Effect of Evolocumab on Cholesterol Synthesis and Absorption

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Running Title (max 60 characters): Evolocumab and cholesterol absorption and synthesis

Abbreviations: CI, confidence interval; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; LDL-R, LDL receptor; LLoQ, lower limit of quantification; LSGM, least squares geometric mean; PCSK9, proprotein convertase subtilisin/kexin type 9; PO, orally; Q2W, once every 2 weeks; QM, monthly; QD, once daily; QW, once a week; SC, subcutaneous; SD, standard deviation; SE, standard error; SEM, standard error of mean

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Abstract

The effects of cholesterol-lowering drugs, including those that reduce cholesterol synthesis (statins) and those that reduce cholesterol absorption (ezetimibe), on cholesterol absorption and synthesis are well understood. PCSK9 inhibitors are a novel class of cholesterol-lowering drugs that robustly reduce LDL-C, but little is known about their effects on cholesterol absorption and synthesis. We evaluated how treatment with evolocumab, a fully human monoclonal IgG2 antibody to PCSK9, affects markers of cholesterol synthesis and absorption by measuring these markers in patients from an evolocumab clinical trial. At 2 weeks, changes in $\beta$-sitosterol/TC from baseline were 4% for placebo, 10% for evolocumab 140 mg (nonsignificant vs placebo), and 26% for evolocumab 420 mg ($p<0.001$ vs placebo). Changes in campesterol/TC at week 2 relative to baseline between placebo and evolocumab were all nonsignificant. Evolocumab had a modest effect on markers of cholesterol synthesis. At 2 weeks, changes in desmosterol/TC were 1% for placebo, 7% for evolocumab 140 mg (nonsignificant vs placebo), and 15% for evolocumab 420 mg ($p<0.01$ vs placebo). Changes from baseline in lathosterol/TC at week 2 between placebo and evolocumab were nonsignificant. These results suggest evolocumab has a modest effect on cholesterol synthesis and absorption despite significant LDL-C lowering.

Key words: Cholesterol/Absorption, Cholesterol/Biosynthesis, Lipids, LDL, Drug therapy

Supplementary key words (limit 5): PCSK9, cholesterol, evolocumab, statin, lipid-lowering
INTRODUCTION

Lowering plasma cholesterol, including LDL-C, has been shown to reduce cardiovascular events (1, 2). Plasma cholesterol concentrations reflect the homeostasis achieved between cholesterol input (endogenous cholesterol synthesis as well as dietary absorption) (3-5) and output (cholesterol catabolism, particularly as bile acids) (6). Cholesterol synthesis and absorption can be measured using biomarkers (3). Specifically, plasma concentrations of the cholesterol precursors lathosterol and desmosterol are markers of cholesterol synthesis while plasma concentrations of the plant sterols β-sitosterol and campesterol are markers of cholesterol absorption (7-9).

The effects of cholesterol-lowering agents, including both those that reduce cholesterol synthesis (statins) and those that reduce cholesterol absorption in the intestines (ezetimibe), on markers of cholesterol absorption or synthesis have been evaluated in many studies (10-21). Ezetimibe has been shown to reduce cholesterol absorption markers while increasing cholesterol synthesis markers (15-20). For example, ezetimibe therapy resulted in a 49% reduction in the campesterol/Total cholesterol (TC) ratio and a 54% increase in the lathosterol/TC ratio (16). The increase in synthesis markers suggests a compensatory mechanism resulting from the inhibition of cholesterol absorption, which may limit the degree of cholesterol lowering that can be achieved with ezetimibe.

Conversely, statins have been shown to reduce cholesterol synthesis markers but increase cholesterol absorption markers (10-18). For example, in patients receiving a maximal dose of either rosvastatin or atorvastatin, the lathosterol/TC ratio was reduced by 64% and 68%, respectively, consistent with decreased cholesterol synthesis (12). Additionally, cholesterol absorption increased with statin treatment as evidenced by an increase in the campesterol/TC ratio of 52% (rosuvastatin) and 72% (atorvastatin) (12). The increase in cholesterol absorption following statin treatment suggests a compensatory mechanism for the statin-induced decreased cholesterol production, which again may limit the degree of cholesterol lowering that can be achieved with statins. Indeed, in hypercholesterolemic patients, ezetimibe added to existing statin therapy resulted in additional LDL-C lowering of 29%, 25%, and 23% in high-, medium-, and low-dose statin groups, respectively (18). Furthermore, those receiving high-dose statins
showed the greatest reduction in cholesterol absorption markers and lowest increase in synthesis markers following the addition of ezetimibe (18).

