CLEAR OUTCOMES Analysis by Glycaemic Status

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On behalf of

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Study Sponsor:
Esperion Therapeutics, Inc.

Background

- In 2021, 529 million individuals were living with diabetes (DM) globally
- Diabetes doubles the risk of atherosclerotic cardiovascular disease
- LDL-C lowering with statins as first-line treatment reduces this risk in patients with DM (CARDS trial)
- Secondary prevention patients with DM derive greater absolute benefits when non-statin LLTs, such as ezetimibe and PCSK9 mAbs, are added to statins
- Many patients are unable to tolerate or maximize a statin leaving them at high residual risk of CVD

Background (cont)

- **Statins increase the risk of new-onset diabetes (NOD) in a dose dependent fashion**
  - Genetics suggest an on-target effect of HMGCoA inhibition
- **In trials with ezetimibe or PCSK9i added to statins there was no excess risk of NOD**
  - Genetics suggest that lower NPC1L1 or PCSK9 activity would increase risk of NOD
- **Genetic studies suggested that lower activity of ACLY, the target of Bempedoic Acid, would reduce CVD with no excess risk of NOD**

CLEAR Outcomes

Patients with, or at high risk for, CVD who are unable or unwilling to take guideline-recommended doses of statins

VISIT T1 (Day 1) (N=13970)

R

1:1

Bempedoic Acid 180 mg QD

End of Study Criteria

1. At least 1,620 adjudicated primary MACE-4
2. At least 810 adjudicated MACE-3
3. At least 24 months since the last patient was randomized

Placebo

Median Follow-Up: 40.6 months

Enrollment: December 2016 – August 2019

Time to Event Outcomes	Bempedoic Acid (N=6992)	Placebo (N=6978)	Bempedoic Acid vs Placebo	
	Events (n), %		HR (95% CI)	*P*-value
MACE-4	819 (11.7)	927 (13.3)	0.87 (0.79-0.96)	0.004
MACE-3	575 (8.2)	663 (9.5)	0.85 (0.76-0.96)	0.006

Prespecified DM Analysis - Endpoints

Efficacy Outcomes

- **MACE-4:** Cardiovascular death, non-fatal MI, non-fatal stroke, or coronary revascularization
- **MACE-3:** Cardiovascular death, non-fatal MI, or non-fatal stroke

Clinical Outcomes

- HbA1c*
- Fasting Glucose*
- New Onset Diabetes

***At 1 year (prespecified); At End of Study (post-hoc)**

Baseline Characteristics - balanced by randomization

Baseline Characteristics	Normoglycaemia (N=1801)		Prediabetes* (N=5796)		Diabetes** (N=6373)	
	Bempedoic Acid (n=937)	Placebo (n=864)	Bempedoic Acid (n=2911)	Placebo (n=2885)	Bempedoic Acid (n=3144)	Placebo (n=3229)
Age, years (SD)	63.7 (10.2)	64.1 (10.5)	65.0 (9.5)	64.8 (9.1)	66.5 (8.1)	66.5 (8.1)
Females, n (%)	475 (50.7%)	434 (50.2%)	1252 (43.0%)	1250 (43.3%)	1634 (52.0%)	1695 (52.5%)
Body mass index*, kg/m^2	27.6 (4.4)	28.0 (4.4)	29.2 (4.7)	29.1 (4.8)	31.2 (5.5)	31.2 (5.6)
Weight, kg (SD)	78.3 (15.0)	79.7 (15.4)	83.5 (16.1)	83.6 (16.2)	86.6 (18.0)	86.7 (18.2)
ASCVD Status Primary Prevention	194 (20.7%)	145 (16.8%)	537 (18.4%)	549 (19.0%)	1369 (43.5%)	1412 (43.7%)

