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Anti-PCSK9 Monotherapy for Hypercholesterolemia

The MENDEL-2 Randomized, Controlled Phase III Clinical Trial of Evolocumab

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Objectives The aim of this study was to compare biweekly and monthly evolocumab with placebo and oral ezetimibe in patients with hypercholesterolemia in a phase III trial.

Background Evolocumab, a fully human monoclonal antibody against proprotein convertase subtilisin/kexin type 9 (PCSK9), significantly reduced LDL-C in phase II trials.

Methods Patients 18 to 80 years of age with fasting low-density lipoprotein cholesterol (LDL-C) ≥100 and <190 mg/dl and Framingham risk scores ≤10% were randomized (1:1:1:1:2:2) to oral placebo and subcutaneous (SC) placebo biweekly; oral placebo and SC placebo monthly; ezetimibe and SC placebo biweekly; ezetimibe and SC placebo monthly; oral placebo and evolocumab 140 mg biweekly; or oral placebo and evolocumab 420 mg monthly.

Results A total of 614 patients were randomized and administered doses. Evolocumab treatment reduced LDL-C from baseline, on average, by 55% to 57% more than placebo and 38% to 40% more than ezetimibe ($p < 0.001$ for all comparisons). Evolocumab treatment also favorably altered other lipoprotein levels. Treatment-emergent adverse events (AEs), muscle-related AEs, and laboratory abnormalities were comparable across treatment groups.

Conclusions In the largest monotherapy trial using a PCSK9 inhibitor to date, evolocumab yielded significant LDL-C reductions compared with placebo or ezetimibe and was well tolerated in patients with hypercholesterolemia. (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2 [MENDEL-2]; NCT01763827) (J Am Coll Cardiol 2014;63:2531–40) © 2014 by the American College of Cardiology Foundation

Despite the success of statin therapy, significant gaps remain in the treatment of hypercholesterolemia. Many patients on statin regimens still experience complications of atherosclerosis. Others have persistently high low-density lipoprotein cholesterol (LDL-C) levels due to severe forms of hypercholesterolemia or poor tolerability of available medications. For these populations, new effective lipid-modifying therapies may offer clinical benefits.

Statin use up-regulates proprotein convertase subtilisin/kexin type 9 (PCSK9) levels; therefore, therapies that target PCSK9 may perform differently as monotherapy than when added to statin treatment. In a previous dose-finding monotherapy study, evolocumab, a fully human monoclonal antibody against PCSK9, reduced placebo-corrected LDL-C levels by 37.3% to 52.5% (1). Evolocumab 140 mg biweekly (every other week) and 420 mg monthly produced

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Abbreviations and Acronyms

AE = adverse event(s)
CV = cardiovascular
HDL-C = high-density lipoprotein cholesterol
LDL-C = low-density lipoprotein cholesterol
Lp(a) = lipoprotein
PCSK9 = proprotein convertase subtilisin/kexin type 9
SC = subcutaneous

the greatest LDL-C reductions with no evidence of dose-limiting adverse events (AEs) (1).

Because anti-PCSK9 antibodies may offer a therapeutic option for patients on or off statin therapy, the MENDEL-2 (Monoclonal Antibody Against PCSK9 to Reduce Elevated LDL-C in Subjects Currently Not Receiving Drug Therapy for Easing Lipid Levels-2) trial was designed to evaluate the efficacy and safety of biweekly and monthly evolocumab at doses anticipated for use in clinical practice in a large population of patients with primary hypercholesterolemia not confounded by statin use or a history of statin intolerance. The MENDEL-2 trial compared subcutaneous (SC) evolocumab with placebo and blinded oral ezetimibe, an agent widely used for patients unable to tolerate statins.

Methods

Patients. Following institutional review board approval and informed consent, 71 study sites in 9 countries enrolled men and women 18 to 80 years of age with fasting LDL-C levels ≥100 mg/dl and <190 mg/dl, triglycerides ≤400 mg/dl, and 10-year Framingham coronary heart disease risk scores ≤10% (2). Patients were randomized 1:1:1:1:2:2 to oral placebo and SC placebo biweekly; oral placebo and SC placebo monthly; ezetimibe and SC placebo biweekly; ezetimibe and SC placebo monthly; oral placebo and evolocumab 140 mg biweekly; or oral placebo and evolocumab 420 mg monthly. Randomization was stratified by LDL-C level (<130 mg/dl vs. ≥130 mg/dl). Patients and study personnel were blinded to treatment assignment and lipid results. Eligible patients could not have used lipid-regulating drugs within 3 months of enrollment.

Key exclusion criteria, study drug preparation, laboratory methods, and statistical analysis are described in the Online Appendix.

Endpoints. Coprimary endpoints were percent change from baseline in LDL-C level averaged at weeks 10 and 12 and at week 12. Key safety endpoints included the incidence of treatment-emergent AEs, serious AEs, development of anti-evolocumab antibodies, and increases of hepatic enzymes 3 times, bilirubin 2 times, and creatine kinase 5 times above the upper limit of normal.

Results

Patients. From January 21 through October 29, 2013, 615 patients were enrolled and randomly assigned to evolocumab (n = 306), placebo (n = 155), or ezetimibe (n = 154). One patient randomized to placebo did not receive study drug and was excluded from the analysis. Baseline characteristics were balanced between groups (Table 1). Ninety-seven percent of patients completed the study (Fig. 1).