Statins have also been associated with an elevation in proprotein convertase subtilisin/kexin type 9 (PCSK9) plasma concentrations (22), and PCSK9 has been shown to increase intestinal lipoprotein production through a variety of mechanisms, including increased apoB stability, activation of microsomal transfer protein (MTP), increased lipidogenesis, and upregulation of NPC1L1 (23). Following statin treatment, there is also an increase in intestinal cholesterol absorption (24). Thus, the statin-induced compensatory increase in intestinal cholesterol absorption may be at least partially mediated by an increase in PCSK9. PCSK9 inhibitors such as evolocumab represent a novel class of cholesterol-lowering therapies. Evolocumab is a fully human monoclonal IgG2 antibody that binds specifically to PCSK9, prevents its interaction with the LDL receptor (LDL-R), and promotes LDL-R recycling. This, in turn, increases LDL-C uptake and clearance by LDL-Rs located on hepatocytes (25). Evolocumab has been shown to significantly reduce LDL-C in a number of different patient populations and as monotherapy or in combination with a statin (26-33), but little is known about how PCSK9 inhibition affects markers of cholesterol absorption and synthesis. Here, in this post-hoc exploratory analysis, we evaluated how treatment with evolocumab affects cholesterol synthesis and absorption by measuring markers of cholesterol synthesis and absorption in patients from the phase two evolocumab monotherapy clinical trial, MENDEL (33).
MATERIALS AND METHODS

MENDEL study design and patients

Plasma samples for biomarker analysis were collected from hypercholesterolemic patients who were not taking any lipid-lowering agents and who were enrolled in a 12-week phase 2 evolocumab monotherapy trial (33). Patients were randomized 1:1 to one of nine treatment groups: subcutaneous (SC) placebo once every 2 weeks (Q2W) or every month (QM), SC evolocumab 70 mg Q2W, 105 mg Q2W, 140 mg Q2W, 280 mg QM, 350 mg QM, or 420 mg QM, and oral placebo or ezetimibe 10 mg once daily (QD). Thus, all patients received injections (placebo or active drug) and all patients received oral placebo or active ezetimibe. Plasma was collected prior to study drug administration (day 1) and on weeks 2, 4, and 12 (Figure 1). For the analysis reported here, we focused on the 140 mg and 420 mg doses and the week 2 and week 12 time points. Complete data sets including all time points and doses are included in the supplementary information. The study protocol was approved by an independent ethics committee or institutional review board at each study center, and all patients provided written consent prior to the initiation of study procedures.

Measurement of cholesterol and plasma sterols

Plasma samples stored at −80°C were sent on dry ice to Boston Heart Diagnostics (Framingham, MA) for the measurement of plasma sterols by gas-liquid chromatography, as previously described (19). Samples were measured for β-sitosterol, campesterol, desmosterol, and lathosterol. Measurement of TC was performed by a central laboratory after a > 9-hour fast (Medpace Reference Laboratories, Cincinnati, OH, USA and Leuven, Belgium) (33). Absolute concentrations of each sterol were recorded and analyzed. The ratio of each sterol to TC was calculated, which is a common practice as plasma sterols are associated with circulating lipoproteins (8).

Data analysis

In this exploratory analysis, samples with sterol concentrations below the lower limit of quantification (LLOQ), were imputed with the value of the LLOQ. For complete details on the number of samples with imputed values, please refer to the supplementary file. Data from placebo patients were pooled as one
cohort since there was no expectation that sterol concentrations would differ between those receiving placebo every two weeks or every four weeks, and LDL-C and TC were not different between these groups (31). Absolute concentrations of each sterol and the sterol/TC ratios were log transformed prior to all analyses.

For data over time analyses, each log transformed marker was analyzed using a repeated-measures mixed-effects model. The independent variables were treatment group, day, and the treatment group by day interaction. Log-transformed baseline marker data were included as a covariate and patient was included as a random effect. For each treatment group by day combination, least square geometric mean (LSGM), LSGM ratios to baseline, percentage change from baseline, and the ratio to placebo along with 95% CIs and $P$ values for the null hypothesis of no difference from placebo were calculated. Additionally, the ratio to ezetimibe was calculated and an additional null hypothesis of no difference from ezetimibe was evaluated.

