Supplementary Material

Effect of Bempedoic Acid vs Placebo Added to Maximally Tolerated Statins on Low-density Lipoprotein Cholesterol in Patients at High Risk for Cardiovascular Disease: The CLEAR Wisdom Randomized Clinical Trial

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eTable 1. Percent Change From Baseline in Triglycerides and HDL-C

Parameter	n	Bempedoic Acid[a]	n	Placebo[a]	LS Mean Difference (95% CI)	*P* Value
Percent change in triglycerides						
Week 12	499	11.0 (2.3)	253	6.1 (2.3)	4.9 (–1.5, 11.3)	.13
Week 24	486	6.4 (2.1)	247	4.7 (2.2)	1.7 (–4.4, 7.8)	.59
Week 52	467	6.0 (1.9)	237	4.8 (2.5)	1.2 (–5.0, 7.4)	.71
Percent change in HDL-C						
Week 12	499	–6.4 (0.7)	253	–0.2 (0.9)	–6.1 (–8.4, –3.9)	< .001
Week 24	486	–4.7 (0.8)	247	0.5 (0.9)	–5.2 (–7.6, –2.9)	<. 001
Week 52	467	–7.4 (0.8)	237	–3.4 (0.8)	–4.0 (–6.3, –1.7)	< .001

[a]Data are least-squares means (standard errors).
Abbreviation: CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LS, least-squares.

eTable 2. Low-Density Lipoprotein Cholesterol (LDL-C) Percent Change From Baseline to Week 12 by Statin Intensity and Background Lipid-Lowering Therapy, Post hoc Subgroup Analysis

Category	n	Bempedoic Acid[a]	n	Placebo[a]	LS Mean Difference (95% CI)	*P* Value
Baseline statin category[b,c]						
None	48	–24.6 (3.6)	29	–2.6 (4.4)	–22.0 (–33.4, –10.6)	< .001
Low/moderate intensity	179	–14.9 (1.6)	89	3.2 (2.1)	–18.1 (–23.4, –12.8)	< .001
High intensity	271	–14.4 (1.5)	135	2.8 (2.1)	–17.2 (–22.3, –12.1)	< .001
Baseline background lipid-lowering therapy category[d]						
Statin alone	399	–14.4 (1.1)	192	3.0 (1.6)	–17.4 (–21.2, –13.6)	< .001
Statin with other lipid-lowering therapy	51	–16.1 (4.3)	32	2.1 (4.9)	–18.3 (–31.2, –5.4)	.006
Nonstatin lipid-lowering therapy only	19	–26.0 (3.9)	15	–8.1 (7.6)	–17.9 (–35.7, –0.1)	.05
No lipid-lowering therapy	29	–23.6 (5.5)	14	3.2 (3.7)	–26.8 (–40.2, –13.3)	< .001

[a]Data are least-squares means (standard errors).
[b]Statin intensity classification is based on the 2013 American College of Cardiology/American Heart Association guidelines (Stone NJ, et al. Circulation. 2014;129[25 Suppl 2]:S1-45).
[c]*P* value for interaction = .72.
[d]*P* value for interaction = .71.
Abbreviations: CI, confidence interval; LS, least-squares.

eTable 3. Post hoc Analysis of the Effect of Study Site on the Primary Endpoint, Percent Change From Baseline to Week 12 in Low-Density Lipoprotein Cholesterol (LDL-C)

Analysis	Bempedoic Acid vs Placebo LS Mean Difference (95% CI)	Between-group Comparison *P* value	Site Effect *P* Value
Primary endpoint analysis	–17.4 (–21.0, –13.9)	< .001	—
Post hoc study site analysis[a]	–17.5 (–21.0, –13.9)	< .001	0.28

[a]Post hoc analysis using a mixed-effect model with site as a random effect
Abbreviations: CI, confidence interval; LS, least-squares.