Did not meet the criteria for either prediabetes or diabetes

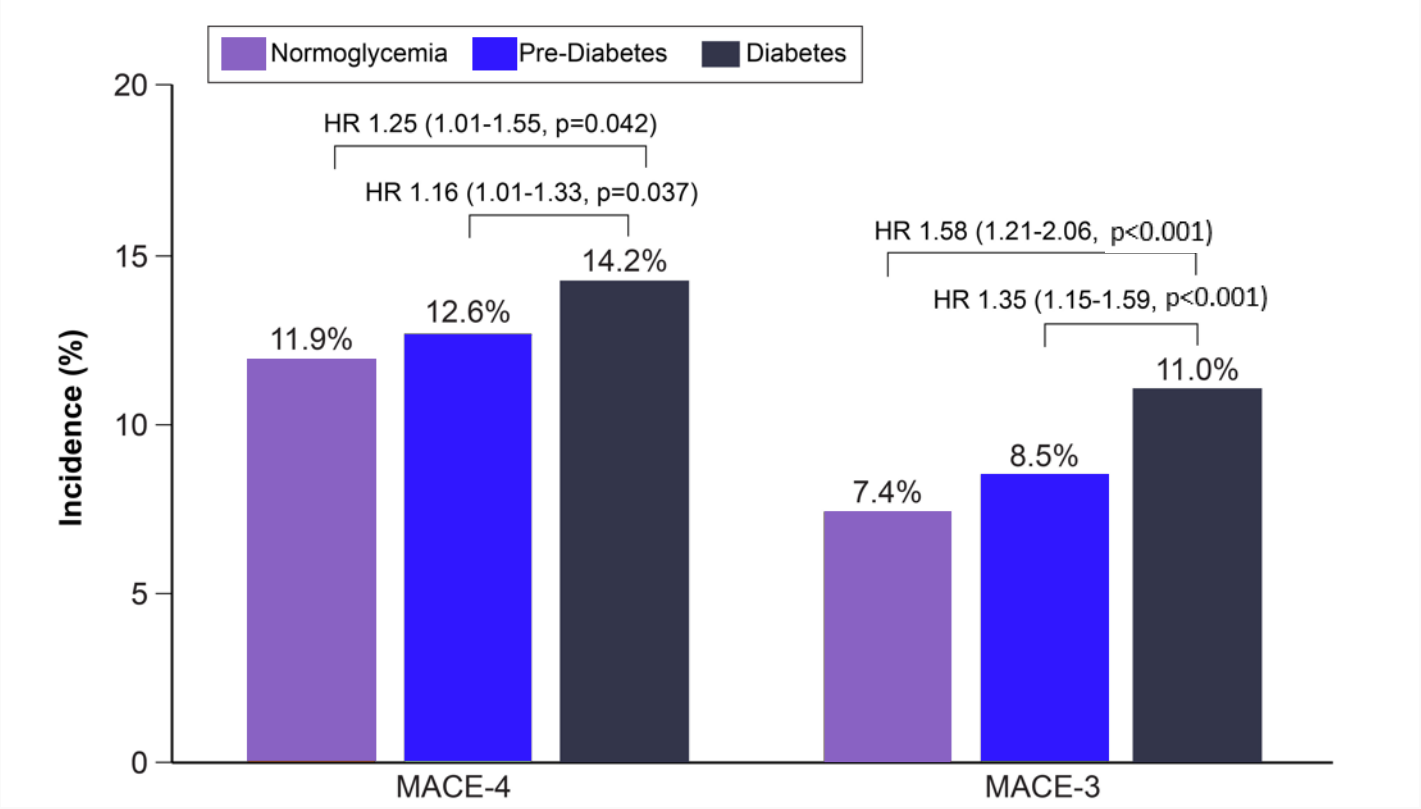
* HbA1c 5·7%-6·4% (39-48 mmol/mol), or ≥1 fasting serum glucose concentration of at least 5·6 mmol/L (100mg/dl), but with no more than one value of ≥7·0 mmol/L (126mg/dl)

** Medical history of diabetes; or use of glucose lowering medication; or HbA1c ≥6·5% (48 mmol/mol); or two or more fasting serum glucose concentration ≥7·0 mmol/L (126 mg/dL)