Pearson’s correlations were evaluated for the assessment of associations between log transformed baseline markers and the LDL-C response at week 2 and changes in absorption marker data and changes in synthesis marker data at week 2. Percent change from baseline in LDL-C at week 2 was used for correlations by treatment group, and dose-adjusted percent change in LDL-C at week 2 (percent change minus mean dose percent change) was used for correlations combining all evolocumab doses. As the greatest reduction in LDL-C was observed during the study at week 2, the week 2 time point was chosen for calculating these changes from baseline.

A level of 0.05 was considered significant for all analyses and since the analyses were exploratory in nature no correction for multiplicity was made.
RESULTS

Baseline Characteristics and Lipid Results

Complete baseline demographics and lipid data from this trial have been reported previously (33). Levels of baseline markers of cholesterol absorption and synthesis, including plasma sterol concentrations, were comparable across all treatment groups (Table 1, Supplementary Table 1).

In this study, LDL-C was reduced by 39% to 51%, and TC was reduced by 27% to 34% relative to baseline after 12 weeks of evolocumab therapy (33).

Effects of evolocumab on cholesterol absorption markers

Consistent with reductions in TC, absolute concentrations of β-sitosterol and campesterol were reduced from baseline in a dose-dependent manner, and were significantly lower at week 2 compared with placebo following treatment with evolocumab (p < 0.001; Table 2, Supplementary Table 2, Supplementary Figure 1). However, when data were expressed as a ratio to TC to account for the clearance of β-sitosterol and campesterol associated with the clearance of circulating lipoproteins, treatment with evolocumab as a monotherapy resulted in increases in these ratios from baseline. Mean percent changes from baseline to week 2 for β-sitosterol/TC were placebo: 4%, evolocumab 140 mg: 10% (not significant, n.s. vs placebo), and evolocumab 420 mg: 26% (p < 0.001 vs placebo). Values for campesterol/TC were placebo: 9%, evolocumab 140 mg: 4% (n.s. vs placebo), and evolocumab 420 mg: 22% (n.s. vs placebo) (Table 2, Figure 2). After 12 weeks, changes relative to baseline for β-sitosterol/TC were: placebo: 1%, evolocumab 140 mg: 15% (p < 0.05 vs placebo), and evolocumab 420 mg: 16% (p < 0.01 vs placebo), and campesterol/TC: placebo: 2%, evolocumab 140 mg: 6% (n.s vs placebo), and evolocumab 420 mg: 14% (n.s vs placebo) (Figure 2, Supplementary Table 3). These effects were in contrast to the decreases observed in patients receiving ezetimibe alone (Table 2, Figure 2, Supplementary Table 3, Supplementary Figure 1).

Effects of evolocumab on cholesterol synthesis markers

As with the absorption markers, reduction in the absolute concentration of synthesis markers mirrored the reductions seen in TC. Absolute concentrations of both cholesterol synthesis markers, lathosterol and...
desmosterol, were significantly reduced compared with placebo by evolocumab treatment in a dose dependent manner, consistent with observed reductions in TC. (Table 2, Supplementary Table 4, Supplementary Figure 2).

When normalized as a ratio to TC, 2 weeks of treatment with evolocumab resulted in no significant changes from baseline compared to placebo for lathosterol/TC (placebo: 2%, evolocumab 140 mg: –1%, and evolocumab 420 mg: 2%), but did result in some significant increases compared to placebo in desmosterol/TC (placebo: 1%, evolocumab 140 mg: 7% (n.s. vs placebo), and evolocumab 420 mg: 15% (p < 0.01 vs placebo) (Table 2, Figure 3). By week 12, no significant increases from baseline compared to placebo in lathosterol/TC were observed (placebo: –3%, evolocumab 140 mg: 4%, and 420 mg: 9%) but some increases compared to placebo in desmosterol/TC (placebo: 1%, evolocumab 140 mg: 10% (n.s. vs placebo), and evolocumab 420 mg: 16% (p < 0.05 compared to placebo)) were apparent (Figure 3, Supplementary Table 5). Desmosterol/TC and lathosterol/TC ratios were both significantly higher in the ezetimibe cohort than in the evolocumab receiving cohorts (p < 0.05 at weeks 2 and 12) Figure 3, Supplementary Table 5).