eTable 4. Positively Adjudicated Clinical Events

Parameter	Patients, n (%)		Relative Risk (95% CI)
	Bempedoic Acid (n = 522)	Placebo (n = 257)	
Patients with any adjudicated clinical endpoint	43 (8.2)	26 (10.1)	0.81 (0.51, 1.29)
Major adverse cardiovascular events (MACE)			
Nonfatal myocardial infarction	6 (1.1)	9 (3.5)	0.33 (0.12, 0.91)
Nonfatal stroke	4 (0.8)	2 (0.8)	0.98 (0.18, 5.34)
Hospitalization for unstable angina	10 (1.9)	4 (1.6)	1.23 (0.39, 3.89)
Coronary revascularization	20 (3.8)	15 (5.8)	0.66 (0.34, 1.26)
Cardiovascular death	4 (0.8)	2 (0.8)	0.98 (0.18, 5.34)
Other adjudicated events			
Noncardiovascular death	2 (0.4)	0	NC
Noncoronary revascularization	6 (1.1)	6 (2.3)	0.49 (0.16, 1.51)
Hospitalization for heart failure	5 (1.0)	2 (0.8)	1.23 (0.24, 6.30)
5-component MACE[a]	32 (6.1)	21 (8.2)	0.75 (0.44, 1.27)
4-component MACE[b]	30 (5.7)	20 (7.8)	0.74 (0.43, 1.27)
3-component MACE[c]	14 (2.7)	12 (4.7)	0.57 (0.27, 1.22)

[a]Includes cardiovascular death, myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization.
[b]Includes cardiovascular death, myocardial infarction, nonfatal stroke, and coronary revascularization.
[c]Includes cardiovascular death, myocardial infarction, and nonfatal stroke.
Abbreviations: CI, confidence interval; NC, not calculated.

eTable 5. Measures of On-Treatment Glucose Control by Baseline Glycemic Status

Population Glycemic Measure	n	Bempedoic Acid	n	Placebo
Patients with diabetes[a]				
Patients with a glucose measurement ≥ 126 mg/dL, n (%)[b]	166	116 (69.9)	86	64 (74.4)
Patients with a glucose measurement ≤ 50 mg/dL, n (%)[b]	166	3 (1.8)	86	1 (1.2)
Change in mean glucose from baseline to week 12, mg/dL[c]	159	–0.3 (30.2)	84	6.7 (34.1)
Patients with an HbA1c measurement ≥ 6.5%, n (%)[b]	166	105 (63.3)	86	59 (68.6)
Change in mean HbA1c from baseline to week 12, %[c]	159	–0.08 (0.50)	84	0.12 (0.76)
Patients with impaired fasting glucose[d]				
Patients with a glucose measurement ≥ 126 mg/dL, n (%)[b]	235	25 (10.6)	107	14 (13.1)
Patients with a glucose measurement ≤ 50 mg/dL, n (%)[b]	235	0	107	0
Change in mean glucose from baseline to week 12, mg/dL[c]	227	0.6 (9.4)	105	2.3 (11.6)
Patients with an HbA1c measurement ≥ 6.5%, n (%)[b]	235	13 (5.5)	107	7 (6.5)
Change in mean HbA1c from baseline to week 12, %[c]	225	–0.07 (0.21)	105	–0.04 (0.23)
Patients without diabetes or impaired fasting glucose				
Patients with a glucose measurement ≥ 126 mg/dL, n (%)[b]	121	2 (1.7)	64	4 (6.3)
Patients with a glucose measurement ≤ 50 mg/dL, n (%)[b]	121	0	64	0
Change in mean glucose from baseline to week 12, mg/dL[c]	112	1.4 (8.6)	64	3.2 (14.3)
Patients with an HbA1c measurement ≥ 6.5%, n (%)[b]	121	0	64	0
Change in mean HbA1c from baseline to week 12, %[c]	111	0.03 (0.22)	64	0.05 (0.18)

[a]Includes patients with a medical history of type 1 or type 2 diabetes or who had laboratory values consistent with diabetes (ie, baseline HbA1c ≥ 6.5% or 2 measurements of fasting plasma glucose ≥ 126 mg/dL between screening and randomization).
[b]Includes events that occurred at any point throughout the 52-week treatment period.
[c]Data are means (standard deviations).
[d]Includes patients with impaired fasting glucose in their medical history or who had laboratory values consistent with impaired fasting glucose (ie, baseline HbA1c of 5.7% to 6.5% or 2 measurements of fasting plasma glucose ≥ 100 mg/dL but not more than 1 measurement ≥ 126 mg/dL between screening and randomization).
Abbreviation: HbA1c, hemoglobin A1c.

eFigure 1. Low-Density Lipoprotein Cholesterol (LDL-C) Percent Change From Baseline to Week 12 by Patient Subgroup. [a]Statin intensity as classified by the investigator prior to randomization. Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LS, least squares.