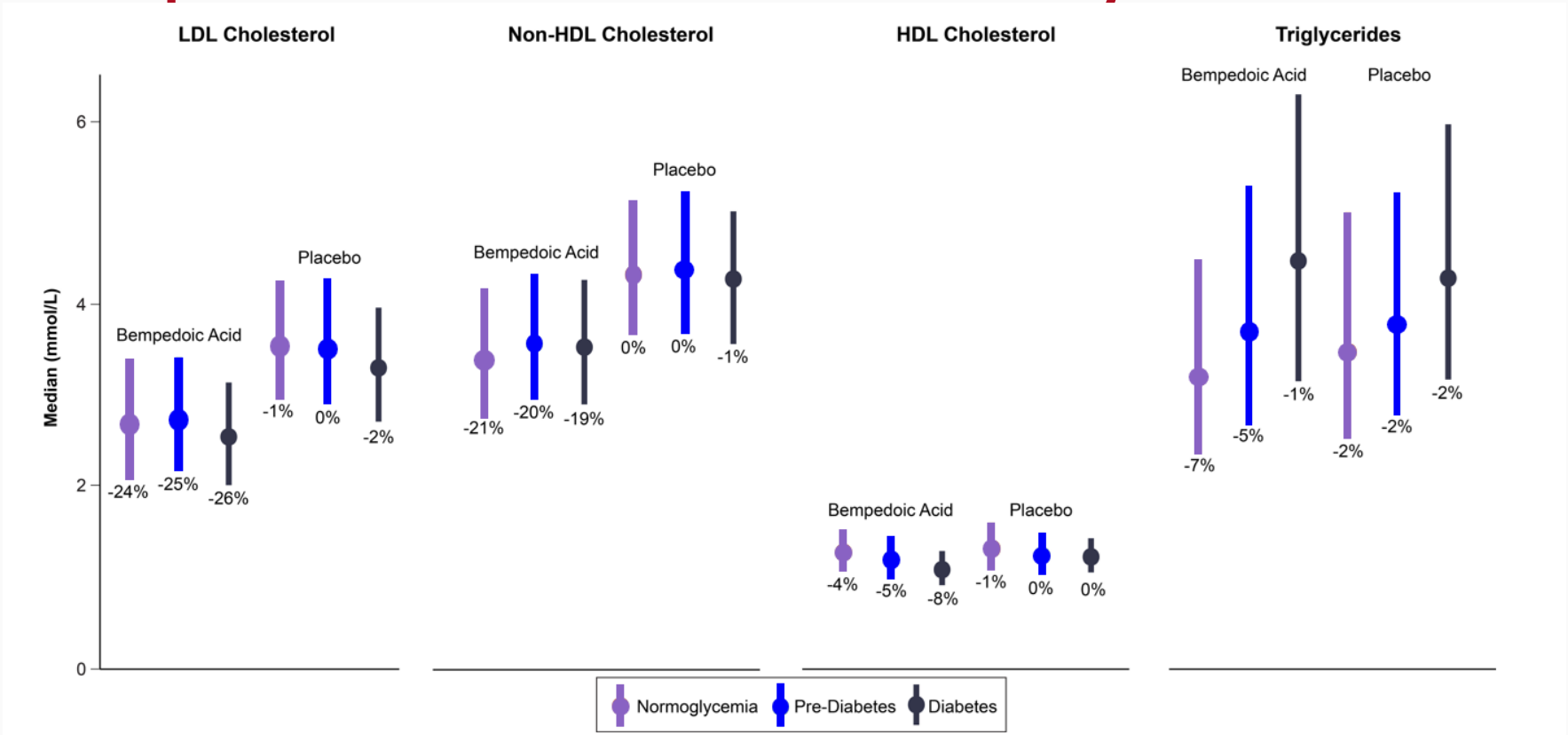
Baseline Characteristics (cont.) - balanced by randomization

Baseline Characteristics	Normoglycaemia (N=1801)		Prediabetes (N=5796)		Diabetes (N=6373)	
	Bempedoic Acid (n=937)	Placebo (n=864)	Bempedoic Acid (n=2911)	Placebo (n=2885)	Bempedoic Acid (n=3144)	Placebo (n=3229)
Duration of follow-up, months	43.0 (9.0)	42.7 (9.6)	42.1 (9.1)	42.0 (9.0)	40.4 (9.4)	40.7 (9.2)
Laboratory values at baseline						
LDL cholesterol, mmol/L	3.7 (0.9)	3.7 (1.0)	3.7 (0.9)	3.7 (0.9)	3.5 (0.8)	3.5 (0.9)
Non-HDL cholesterol, mmol/L	4.4 (1.0)	4.5 (1.1)	4.6 (1.1)	4.6 (1.1)	4.5 (1.0)	4.5 (1.0)
HDL cholesterol, mmol/L	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.3)
Triglycerides, mmol/L	1.5 (1.1 – 2.1)	1.6 (1.2 – 2.1)	1.7 (1.3 – 2.3)	1.7 (1.3 – 2.3)	2.0 (1.5 – 2.7)	2.0 (1.5 – 2.6)
Haemoglobin A1c, %	5.3 (0.2)	5.3 (0.2)	5.7 (0.3)	5.7 (0.3)	7.0 (1.1)	7.0 (1.2)
Fasting glucose, mmol/L	5.0 (0.3)	5.0 (0.3)	5.8 (0.6)	5.8 (0.6)	7.8 (2.3)	7.8 (2.3)
Baseline Medications						
Statin	211 (22.5%)	192 (22.2%)	677 (23.3%)	661 (22.9%)	713 (22.7%)	720 (22.3%)
Ezetimibe	142 (15.2%)	116 (13.4%)	378 (13.0%)	397 (13.8%)	283 (9.0%)	296 (9.2%)

