LDL-C Reduction with Bempedoic Acid in High-Risk Statin-Intolerant Patients Without ASCVD: CLEAR Outcomes

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BACKGROUND

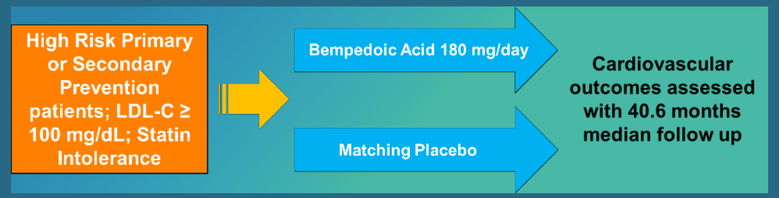
- Global guidelines uniformly endorse reducing LDL cholesterol (LDL-C) to reduce cardiovascular (CV) risk in patients with atherosclerotic CV disease (ASCVD, secondary prevention) or at high risk for a first major CV event (primary prevention). [1,2]
- Hypercholesterolemia is often untreated or undertreated. [3,4,5]
- Statin intolerance, typically manifesting as myalgia, is a major contributor to inadequate LDL-C control.[6,7]
- Bempedoic acid, an ATP citrate lyase inhibitor, inhibits hepatic cholesterol synthesis upstream of HMG-Co-A reductase, the enzyme inhibited by statins.[8]
- Bempedoic acid (BA) is a pro-drug activated in the liver, but not peripheral tissues, which may explain the low incidence of muscle-related adverse events with this agent.[8]
- Appropriate LDL-C management is a particular issue among primary prevention patients, including women and those with diabetes, representing opportunities for improving clinical outcomes in such patients.
- Clinical trials for LDL-C lowering in primary prevention were conducted years ago, suggesting possible outdated guidance, further fueling questions whether cholesterol-lowering benefits exceed potential harm in primary prevention patients.[9,10]
- Additional therapeutic options and clinical CV outcome trial data are needed for high risk secondary and primary CV prevention patients with statin intolerance; such strategies, including use of BA, have broad potential clinical relevance.

CLEAR Outcomes: Primary Report[11]

- 13,970 patients with, or at high risk of , CVD and unable or unwilling to tolerate guideline-recommended statin doses.
- Patients randomized to either BA 180 mg (N=6992) or placebo (N=6978) in blinded fashion.
- Randomization to BA resulted in an observed 21% decrease in LDL-C vs placebo and a 13% reduction in the risk of major adverse CV events (death from CV causes, non-fatal myocardial infarction, non-fatal stroke, and coronary revascularization).
- Given CLEAR Outcomes enrollment included high risk primary prevention patients (capped at 30%), analysis of BA vs placebo results in this population provides a unique opportunity.

METHODS

CLEAR Outcomes Trial Design



Definition of High Risk

- Reynolds Risk score >30%, or
- SCORE risk >7.5% over 10 years, or
- Patients with Type 1 or 2 diabetes, aged >65 years (women) or >60 years (men), or
- Coronary Artery Calcium score of >400 AU at any time in the past

Definition of Statin Intolerance

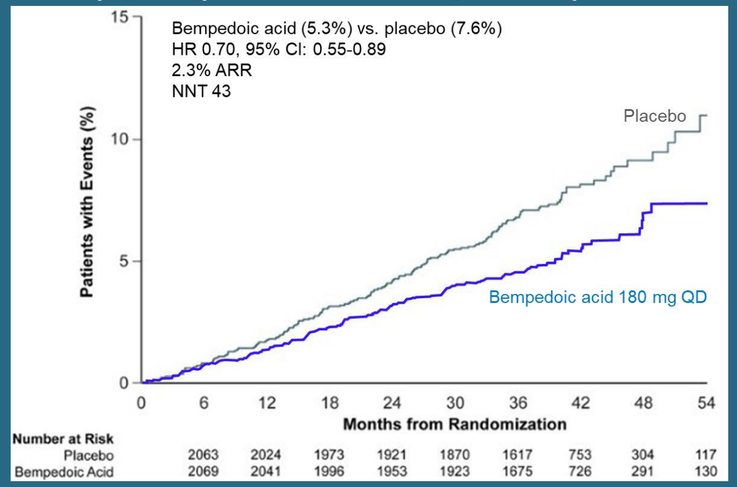
- An adverse effect that started or increased during statin therapy and resolved or improved after therapy discontinued.
- Intolerance to 2 or more statins or 1 statin if unwilling to attempt a second statin or advised by physician to not attempt second statin. Very low dose statin therapy permitted (< lowest approved dose)