Efficacy outcomes. LDL-C. Significant reductions in LDL-C levels from baseline occurred within 2 weeks in both biweekly and monthly evolocumab groups and were subsequently sustained for the duration of the trial. At 12 weeks, LDL-C levels had decreased from baseline, on average, by 57.0% (95% CI: −59.5% to −54.6%) with biweekly evolocumab compared with 0.1% (95% CI: −3.2% to 3.4%) for

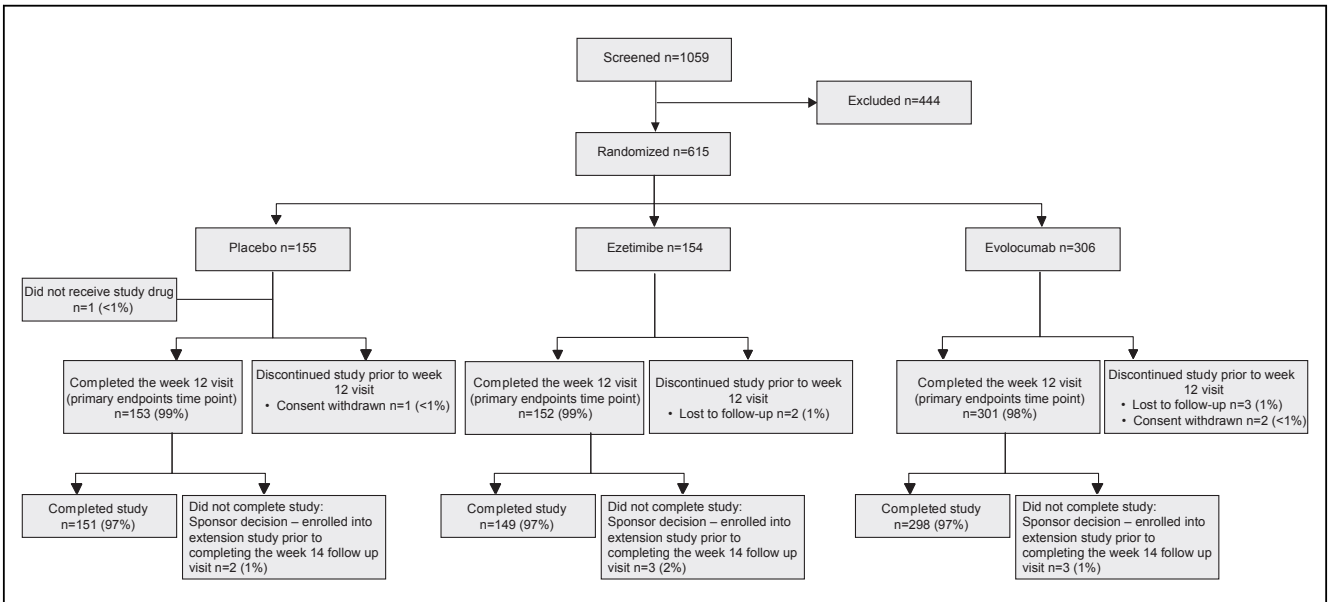

Figure 1 Patient Allocation and Disposition (CONSORT Diagram)

Table 1 Baseline Characteristics of Patients

	Biweekly*			Monthly		
	PBO q2w + PBO qd n = 76	PBO q2w + EZE qd n = 77	EVO 140 mg q2w + PBO qd n = 153	PBO Monthly + PBO qd n = 78	PBO Monthly + EZE qd n = 77	EVO 420 mg Monthly + PBO qd n = 153
Age, yrs	54 ± 10	54 ± 11	53 ± 14	53 ± 11	53 ± 13	53 ± 12
Male	28 (37)	24 (31)	49 (32)	13 (40)	25 (33)	52 (34)
Race						
White	63 (83)	63 (82)	132 (86)	63 (81)	60 (78)	129 (84)
Black	4 (5)	6 (8)	9 (6)	6 (8)	6 (8)	9 (6)
Asian	9 (12)	7 (9)	12 (8)	8 (10)	10 (13)	12 (8)
Other	0	1 (1)	0	1 (1)	1 (1)	3 (2)
Lipid parameters						
LDL-C, mg/dl†	140 ± 21	143 ± 24	142 ± 22	144 ± 24	144 ± 23	144 ± 23
Apolipoprotein B, mg/dl	104 ± 17	107 ± 20	105 ± 17	107 ± 20	106 ± 18	108 ± 18
Lipoprotein(a), nmol/l	21 (9, 49)	28 (11, 120)	20 (7, 58)	22 (7, 62)	28 (12, 64)	28 (9, 104)
Non–HDL-C, mg/dl	167 ± 26	169 ± 29	167 ± 26	173 ± 31	169 ± 27	170 ± 27
Apolipoprotein A1, mg/dl	163 ± 36	160 ± 27	157 ± 28	156 ± 31	155 ± 31	158 ± 27
Apolipoprotein B/ apolipoprotein A1 ratio	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
Triglycerides, mg/dl	114 (83, 178)	113 (84, 158)	112 (82, 148)	118 (86, 179)	117 (90, 159)	119 (83, 169)
HDL-C, mg/dl	57 (44, 77)	59 (47, 70)	53 (45, 67)	54 (45, 66)	54 (42, 68)	57 (47, 66)
VLDL-C, mg/dl	23 (17, 34)	23 (17, 32)	23 (17, 30)	24 (17, 36)	24 (18, 32)	24 (17, 34)
TC/HDL-C ratio	4 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1	4 ± 1
Free PCSK9, ng/ml	281 ± 89	270 ± 94	272 ± 81	270 ± 82	265 ± 94	274 ± 84
Cardiovascular risk factors						
Current cigarette use	6 (8)	11 (14)	13 (9)	8 (10)	15 (20)	19 (12)
Type 2 diabetes mellitus	0	0	0	1 (1)	0	0
Hypertension	12 (16)	19 (25)	53 (35)	19 (24)	23 (30)	50 (33)
Family history of premature CHD	4 (5)	10 (13)	20 (13)	2 (3)	7 (9)	18 (12)
Low HDL-C	20 (26)	14 (18)	36 (24)	21 (27)	26 (34)	31 (20)
≥2 CV risk factors	8 (11)	9 (12)	28 (18)	9 (12)	20 (26)	29 (19)
Risk factors for metabolic syndrome						
Increased waist circumference‡	33 (43)	43 (56)	85 (56)	45 (58)	43 (56)	65 (43)
Triglycerides ≥150 mg/dl	26 (34)	21 (27)	37 (24)	25 (32)	23 (30)	48 (31)
Low HDL-C§	20 (26)	14 (18)	36 (24)	21 (27)	26 (34)	31 (20)
Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or hypertension	34 (45)	44 (57)	93 (61)	41 (53)	43 (56)	88 (58)
Fasting glucose ≥110 mg/dl	12 (16)	19 (25)	30 (20)	22 (28)	14 (18)	31 (20)
Patients with baseline metabolic syndrome (≥3 risk factors)	18 (24)	26 (34)	52 (34)	28 (36)	24 (31)	39 (26)
Blood pressure, mm Hg						
Systolic	125 ± 15	127 ± 13	128 ± 14	125 ± 12	126 ± 14	125 ± 13
Diastolic	77 ± 10	80 ± 9	80 ± 9	80 ± 9	79 ± 8	78 ± 9
Glucose, mg/dl	92 ± 9	94 ± 10	93 ± 8	95 ± 11	92 ± 10	94 ± 10