Relationship between baseline cholesterol absorption and synthesis markers and achieved LDL-C
Following evolocumab treatment, a positive correlation was noted between baseline levels of cholesterol absorption markers and the dose-adjusted percent change in LDL-C at week 2 for \( \beta \)-sitosterol (\( r = 0.17, p = 0.009 \); Figure 4A, \( \beta \)-sitosterol_TC (\( r = 0.13, p = 0.05 \); Figure 4B) and campesterol (\( r = 0.13, p = 0.05 \); Figure 4C), while baseline levels of cholesterol synthesis markers were shown to have a negative correlation between desmosterol/TC ratio and LDL-C (\( r = –0.18; p = 0.005 \); Figure 4D). No significant correlations were observed for 140 mg or 420 mg dose groups. No significant correlations were seen following treatment with ezetimibe or placebo. Correlations between changes in absorption and changes in synthesis markers are detailed in the supplementary information (Supplementary Tables 6 and 7).

DISCUSSION
Reduction of plasma LDL-C remains a mainstay of cardiovascular disease treatment and prevention. Monoclonal antibodies against PCSK9, such as evolocumab, represent a novel treatment option to
robustly reduce circulating levels of LDL-C. As studies with statins and ezetimibe have shown, pharmacologic reductions in LDL-C resulting from reduced cholesterol synthesis or absorption can lead to compensatory responses. Because of these observations, we sought to evaluate if treatment with evolocumab would affect levels of cholesterol absorption or synthesis biomarkers. To our knowledge, this is the first manuscript describing the effects of PCSK9 inhibition on markers of cholesterol absorption and synthesis in human patients.

Following treatment with evolocumab, we observed reductions in the absolute concentrations of both synthesis and absorption markers in a dose-dependent manner. This was in contrast to ezetimibe-treated patients who showed reductions in the absolute concentrations of absorption markers and increases in the absolute concentrations of the synthesis markers. Though not tested here directly, previous studies have shown that absolute concentrations of synthesis markers are significantly reduced by statins, while the absolute concentration of absorption markers are increased (11-13, 16, 17).

However, as changes in both cholesterol synthesis and absorption markers correlate strongly with changes in TC, it is not unexpected that absolute concentrations of these markers would decrease in the setting of robust cholesterol reductions. In order to account for the significant reductions in TC that occur with evolocumab therapy, the ratio of cholesterol absorption and synthesis markers to TC was also evaluated as is routinely done in these studies where significant changes in cholesterol occur with pharmacological intervention. Following treatment with evolocumab, we observed increases in the β-sitosterol/TC and campesterol/TC ratios ranging from 4%–26%. These increases only achieved statistical significance compared with placebo for β-sitosterol/TC at week 12 for the 140 mg dose and at weeks 2 and 12 for the 420 mg dose. These relatively modest increases in cholesterol absorption markers/TC ratio differ significantly from the much higher elevations (up to 96% increase)(10) in cholesterol absorption markers/TC seen with maximal doses of statins. These modest increases are also in contrast to what we observed in ezetimibe-treated patients, where we observed decreases in the β-sitosterol/TC and campesterol/TC ratios, consistent with ezetimibe’s known mechanism of action of decreasing cholesterol absorption. These results suggest that while the significant LDL-C lowering that occurs with evolocumab
monotherapy may be associated with a slight increase in cholesterol absorption, the increase is much less than that seen with statins.

Evolocumab treatment had a small impact on markers of cholesterol synthesis. The ratios of lathosterol/TC and desmosterol/TC remained essentially unchanged or were slightly increased, especially as measured by desmosterol. The slight increase in synthesis of 15-16% observed in the 420 mg cohort for desmosterol/TC is somewhat surprising given that one would expect an increase in hepatic free cholesterol given the degree of LDL-C lowering observed at this dose. Although not measured in this study, an increase in free cholesterol secretion into the bile may account for this observation and should be followed up on in future studies. The modest effects on synthesis markers are in contrast with the increases in cholesterol synthesis markers seen in ezetimibe-treated patients and the decreases in these markers that have been reported with statins (10-18). These data indicate that the LDL-C reductions seen with evolocumab treatment are not due to decreased cholesterol production and that evolocumab, unlike ezetimibe, does not induce a compensatory response of increased cholesterol synthesis. Thus the mechanism of decreased LDL-C with evolocumab is due to increased catabolism rather than decreased production of cholesterol.

Finally, we observed that higher baseline cholesterol synthesis (as evidenced by higher desmosterol/TC ratios) and lower baseline cholesterol absorption (as evidence by lower β-sitosterol, β-sitosterol/TC, and campesterol at baseline) were associated with greater LDL-C lowering with evolocumab, although this association was modest (r = –0.18 for synthesis and r = 0.13 to 0.17 for absorption). Given this weak association, patients are expected to have a similar degree of LDL-C reduction with evolocumab treatment regardless of their baseline rates of cholesterol production or absorption, and it is not necessary to measure these prior to treatment.