Incidence of Cardiovascular Events in the Placebo Group Increased Across Glycaemic Strata



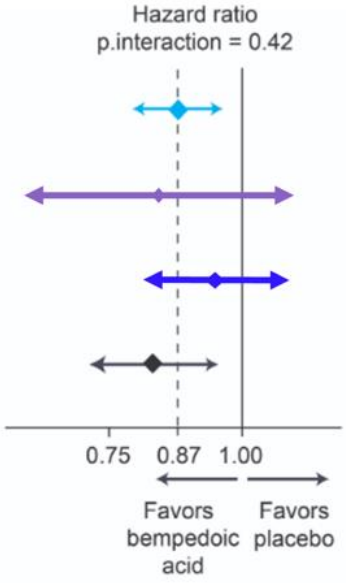
At 6 months LDL-C and non-HDL-C reductions with Bempedoic Acid were similar across Glycaemia Strata

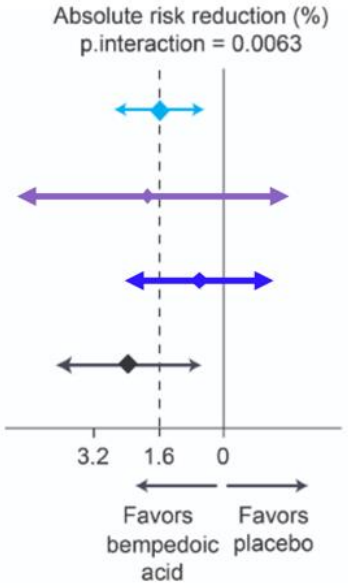


Error bars are IQRs. Median within-patient percentage changes from baseline are shown below each data point.

Bempedoic Acid provided similar relative but greater absolute benefits on MACE-4 in those with DM

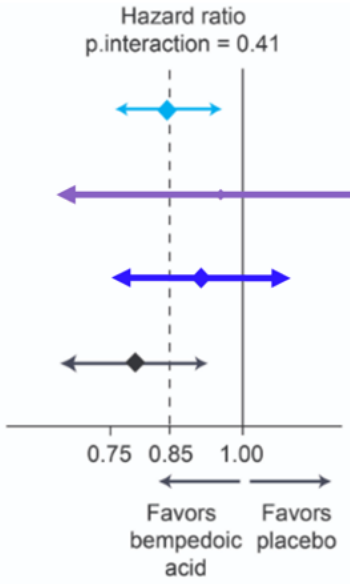
	Bempedoic Acid n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Absolute Reduction (95% CI)
Overall	819/6992 (11.7%)	927/6978 (13.3%)	0.87 (0.79, 0.96)	1.6% (0.5%, 2.7%)
Normoglycemia	95/937 (10.1%)	103/864 (11.9%)	0.84 (0.63, 1.10)	1.9% (-1.12%, 4.8%)
Pre-Diabetes	350/2911 (12.0%)	364/2885 (12.6%)	0.94 (0.81, 1.09)	0.6% (-1.1%, 2.3%)
Diabetes	374/3144 (11.9%)	460/3229 (14.2%)	0.83 (0.72, 0.95)	2.4% (0.7%, 4.0%)