PURPOSE

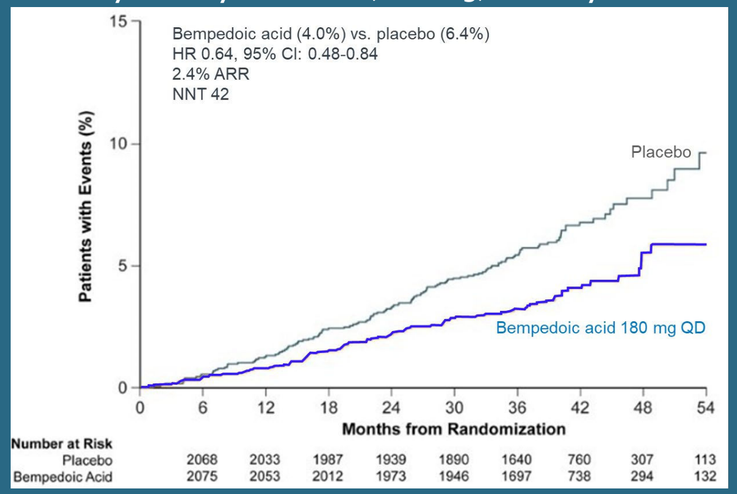
Describe the effect of bempedoic acid on CV outcomes in the 30.1% (4206) of primary prevention patients enrolled in the CLEAR Outcomes study[12]

RESULTS

Primary Efficacy End Point (MACE-4): Primary Prevention



Secondary Efficacy End Point (MACE-3): Primary Prevention



CONCLUSIONS

- Bempedoic acid was well-tolerated in primary prevention patients unable or unwilling to take statins.
- Bempedoic acid lowered LDL-C by 21.3% and hsCRP by 21.5% with small increases in the incidence of gout and cholelithiasis.
- Bempedoic acid significantly lowered cardiovascular risk, including the risk of major adverse cardiovascular events, compared to placebo
- These findings suggest significant benefits from lowering LDL-C and hsCRP with bempedoic acid in high-risk primary prevention patients unable or unwilling to take a statin.

LIMITATIONS

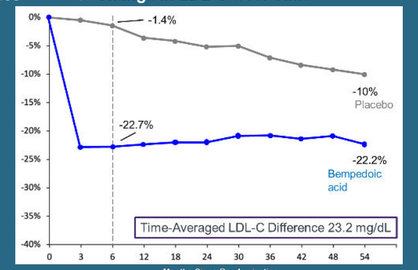
- This was a secondary analysis of a subpopulation in a larger randomized trial.
- Such analyses can result in false positive findings due to testing of multiple subgroups.
- The inclusion of statin intolerant patients resulted in a relatively high baseline LDL cholesterol.
- These were patients at high risk of a first cardiovascular event. Results may not apply to lower risk populations.