Values are n (%), mean ± SD, or median (Q1, Q3). *Every 2 weeks. †Calculated LDL-C was replaced by ultracentrifugation LDL-C from the same blood sample, if available, when calculated LDL-C was <40 mg/dl or triglycerides were >400 mg/dl. ‡Defined as ≥102 cm for non-Asian men, ≥88 cm for non-Asian women, ≥90 cm for Asian men, and ≥80 cm for Asian women. §Baseline of <40 mg/dl in men and <50 mg/dl in women.

CHD = coronary heart disease; CV = cardiovascular; EVO = evolocumab; EZE = ezetimibe; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PBO = placebo; PCSK9 = proprotein convertase subtilisin/kexin type 9; q2w = every 2 weeks; qd = daily; TC = total cholesterol; VLDL-C = very-low-density lipoprotein cholesterol.

placebo and 17.8% (95% CI: −21.0% to −14.5%) for ezetimibe ($p < 0.001$) (Fig. 2). For patients administered monthly evolocumab, the mean 12-week LDL-C reduction was 56.1% (95% CI: −58.3% to −53.9%) versus 1.3% (95% CI: −4.4% to 1.7%) for placebo and 18.6% (95% CI: −21.6% to −15.5%) for ezetimibe ($p < 0.001$). LDL-C percent changes from baseline for the mean of weeks 10 and 12 and the absolute mean reductions in LDL-C levels were significant in all evolocumab groups compared with placebo and ezetimibe ($p < 0.001$) (Table 2). Patients in the evolocumab groups achieved a level of LDL-C <70 mg/dl at much higher rates (72% and 69%) than placebo (0% and 1%) or ezetimibe (2% and 1%) group patients for the mean of weeks 10 and 12 and at week 12, respectively. At week 12, LDL-C was

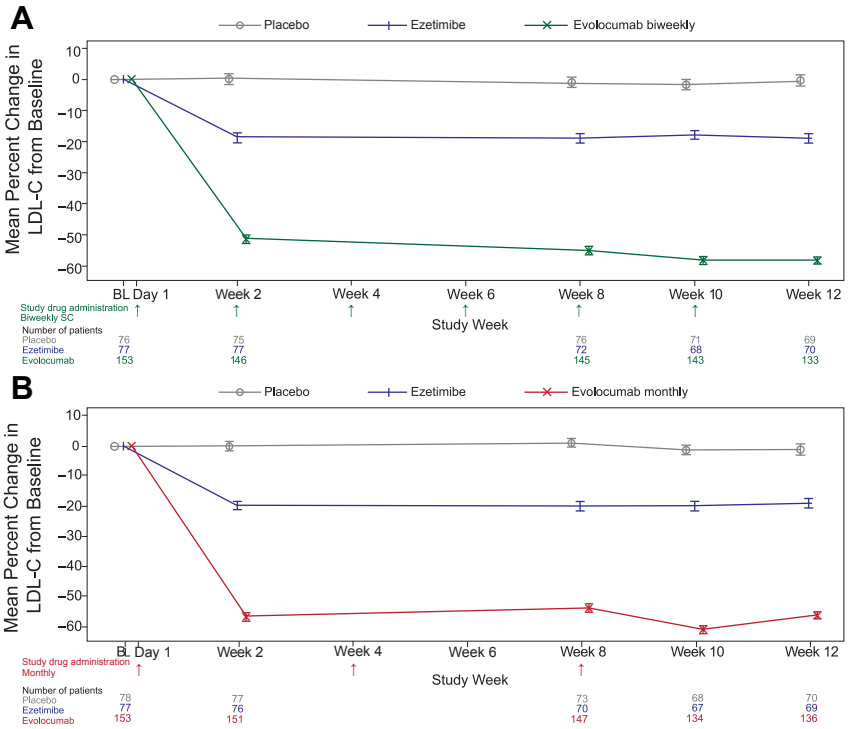

Figure 2 **Percent Change in LDL-C Levels From Baseline to Week 12 With Evolocumab**

(A) Biweekly. **(B)** Monthly. **Vertical lines** represent SE of the mean. Plot is based on observed data with no imputation for missing values. BL = baseline; LDL-C = low-density lipoprotein cholesterol; SC = subcutaneous.