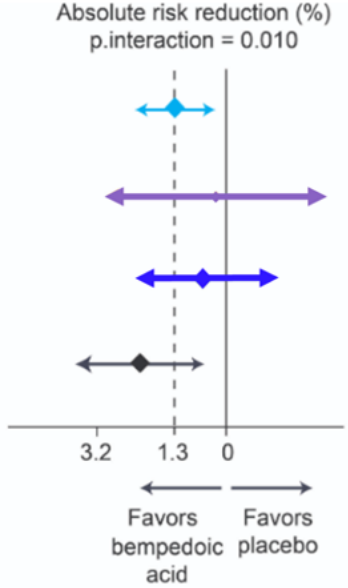




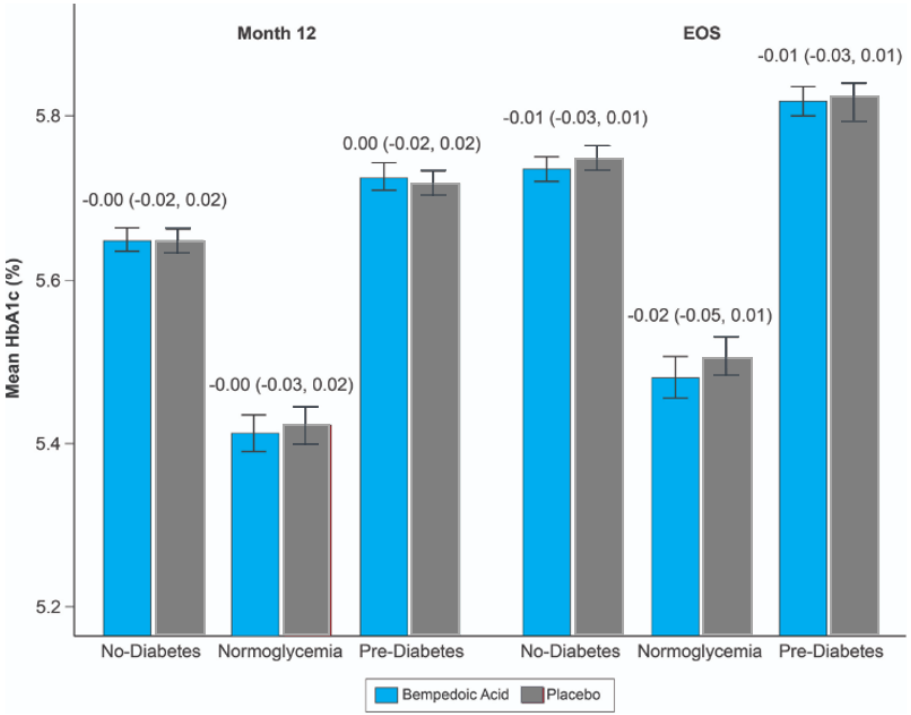
Bempedoic Acid provided similar relative but greater absolute benefits on MACE-3 in those with DM

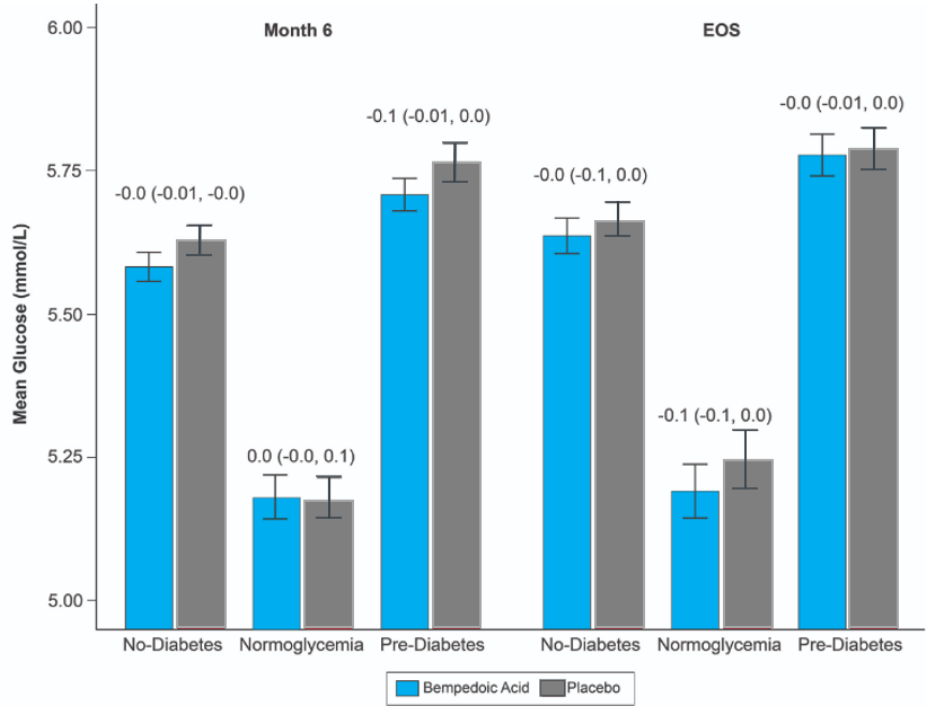
	Bempedoic Acid n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	Absolute Reduction (95% CI)
Overall	575/6992 (8.2%)	663/978 (9.5%)	0.85 (0.76, 0.96)	1.3% (0.3%, 2.2%)
Normoglycemia	67/937 (7.2%)	64/864 (7.4%)	0.96 (0.68, 1.35)	0.3% (-2.1%, 2.7%)
Pre-Diabetes	229/2911 (7.9%)	244/2885 (8.5%)	0.92 (0.77, 1.10)	0.6% (-0.8%, 2.0%)
Diabetes	279/3144 (8.9%)	355/3229 (11.0%)	0.80 (0.68, 0.93)	2.1% (0.7%, 3.6%)