RESULTS

Primary Prevention Patients: Baseline Characteristics

Characteristic	Bempedoic Acid (N=2100)	Placebo (N=2106)
Age mean (SD), years	67.9 (6.9)	68.0 (6.8)
Female Sex	58.8%	59.2%
White	92.2%	90.8%
Hispanic or Latino	19%	17.9%
Diabetes	65.2%	67.0%
Baseline Statin Use	18.8%	19.8%
BMI, mean (SD)	30.2 (5.3)	30.4 (5.4)
LDL cholesterol, mean (SD), mg/dL	142.2 (34.5)	142.7 (35.9)
hsCRP, median (IQR), mg/L	2.4 (1.2-4.5)	2.4 (1.2-4.6)

% Change in LDL-C Over Time



Note: Over the duration of the study, among placebo patients, 12.4% received additional lipid-lowering therapy, compared with 6.7% of bempedoic acid patients

Change in hsCRP for Bempedoic Acid Compared with Placebo at 12 Months

	Bempedoic Acid			Placebo			BA vs. Placebo (95% CI)	
	Baseline	12 Month	Change (95% CI)	Baseline	12 Month	Change (95% CI)	mg/L	% difference
hsCRP, mg/L	2.39 (1.2 to 4.5)	1.75 (0.87 to - 3.49)	-0.34 (-0.42 to - 0.29)	2.44 (1.2 to 4.6)	2.52 (1.2 to 5.0)	0.01 (-0.04 to 0.09)	-0.56 (-0.68 to - 0.44)	-21.5 (-25.4 to - 17.6)

Efficacy End Points for the Bempedoic Acid Treatment Compared with Placebo

Outcome	Bempedoic Acid (N=2100)	Placebo (N=2106)	Bempedoic acid vs. Placebo	
	Events, n (%)		Hazard Ratio[a] (95% CI)	P Value[b*]
Primary efficacy endpoint MACE-4	111(5.3)	161 (7.6)	0.70 (0.55-0.89)	0.002
Secondary efficacy endpoints				
MACE-3	83 (4.0)	134 (6.4)	0.64 (0.48-0.84)	<0.001
Endpoint Components				
All-cause mortality	75 (3.6)	109 (5.2)	0.73 (0.54-0.98)	
Cardiovascular death	37 (1.8)	65 (3.1)	0.61 (0.41-0.92)	
Fatal and non-fatal MI	29 (1.4)	47 (2.2)	0.61 (0.39-0.98)	
Fatal and non-fatal stroke	27(1.3)	37 (1.8)	0.76 (0.46-1.26)	
Coronary Revascularization	50 (2.4)	68 (3.2)	0.71 (0.49-1.03)	
Hospitalization for UA	10 (0.5)	17 (0.8)	0.58 (0.26-1.27)	

Investigator Reported Adverse Events

Characteristic	Bempedoic Acid (N=2104)	Placebo (N=2101)
Serious Treatment Emergent AE	418 (19.9)	438 (20.8)
AE leading to drug discontinuation	209 (9.9)	209 (9.9)
Any Muscle Disorder	269 (12.8)	291 (13.9)
Worsening Hyperglycemia	297/1372 (21.6)	294/1408 (20.9)
New Onset Diabetes	47/732 (6.4)	48/693 (6.9)
Elevated Hepatic Enzymes	94 (4.5)	55 (2.6)
Renal Impairment	216 (10.3)	170 (8.1)
Cholelithiasis	53 (2.5)	24 (1.1)
Gout	55 (2.6)	41 (2.0)
Uric acid>8.5 mg/dL	215/1996 (10.8)	82/1993 (4.1)

Abbreviations:LDL-C=low-density lipoprotein cholesterol; hsCRP=high sensitivity C-reactive protein; CI: confidence interval; SD: standard deviation; IQR: interquartile range; MACE=major adverse cardiovascular event; MACE-4=death from cardiovascular causes, nonfatal MI, nonfatal stroke, or coronary revascularization; MACE-3=CV death, nonfatal stroke, nonfatal MI; HR=hazard ratio; QD=once daily; MI=myocardial infarction; RRR=relative risk reduction; ARR=absolute risk reduction; NNT=number needed to treat; AE= adverse event; UA=unstable angina

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