59 ± 22 mg/dl and 63 ± 20 mg/dl with biweekly and monthly evolocumab, respectively.

All patients treated with evolocumab experienced LDL-C reductions compared with their individual baseline levels versus 92.9% and 91.3% of ezetimibe-treated patients in the biweekly and monthly groups (Fig. 3). Evolocumab treatment in the biweekly and monthly groups led to LDL-C decreases of >50% in 75.7% and 78.7% of patients when evaluated by LDL-C level averaged at weeks 10 and 12 and 76.7% and 72.1% at week 12, respectively.

Evolocumab demonstrated consistent LDL-C effects regardless of age, sex, race, region, or baseline levels of LDL-C, triglycerides, or PCSK9 (Fig. 4), except for biweekly evolocumab compared with placebo in patients with metabolic syndrome, who had greater responses than patients without metabolic syndrome (Fig. 4), an effect not seen with monthly administration.

OTHER LIPIDS. Evolocumab significantly decreased levels of apolipoprotein B, lipoprotein a (Lp[a]), and non–high-density lipoprotein cholesterol (HDL-C) and the ratios of total cholesterol to HDL-C and apolipoprotein B to apolipoprotein A1 (Table 2). Significant HDL-C increases were observed with evolocumab ($p < 0.05$). Triglyceride and very-low-density lipoprotein cholesterol levels were significantly lowered with monthly evolocumab versus

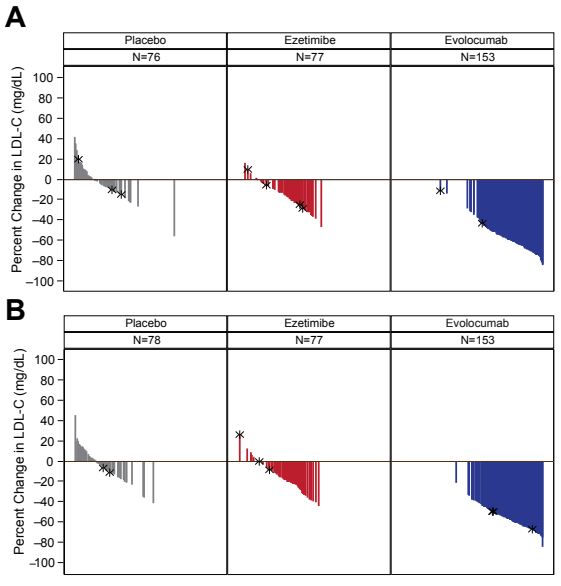

Figure 3 **Individual Patient Percent Change in LDL-C Levels From Baseline to Week 12 With Evolocumab**

(A) Biweekly. **(B)** Monthly. *Patients who terminated SC or oral study drug early. Abbreviations as in Figure 2.

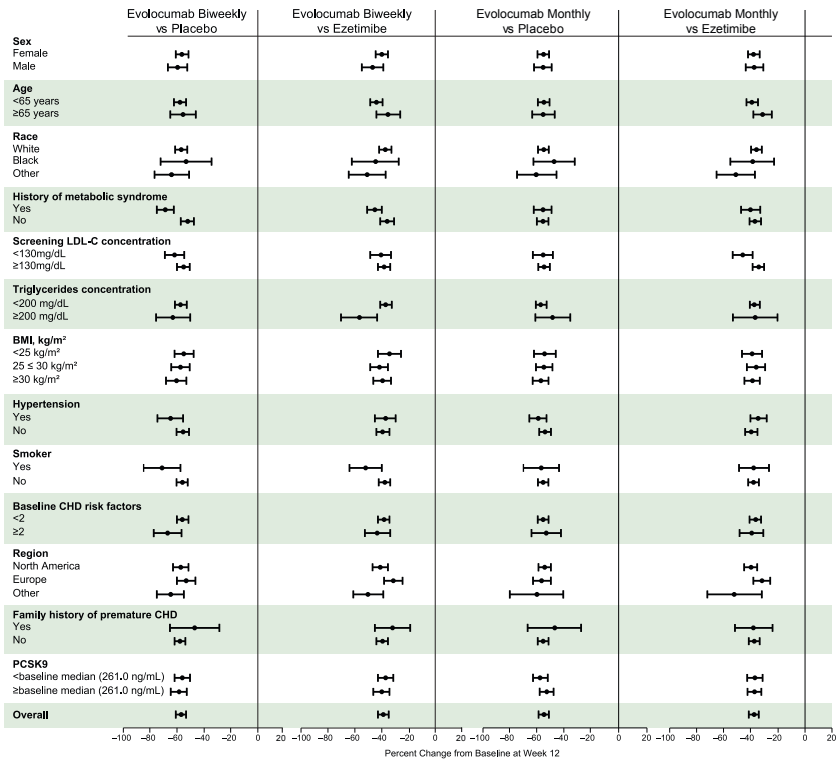

Figure 4 **Treatment Differences of Percent Change in LDL-C Levels From Baseline to Week 12 With Evolocumab Administered Biweekly and Monthly Versus Placebo or Ezetimibe According to Subgroups of Patients**

When the calculated LDL-C level was <40 mg/dl or triglycerides were >400 mg/dl, calculated LDL-C was replaced with ultracentrifugation LDL-C from the same blood sample, if available. Least-squares mean differences and 95% CI are from the repeated-measures model. No imputation was used for missing values. BMI = body mass index; CHD = coronary heart disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; other abbreviations as in Figure 2.

placebo or ezetimibe and in some comparisons in the biweekly group.