In conclusion, evolocumab as monotherapy resulted in marked TC and LDL-C lowering. Evolocumab had a modest effect on markers of cholesterol absorption and synthesis, and baseline levels of cholesterol synthesis or absorption were weakly correlated with the degree of LDL-C lowering seen with evolocumab.
treatment. These observations are not unexpected, given the mechanism of action of evolocumab (increased clearance of LDL-C).
DISCLOSURES

This study was funded by Amgen Inc. All authors are current or former Amgen employees and hold Amgen stock/stock options.

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REFERENCES


### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab SC 140 mg Q2W (n = 45)</th>
<th>Evolocumab SC 420 mg QM (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, %</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td>Age, years, mean ± SD</td>
<td>53 ± 12</td>
<td>50 ± 12</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean ± SD</td>
<td>30 ± 6.3</td>
<td>32 ± 7.6</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL, mean ± SD</td>
<td>220 ± 27</td>
<td>221 ± 29</td>
</tr>
<tr>
<td>LDL-C, mg/dL, mean ± SD</td>
<td>140 ± 21</td>
<td>141 ± 21</td>
</tr>
<tr>
<td>HDL-C, mg/dL, mean ± SD</td>
<td>56 ± 16</td>
<td>50 ± 15</td>
</tr>
<tr>
<td>Triglycerides, mg/dL, mean ± SD</td>
<td>124 ± 58</td>
<td>152 ± 91</td>
</tr>
<tr>
<td>β-sitosterol, mg/L, LSGM (95% CI)</td>
<td>2.0 (1.9, 2.2)</td>
<td>2.1 (1.9, 2.2)</td>
</tr>
<tr>
<td>β-sitosterol/TC, 100x μmol/mmol, LSGM (95% CI)</td>
<td>87 (81, 93)</td>
<td>88 (82, 94)</td>
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<tr>
<td>Desmosterol, mg/L, LSGM (95% CI)</td>
<td>2 (1, 2)</td>
<td>2 (1, 2)</td>
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<tr>
<td>Desmosterol/TC, 100x μmol/mmol, LSGM (95% CI)</td>
<td>69 (66, 73)</td>
<td>71 (68, 75)</td>
</tr>
<tr>
<td>Campesterol, mg/L, LSGM (95% CI)</td>
<td>3.1 (2.8, 3.4)</td>
<td>3.1 (2.8, 3.4)</td>
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<tr>
<td>Campesterol/TC, 100x μmol/mmol, LSGM (95% CI)</td>
<td>135 (124, 148)</td>
<td>134 (123, 147)</td>
</tr>
<tr>
<td>Lathosterol, mg/L, LSGM (95% CI)</td>
<td>2.7 (2.5, 2.9)</td>
<td>2.7 (2.5, 3.0)</td>
</tr>
<tr>
<td>Lathosterol/TC, 100x μmol/mmol, LSGM (95% CI)</td>
<td>123 (114, 133)</td>
<td>124 (115, 134)</td>
</tr>
</tbody>
</table>
CI, confidence interval; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; LSGM, least squares geometric mean; Q2W, once every 2 weeks; QM, monthly; SD, standard deviation; TC, total cholesterol.
### TABLE 2. Cholesterol Absorption and Synthesis Markers at Weeks 0 (Day 1) and 2