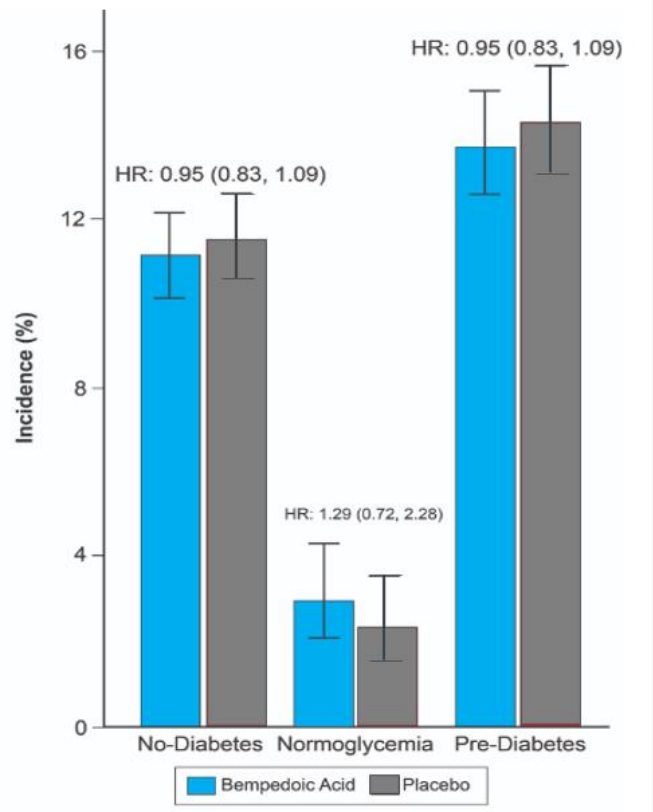
Bempedoic Acid did not worsen HbA1c or glucose levels in those without diabetes