Safety outcomes. Treatment-emergent AEs occurred in 134 evolocumab-treated patients (44%), 68 placebo-treated patients (44%), and 70 ezetimibe-treated patients (46%) (Table 3). No deaths or cardiovascular (CV) endpoints were reported. Four serious AEs occurred in the evolocumab groups (1.3%) versus 1 each in the placebo (0.6%) and ezetimibe (0.6%) groups. In 2 cases, local investigators considered that events were related to the study drug: 1) acute pancreatitis in a patient with a history of cholecystectomy, long-term alcohol intake, and concomitant use of valproate semisodium on monthly evolocumab; and 2) transaminase and creatine kinase levels 8 times the upper limit of normal in a patient on biweekly evolocumab that returned to normal after study drug discontinuation. AEs led to study drug discontinuation in 6 (3.9%), 5 (3.2%), and 7 (2.3%) patients in the placebo, ezetimibe, and evolocumab groups, respectively.

Rates of potential muscle-related AEs and laboratory abnormalities were comparable across treatment groups. Injection-site reactions were reported in 5% of each group; none led to discontinuation of study drug. No neutralizing or binding antibodies were detected during the study.

Discussion

In the largest monotherapy trial with a PCSK9 inhibitor to date, evolocumab rapidly and markedly lowered LDL-C and apolipoprotein B levels over 12 weeks compared with placebo or ezetimibe. Evolocumab also showed favorable effects on HDL-C, triglyceride, and Lp(a) levels. The LDL-C reductions were comparable across patient subgroups based on age, race, sex, or geographic location, with all patients responding to therapy, as defined by LDL-C levels that decreased from baseline. LDL-C reductions of >50% were reported in 72% of evolocumab patients.

AEs, serious AEs, or events of interest occurred at comparable rates between groups. Further, injection-site reactions were infrequent and did not differ across groups or between the evolocumab arms. Because of similar efficacy and tolerability between the evolocumab regimens studied,

Table 2 Lipid Efficacy Outcomes Averaged at Weeks 10 and 12 and at Week 12

	Biweekly			Monthly		
	PBO q2w + PBO qd (n = 76)	PBO q2w + EZE qd (n = 77)	EVO 140 mg q2w + PBO qd (n = 153)	PBO Monthly + PBO qd (n = 78)	PBO Monthly + EZE qd (n = 77)	EVO 420 mg Monthly + PBO qd (n = 153)
LDL-C						
% Change from baseline, mean of weeks 10 and 12*	−0.4 (−3.3, 2.4)	−17.5 (−20.4, −14.7)	−56.9 (−59.0, −54.8)	−1.4 (−4.1, 1.3)	−19.1 (−21.9, −16.4)	−58.8 (−60.8, −56.8)
Treatment difference vs. placebo			−56.5 (−60.0, −53.0)			−57.4 (−60.7, −54.1)
Treatment difference vs. ezetimibe			−39.4 (−42.9, −35.9)			−39.7 (−43.0, −36.4)
% Change from baseline, week 12*	0.1 (−3.2, 3.4)	−17.8 (−21.0, −14.5)	−57.0 (−59.5, −54.6)	−1.3 (−4.4, 1.7)	−18.6 (−21.6, −15.5)	−56.1 (−58.3, −53.9)
Treatment difference vs. placebo			−57.1 (−61.1, −53.1)			−54.8 (−58.5, −51.1)
Treatment difference vs. ezetimibe			−39.3 (−43.3, −35.3)			−37.6 (−41.2, −33.9)
Adjusted† p value vs. placebo			<0.001			<0.001
Adjusted† p value vs. ezetimibe			<0.001			<0.001
Other lipid parameters						
Apolipoprotein B						
% Change from baseline, mean of weeks 10 and 12	0.05 (−2.9, 3.0)	−13.5 (−16.5, −10.5)	−47.0 (−49.3, −44.8)	1.5 (−1.2, 4.3)	−14.8 (−17.6, −11.9)	−49.4 (−51.4, −47.4)
Treatment difference vs. placebo			−47.1 (−50.7, −43.5)			−50.9 (−54.3, −47.6)
Treatment difference vs. ezetimibe			−33.6 (−37.2, −30.0)			−34.6 (−38.0, −31.3)
% Change from baseline, week 12	0.6 (−2.5, 3.7)	−13.2 (−16.3, −10.1)	−47.2 (−49.5, −44.9)	1.8 (−1.2, 4.9)	−14.0 (−17.1, −11.0)	−46.6 (−48.8, −44.4)
Treatment difference vs. placebo			−47.8 (−51.6, −44.1)			−48.4 (−52.1, −44.8)
Treatment difference vs. ezetimibe			−34.0 (−37.8, −30.3)			−32.6 (−36.2, −28.9)
Adjusted† p value vs. placebo			<0.001			<0.001
Adjusted† p value vs. ezetimibe			<0.001			<0.001
Lipoprotein (a)‡						
% Change from baseline, mean of weeks 10 and 12	0.1 (−11.1, 11.5)	0.0 (−9.6, 10.3)	−18.4 (−37.5, 0.0)	0.0 (−11.8, 8.3)	−2.1 (−18.2, 5.6)	−19.2 (−38.8, −4.8)
Treatment difference vs. placebo			−18.5 (−25.3, −11.7)			−19.2 (−23.2, −15.3)
Treatment difference vs. ezetimibe			−18.4 (−24.4, −12.4)			−17.2 (−23.2, −11.1)
% Change from baseline, week 12	0.0 (−8.5, 17.5)	0.0 (−9.1, 12.5)	−20.4 (−39.5, 0.0)	0.0 (−10.5, 8.1)	−2.1 (−17.2, 8.3)	−17.8 (−38.5, 0.0)
Treatment difference vs. placebo			−20.4 (−27.8, −13.1)			−17.8 (−24.5, −11.1)
Treatment difference vs. ezetimibe			−20.4 (−28.1, −12.7)			−15.8 (−24.4, −7.1)
Adjusted† p value vs. placebo			<0.001			<0.001
Adjusted† p value vs. ezetimibe			<0.001			<0.001
Non–HDL-C						
% Change from baseline, mean of weeks 10 and 12	−1.4 (−4.1, 1.2)	−14.6 (−17.3, 12.0)	−50.2 (−52.2, −48.3)	1.3 (−1.1, 3.8)	−16.5 (−19.0, −14.0)	−52.0 (−53.7, −50.2)
Treatment difference vs. placebo			−48.8 (−52.0, −45.6)			−53.3 (−56.2, −50.3)
Treatment difference vs. ezetimibe			−35.6 (−38.8, −32.4)			−35.5 (−38.4, −32.5)
% Change from baseline, week 12	−0.3 (−3.2, 2.6)	−14.9 (−17.8, −12.0)	−50.1 (−52.3, −48.0)	1.5 (−1.2, 4.2)	−16.5 (−19.2, −13.7)	−49.7 (−51.7, −47.7)
Treatment difference vs. placebo			−49.8 (−53.3, −46.3)			−51.2 (−54.5, −47.9)
Treatment difference vs. ezetimibe			−35.2 (−38.7, −31.7)			−33.2 (−36.5, −29.9)
Adjusted† p value vs. placebo			<0.001			<0.001
Adjusted† p value vs. ezetimibe			<0.001			<0.001