<table>
<thead>
<tr>
<th>Marker</th>
<th>Dose</th>
<th>Week 0 (Day 1)</th>
<th>Week 2</th>
<th>Mean % change (95% CI)</th>
<th>pvalue</th>
<th>Week 0 (Day 1)</th>
<th>Week 2</th>
<th>Mean % change (95% CI)</th>
<th>pvalue</th>
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<tr>
<td></td>
<td>n, LSGM</td>
<td>n, LSGM</td>
<td></td>
<td></td>
<td></td>
<td>n, LSGM</td>
<td>n, LSGM</td>
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<tr>
<td></td>
<td><strong>Absolute Concentration</strong> (mg/L)</td>
<td><strong>Ratio to Total Cholesterol (TC) 100x μmol/mmol TC</strong></td>
<td></td>
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<tr>
<td>Absorption</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-sitosterol</td>
<td>Placebo</td>
<td>87, 2.1</td>
<td>77, 2.2</td>
<td>4 (–2, 11)</td>
<td>87, 90</td>
<td>77, 92</td>
<td>4 (–2, 11)</td>
<td></td>
<td>0.29</td>
</tr>
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<td></td>
<td>Evolocumab SC 140 mg Q2W</td>
<td>45, 2.0</td>
<td>44, 1.5</td>
<td>–27 (–33, –20)</td>
<td>&lt;0.001</td>
<td>45, 87</td>
<td>44, 99</td>
<td>10 (2, 19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Evolocumab SC 420 mg QM</td>
<td>43, 2.1</td>
<td>31, 1.5</td>
<td>–27 (–34, –20)</td>
<td>&lt;0.001</td>
<td>43, 88</td>
<td>31, 113</td>
<td>26 (15, 38)</td>
<td>&lt;0.001</td>
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<td>Synthesis</td>
<td>Campesterol</td>
<td>Placebo</td>
<td>87, 3.2</td>
<td>77, 3.4</td>
<td>9 (0.7, 18)</td>
<td>87, 140</td>
<td>77, 149</td>
<td>9 (1, 18)</td>
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<td></td>
<td>Evolocumab SC 140 mg Q2W</td>
<td>45, 3.1</td>
<td>44, 2.2</td>
<td>–30 (–37, –22)</td>
<td>&lt;0.001</td>
<td>45, 135</td>
<td>44, 145</td>
<td>4 (–6, 16)</td>
<td>0.48</td>
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<td>Evolocumab SC 420 mg QM</td>
<td>43, 3.1</td>
<td>31, 2.3</td>
<td>–30 (–38, –21)</td>
<td>&lt;0.001</td>
<td>43, 134</td>
<td>31, 172</td>
<td>22 (8, 36)</td>
<td>0.13</td>
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<td>Lathosterol</td>
<td>Evolocumab SC 140 mg Q2W</td>
<td>45, 2.7</td>
<td>44, 1.8</td>
<td>–34 (–40, –28)</td>
<td>&lt;0.001</td>
<td>45, 123</td>
<td>44, 121</td>
<td>–1 (–10, 8)</td>
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<td>Treatment</td>
<td>Baseline Mean</td>
<td>Baseline Median</td>
<td>Change from Baseline</td>
<td>P Value</td>
<td>Placebo Baseline Mean</td>
<td>Placebo Baseline Median</td>
<td>Change from Placebo</td>
<td>P Value</td>
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<tr>
<td>Evolocumab SC 420 mg QM</td>
<td>43.2</td>
<td>31.6</td>
<td>-41 (-47, -35)</td>
<td>&lt;0.001</td>
<td>43.124</td>
<td>31.124</td>
<td>2 (-8, 13)</td>
<td>0.95</td>
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<tr>
<td>Evolocumab SC 140 mg Q2W</td>
<td>45.1</td>
<td>44.1</td>
<td>-29 (-34, -24)</td>
<td>&lt;0.001</td>
<td>45.69</td>
<td>44.75</td>
<td>7 (0.5, 13)</td>
<td>0.13</td>
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<td>Evolocumab SC 420 mg QM</td>
<td>43.1</td>
<td>31.0</td>
<td>-34 (-39, -28)</td>
<td>&lt;0.001</td>
<td>43.71</td>
<td>31.81</td>
<td>15 (7, 23)</td>
<td>0.002</td>
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*P* value associated with change from baseline compared with corresponding placebo.

CI, confidence interval; LSGM, least squares geometric mean; Q2W, once every 2 weeks; QM, monthly; SC, subcutaneous; TC, total cholesterol.
Figure 1. Design of the MENDEL-1 monotherapy study (33).
Figure 2. Mean percent change from baseline in cholesterol absorption markers. P values calculated versus placebo. *P < .05; †P < .001. SE, standard error; TC, total cholesterol.
Figure 3. **Mean** percent change from baseline in markers of cholesterol synthesis. P values calculated versus placebo. *P < .05; †P < .01. SE, standard error; TC, total cholesterol.
Figure 4 Scatter plots of percent change from baseline in LDL-C at week 2 and (4A) baseline β-sitosterol [\(r = 0.17\) (\(p < 0.01\)) for the evolocumab group], (4B) β-sitosterol/TC [\(r = 0.13\) (\(p < 0.05\)) for the evolocumab group], (4C) campesterol [\(r = 0.13\) (\(p < 0.05\)) for the evolocumab group] (4D) baseline desmosterol/TC [\(r = -0.18\) (\(p < 0.01\)) for evolocumab group]. Solid lines indicate regression line. LDL-C, LDL-cholesterol; TC, total cholesterol.