline binding antibodies   | 0.0                  | 0.3                 | 0.0                     | 0.0                 |
| Abbreviations: ALT/AST, alanine aminotransferase/aspartate aminotransferase; CK, creatine kinase; EvoMab, evolocumab; MetS, metabolic syndrome; Pbo, placebo; ULN, upper limit of normal. |                      |                     |                         |                     |
| *At any post-baseline study visit   |                      |                     |                         |                     |

**Table 4. New Onset Diabetes\***

|  | <b>Placebo</b> | <b>Evolocumab</b> | <b>P-value†</b> |
|--|----------------|-------------------|-----------------|
| All subjects - N   | 259            | 522               |                 |
| Postbaseline new-onset diabetes – n (%)  | 17 (6.6%)      | 29 (5.6%)         | 0.629           |
| Baseline normoglycaemia (FPG < 5.6 mmol/L) - N   | 160            | 328               |                 |
| Postbaseline new-onset diabetes – n (%)  | 3 (1.9%)       | 9 (2.7%)          | 0.759           |
| Baseline IFG (FPG 5.6 – 6.9 mmol/L) - N  | 99             | 194               |                 |
| Postbaseline new-onset diabetes – n (%)  | 14 (14.1%)     | 20 (10.3%)        | 0.340           |
| <p>To convert variables from SI units (mmol/L) to conventional units (mg/dL) multiply by 18.02 for glucose</p> <p>Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose.</p> <p>*Postbaseline FPG <math>\geq 7.0</math> mmol/L, HbA1c <math>\geq 6.5\%</math>, adverse event of diabetes mellitus, or diabetes medication use</p> <p>†P values calculated using Fisher's exact test with no multiplicity adjustment. All p values are nominal.</p> |                |                   |                 |





**Figure 1.** Impact of Evolocumab on Fasting Plasma Glucose and HbA<sub>1c</sub>. Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; MetS, metabolic syndrome; SE, standard error.