Continued on the next page

Table 2 Continued

	Biweekly			Monthly		
	PBO q2w + PBO qd (n = 76)	PBO q2w + EZE qd (n = 77)	EVO 140 mg q2w + PBO qd (n = 153)	PBO Monthly + PBO qd (n = 78)	PBO Monthly + EZE qd (n = 77)	EVO 420 mg Monthly + PBO qd (n = 153)
Apolipoprotein B/apolipoprotein A1 ratio						
% Change from baseline, mean of weeks 10 and 12	1.0 (−2.3, 4.3)	−13.4 (−16.7, −10.1)	−48.1 (−50.6, −45.7)	3.9 (0.4, 7.3)	−14.5 (−18.0, −11.0)	−51.1 (−53.6, −48.6)
Treatment difference vs. placebo			−49.1 (−53.1, −45.1)			−55.0 (−59.1, −50.8)
Treatment difference vs. ezetimibe			−34.7 (−38.7, −30.7)			−36.6 (−40.8, −32.4)
% Change from baseline, week 12	1.1 (−2.4, 4.6)	−12.7 (−16.2, −9.2)	−48.5 (−51.0, −45.9)	4.5 (0.8, 8.3)	−14.3 (−18.1, −10.5)	−48.3 (−51.0, −45.5)
Treatment difference vs. placebo			−49.6 (−53.8, −45.4)			−52.8* (−57.3, −48.3)
Treatment difference vs. ezetimibe			−35.8 (−40.0, −31.6)			−34.0 (−38.5, −29.5)
Adjusted† p value vs. placebo			<0.001			<0.001
Adjusted† p value vs. ezetimibe			<0.001			<0.001
Triglycerides‡						
% Change from baseline, mean of weeks 10 and 12	−3.9 (−18.9, 11.2)	−1.5 (−15.0, 18.4)	−9.2 (−24.2, 11.0)	4.9 (−12.7, 31.7)	−4.0 (−17.7, 10.4)	−15.7 (−28.2, 6.4)
Treatment difference vs. placebo			−5.3 (−13.3, 2.7)			−20.6 (−31.0, −10.2)
Treatment difference vs. ezetimibe			−7.7 (−16.9, 1.5)			−11.7 (−21.2, −2.3)
% Change from baseline, week 12	−1.9 (−18.6, 11.5)	0.0 (−13.3, 17.5)	−8.1 (−26.1, 10.1)	2.0 (−16.6, 33.8)	−2.4 (−19.34, 12.9)	−15.6 (−30.0, 1.5)
Treatment difference vs. placebo			−6.2 (−16.4, 4.0)			−17.7 (−21.7, −8.6)
Treatment difference vs. ezetimibe			−8.1 (−17.5, 1.3)			−13.2 (−21.7, −4.8)
Adjusted† p value vs placebo			0.72			<0.001
Adjusted† p value vs ezetimibe			0.027			0.044
HDL-C‡						
% Change from baseline, mean of weeks 10 and 12	−1.6 (−8.4, 5.0)	−0.9 (−10.1, 7.3)	3.9 (−1.4, 11.6)	−4.7 (−10.6, −0.6)	0.0 (−7.0, 8.7)	3.8 (−2.6, 11.9)
Treatment difference vs. placebo			5.5 (2.2, 8.8)			8.5 (5.5, 11.4)
Treatment difference vs. ezetimibe			4.8 (0.9, 8.8)			3.8 (−0.8, 8.4)
% Change from baseline, week 12	−1.2 (−9.1, 6.1)	−2.8 (−8.6, 8.7)	4.8 (−2.9, 12.8)	−5.3 (−11.3, 2.3)	−1.5 (−6.7, 8.2)	4.1 (−2.7, 11.2)
Treatment difference vs. placebo			5.9 (1.7, 10.2)			9.3 (5.3, 13.3)
Treatment difference vs. ezetimibe			7.6 (3.1, 12.0)			5.5 (2.2, 8.8)
Adjusted† p value vs. placebo			0.007			<0.001
Adjusted† p value vs. ezetimibe			0.013			0.044
VLDL-C‡						
% Change from baseline, mean of weeks 10 and 12	−3.8 (−19.2, 10.0)	−2.7 (−16.5, 16.7)	−8.4 (−25.4, 10.9)	4.2 (−13.6, 27.9)	−3.3 (−20.0, 9.5)	−16.2 (−28.0, 5.5)
Treatment difference vs. placebo			−4.6 (−11.3, 2.1)			−20.4 (−30.1, −10.7)
Treatment difference vs. ezetimibe			−5.7 (−14.1, 2.7)			−12.8 (−22.1, −3.5)
% Change from baseline, week 12	−1.6 (−20.0, 10.5)	−0.9 (−12.3, 12.9)	−9.5 (−26.8, 10.3)	0.0 (−16.7, 33.3)	−3.6 (−19.2, 14.3)	−16.3 (−30.7, 2.5)
Treatment difference vs. placebo			−7.9 (−18.8, 2.9)			−16.3 (−25.6, −7.0)
Treatment difference vs. ezetimibe			−8.6 (−18.1, 0.9)			−12.7 (−20.9, −4.5)
Adjusted† p value vs. placebo			0.72			<0.001
Adjusted† p value vs. ezetimibe			0.082			0.044