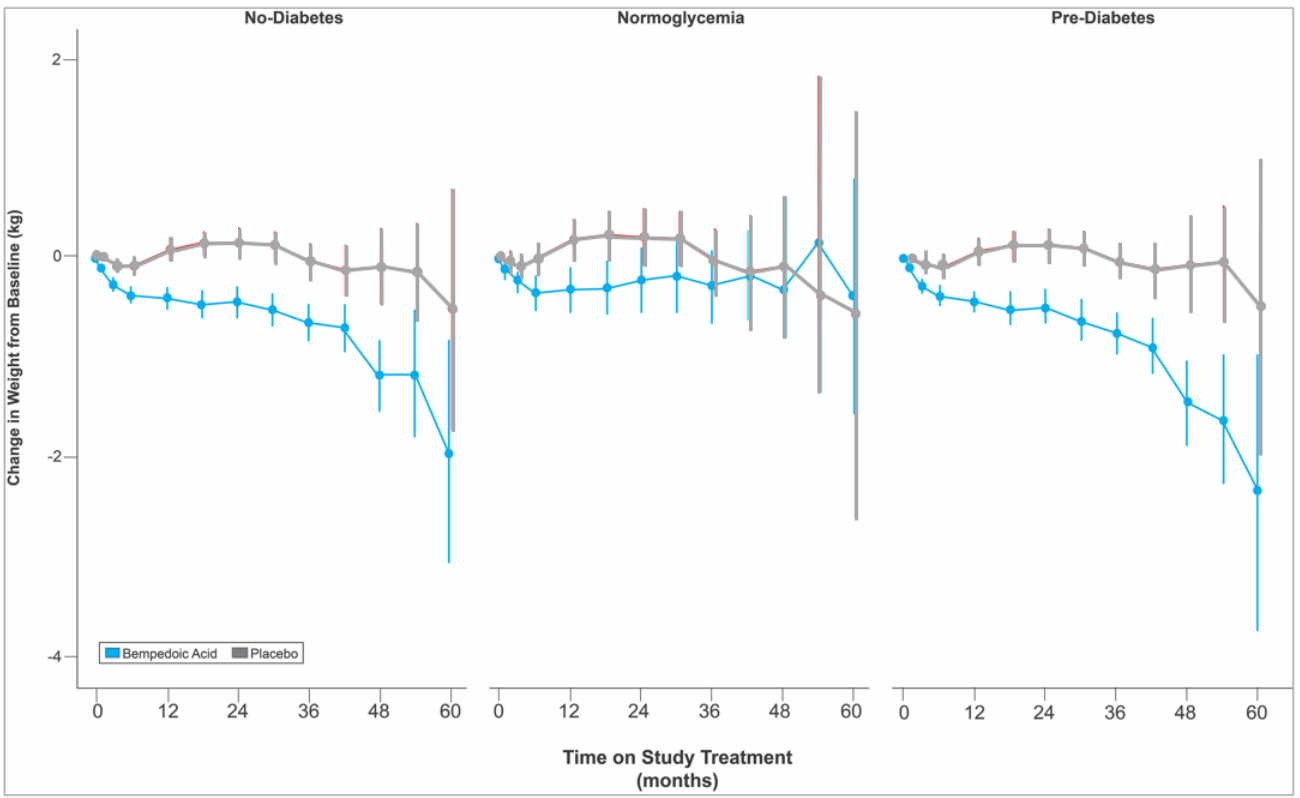


Bempedoic Acid did not increase the risk of New Onset Diabetes

- Individuals with normoglycaemia or prediabetes at baseline were considered to have NOD during the trial if one or more of the following criteria were met as defined in the ADA guidelines:
  - HbA_{1c} value of 6·5% or higher; or
  - Fasting serum glucose value of at least 7·0 mmol/L; or,
  - Two-hour post prandial glucose ≥11·1 mmol/L during an oral glucose tolerance test; or,
  - In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose ≥ 11·1 mmol/L, or initiation of glucose lowering therapies.
  - In the absence of unequivocal hyperglycaemia, diagnosis required two abnormal test results from the same sample or in two separate test results.



Weight was lower in Bempedoic Acid treated patients compared to Placebo



Concordance of Mendelian Randomization and Pharmacotherapy RCTs

	Enhancing LDL Receptor Activity							
Pathway	**Cholesterol synthesis pathway**				**Cholesterol absorption**		**LDL receptor degradation**	
Target	**ACLY**		**HMGCoA**		**NPC1L-1**		**PCSK9**	
Mechanism of lowering	***Genetically Lower***	***Bempedoic Acid***	***Genetically lower***	***Statins***	***Genetically lower***	***Ezetimibe***	***Genetically lower***	***PCSK9i MAbs***
Efficacy								
LDL-C	Lower	Lower	Lower	Lower	Lower	Lower	Lower	Lower
CVD	Lower	Lower	Lower	Lower	Lower	Lower	Lower	Lower
Safety								
Weight or BMI	Lower	Lower	Higher	Higher	Unknown	Unknown	Unknown	Unknown
HbA1c/glucose	Neutral	Neutral	Higher	Higher	Higher	Neutral	Higher	Neutral
New Onset Diabetes	Neutral	Neutral	Higher	Higher	Higher	Neutral	Higher	Neutral

ACLY = ATP-citrate lyase; HMGCoA = 3-hydroxy-3-methylglutaryl coenzyme-A; NPC1L-1 = Niemann–Pick C1-like 1; PCSK9 = proprotein convertase subtilisin/kexin type 9; LDL = low density lipoprotein; LDL-C = low density lipoprotein cholesterol; CVD = cardiovascular disease; BMI = body mass index

Conclusion

- In patients with DM unwilling or unable to take guideline-recommended doses of statins, Bempedoic Acid significantly reduced cardiovascular risk with large absolute benefits as monotherapy
- In patients without DM at baseline, there were no adverse effects of Bempedoic Acid on measures of glycaemia or risk of New Onset Diabetes
- These data validate prior genetic data for ACLY inhibition for reducing LDL-C and risk of CV disease with no adverse effect on measures of glycaemia