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Table 2 Continued

	Biweekly			Monthly		
	PBO q2w + PBO qd (n = 76)	PBO q2w + EZE qd (n = 77)	EVO 140 mg q2w + PBO qd (n = 153)	PBO Monthly + PBO qd (n = 78)	PBO Monthly + EZE qd (n = 77)	EVO 420 mg Monthly + PBO qd (n = 153)
LDL-C achievement <70 mg/dl, n (%)						
Mean of weeks 10 and 12	0	1 (1.3)	103 (73.6)	0	2 (2.8)	107 (71.3)
Treatment difference vs. placebo			73.6 (64.4, 80.2)			71.3 (62.2, 78.0)
Treatment difference vs. ezetimibe			72.2 (62.4, 78.9)			68.6 (58.3, 75.5)
Week 12	1 (1.4)	1 (1.4)	97 (72.9)	0	1 (1.4)	89 (65.4)
Treatment difference vs. placebo			71.5 (61.2, 78.4)			65.4 (55.6, 72.9)
Treatment difference vs. ezetimibe			71.5 (61.3, 78.4)			64.0 (53.5, 71.6)
Adjusted† p value vs. placebo			<0.001			<0.001
Adjusted† p value vs. ezetimibe			<0.001			<0.001

*Coprimary endpoint. †Multiplicity adjustment was based on a combination of sequential testing, the Hochberg procedure, and the fallback procedure to control the overall significance level for all primary and secondary endpoints. Data are least-squares mean (95% CI). ‡Median (Q1, Q3) treatment difference. Calculated LDL-C was replaced by ultracentrifugation LDL-C from the same blood sample, if available, when calculated LDL-C was <40 mg/dl or triglycerides were >400 mg/dl. Least-squares mean from the repeated-measures model, including treatment group, stratification factor, scheduled visit, and interaction of treatment with scheduled visits as covariates.

Abbreviations as in Table 1.

future clinical decisions about administration may reflect individual patient preferences for biweekly or monthly treatment.

The task of defining appropriate target populations for anti-PCSK9 therapy will likely generate vigorous debate. Evidence suggests that substantial benefits should accrue from additional incremental LDL-C reductions in at-risk patients, including results from randomized clinical trials, meta-analyses, and Mendelian randomization studies (3–6). However, the demonstration of incremental improvements in clinical outcomes derived from "highly" compared with "moderately" effective statin regimens contrasts with the lack of benefit observed in randomized trials adding fenofibrate or niacin to patients already receiving stable statin doses (7,8). Based largely on these findings, recent American College of Cardiology (ACC)/American Heart Association (AHA) treatment guidelines advocated using high doses of effective statin therapy and de-emphasized LDL-C targets when treating hypercholesterolemia (9).

Although the ACC/AHA task force tried to simplify lipid management by emphasizing statin use, the guidelines acknowledged the limits of statin therapy. Subsequently, the researchers recommended nonstatin therapies reported to improve outcomes in clinical trials when patients have inadequate response to statins or remain at high risk despite statin therapy (Section 6.3.2) (9). This guidance will likely require reevaluation given the large LDL-C reductions produced by evolocumab and other investigational medicines (10) compared with older nonstatin therapies. Cost considerations will also require evaluation.

The MENDEL-2 trial used ezetimibe as a comparator because we anticipate that as with ezetimibe, PCSK9 inhibitors will find use predominantly as second-line therapy to statins. Clinicians often prescribe ezetimibe, an agent currently under investigation for its effect on CV outcomes, as monotherapy for hypercholesterolemia in patients who cannot tolerate statins or as combination therapy for those requiring additional lipid effects while receiving statins (11). Given the greater lipid effects of anti-PCSK9 antibodies compared with ezetimibe, several hyperlipidemic populations might derive incremental benefits from this novel treatment approach. The largest of these groups consists of statin-intolerant patients. Other groups include patients with historically poor LDL-C–lowering responses to statins, those with statin contraindications due to drug-drug interactions, and those with elevations of Lp(a) levels, an independent CV risk factor that is not responsive to statins. Additionally, parenteral therapy may produce better lipid results in a subset of patients who experience particular difficulty with daily oral treatment compliance.

Study limitations. Although the MENDEL-2 trial demonstrated favorable efficacy and tolerability within a large cohort not receiving statins, the study did not specifically evaluate statin intolerance or elevated Lp(a) levels. By

Table 3 Adverse Events

	Placebo		Ezetimibe		Evolocumab	
	PBO q2w + PBO qd (n = 76)	PBO Monthly + PBO qd (n = 78)	PBO q2w + EZE qd (n = 77)	PBO Monthly + EZE qd (n = 77)	EVO 140 mg q2w + PBO qd (n = 153)	EVO 420 mg Monthly + PBO qd (n = 153)
Treatment emergent AEs						
Any	34 (45)	34 (44)	35 (46)	35 (46)	73 (48)	61 (40)
Serious*	0	1 (1)	0	1 (1)	3 (2)	1 (1)
Leading to discontinuation of study drug	3 (4)	3 (4)	4 (5)	1 (1)	4 (3)	3 (2)
Treatment-related serious†	0	0	0	0	1 (1)	1 (1)
Deaths	0	0	0	0	0	0
Common treatment-emergent AEs‡						
Headache	3 (4)	1 (1)	4 (5)	1 (1)	5 (3)	5 (3)
Diarrhea	5 (7)	1 (1)	2 (3)	1 (1)	4 (3)	5 (3)
Nasopharyngitis	1 (1)	2 (3)	4 (5)	2 (3)	3 (2)	3 (2)
Muscle and liver function labs						
Creatine kinase >5 × ULN	1 (1)	1 (1)	0	0	1 (1)	1 (1)
Creatine kinase >10 × ULN	1 (1)	1 (1)	0	0	1 (1)	0
ALT or AST >3 × ULN§	2 (3)	3 (4)	1 (1)	0	3 (2)	0
ALT or AST >5 × ULN	1 (1)	1 (1)	0	0	1 (1)	0
Total bilirubin at week 12, μmol/l	7.3 ± 3.4	8.3 ± 4.4	8.0 ± 4.1	8.2 ± 4.8	7.8 ± 3.9	7.5 ± 4.1
Potential muscle events‖	3 (4)	3 (4)	2 (3)	3 (4)	6 (4)	2 (1)
Myalgia	1 (1)	2 (3)	2 (3)	1 (1)	2 (1)	1 (1)
Musculoskeletal pain	2 (3)	0	0	1 (1)	3 (2)	0
Potential injection-site reactions‖	2 (3)	6 (8)	4 (5)	3 (4)	10 (7)	6 (4)
Erythema	0	3 (4)	1 (1)	1 (1)	4 (3)	1 (1)
Pain	0	2 (3)	0	1 (1)	2 (1)	3 (2)
Bruising	0	2 (3)	2 (3)	1 (1)	3 (2)	0
Antibodies						
Binding	NA	NA	NA	NA	0	0
Neutralizing	NA	NA	NA	NA	0	0
Neurocognitive AEs¶	0	0	0	0	0	0

Values are n (%) or mean ± SD. *Defined as fatal, life threatening, requiring or prolonging hospital admission, causing persistent or substantial disability, incapacity, or a congenital anomaly or birth defect. †Treatment-related AEs were those considered possibly related to the study drug by the investigator. ‡Reported in ≥5% of patients in one or more treatment arms. §Elevated levels led to study drug discontinuation in 1 placebo and 1 evolocumab patient. ‖Searched using standard Medical Dictionary for Regulatory Activities queries with a broad search strategy; reported in ≥3% of patients in one or more treatment arms. ¶Searched using HLGT terms: deliria (including confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; mental impairment disorders.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; NA = not applicable; ULN = upper limit of normal; other abbreviations as in Table 1.

design, as an early evaluation of the safety and efficacy of evolocumab monotherapy at doses anticipated for use in clinical practice, the MENDEL-2 study enrolled patients with Framingham risk scores ≤10%, some of whom might not receive drug therapy under the new guidelines. Future studies should refine the target populations for anti-PCSK9 monotherapy by enrolling higher-risk patients with statin intolerance, severe statin nonresponsiveness, or isolated Lp(a) elevations.

An additional limitation of the MENDEL-2 trial was the 12-week duration. Hyperlipidemia requires chronic administration of therapy; therefore, ongoing studies of evolocumab will require extended observation periods. To date, these assessments have appeared favorable (12). Continued open-label monitoring and future outcomes trials will ultimately provide a better understanding of the AE profile, particularly the long-term acceptance of parenteral therapy for hypercholesterolemia and the development of antidrug antibodies. Further, longer-term observation of treated patients who fail statins, either due to inadequate efficacy or intolerance, will address how anti-PCSK9 monotherapy may fit into the treatment paradigm for hyperlipidemia.

Conclusions

The MENDEL-2 trial demonstrated robust reductions in LDL-C levels with evolocumab monotherapy in adults with hypercholesterolemia regardless of sex, age, race, or CV risk factors. LDL-C reductions were comparable between biweekly and monthly administration, with good tolerability and safety. Based on these favorable results, the MENDEL-2 study provides the rationale for future investigations involving higher-risk patients who might benefit from anti-PCSK9 monotherapy.

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Key Words: evolocumab ■ dyslipidemia ■ monotherapy ■ PCSK9 inhibition.

APPENDIX

For an expanded Methods section, please see the online version of this article.