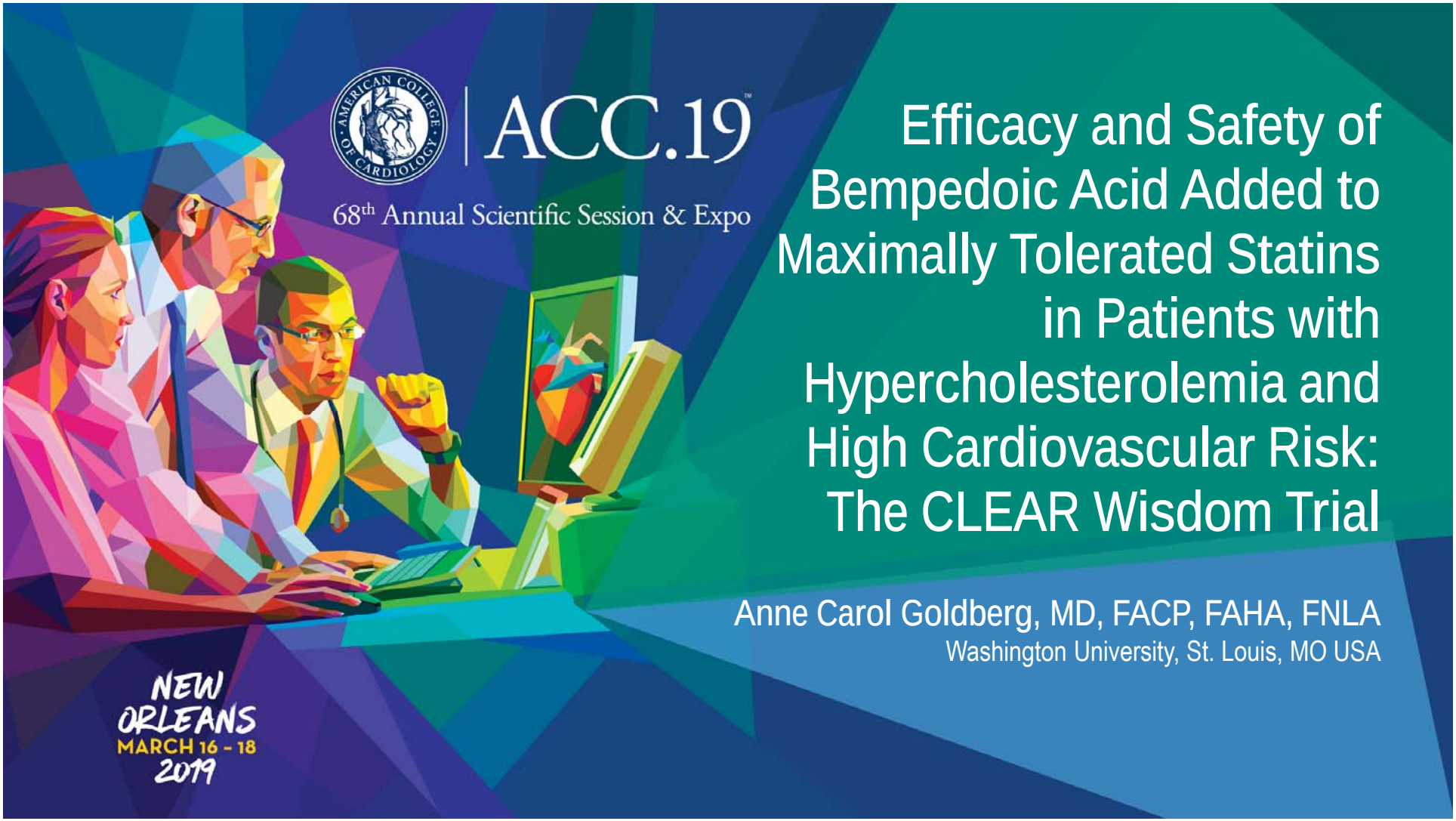

Efficacy and Safety of Bempedoic Acid Added to Maximally Tolerated Statins in Patients with Hypercholesterolemia and High Cardiovascular Risk: The CLEAR Wisdom Trial

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Disclosures

Individual disclosures*

- AC Goldberg: Grants/Research support: Amgen, Amarin, Pfizer, Regeneron, Sanofi, IONIS; Honoraria: National Lipid Association, Esperion, Novartis, AKCEA, Regeneron/Sanofi, 23andMe, Merck
- LA Leiter: Grants/Research Support; Speakers Bureau; and/or Honoraria: Amgen, AstraZeneca, Esperion, HLS, Kowa, The Medicines Co, Sanofi/Regeneron
- ESG Stroes: Grants/Research Support: Amgen, Sanofi, Resverlogix, and Athera; Consultant: Amgen, Sanofi, Esperion, Novartis, and Ionis Pharmaceuticals
- SJ Baum: Consultant, Speaker, and/or Scientific Advisory Board: Akcea, Amgen, Aralez, Boehringer Ingelheim Pharmaceutical, Cleveland Heart Labs, GLG Group, Guidepoint Global, Novo Nordisk, Regeneron, Sanofi
- JC Hanselman: Employment: Esperion
- LT Bloedon: Employment: Esperion
- X Zhao: Employment: Esperion
- B Duell: Institutional Grants or Honoraria: Akcea, Astra Zeneca, Daichii-Sankyo, Esperion, Regeneron, Regenxbio, Retrophin

The CLEAR Wisdom Trial was sponsored and funded by Esperion Therapeutics, Inc.

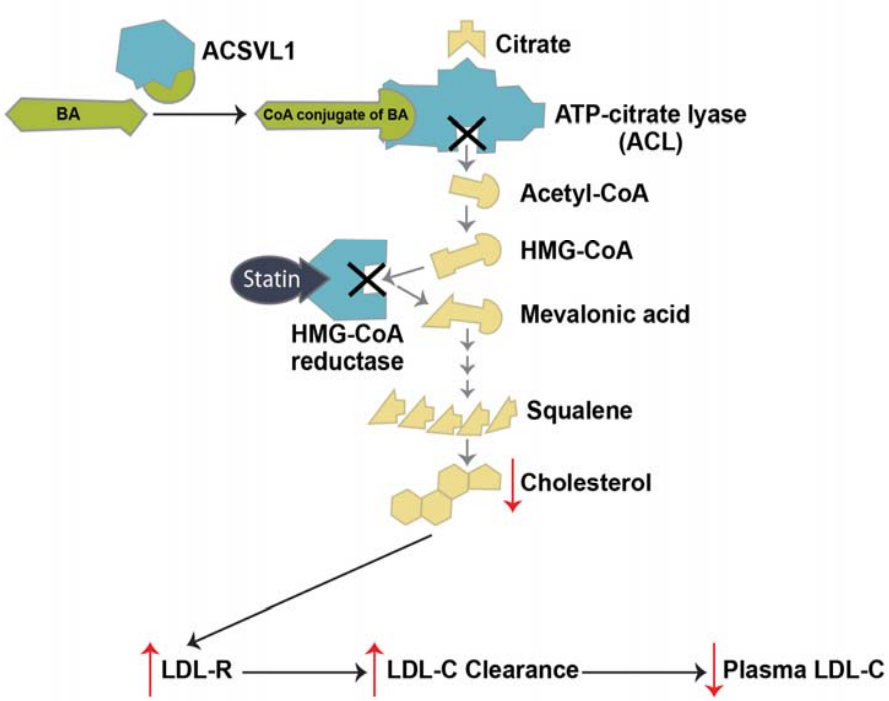
*Including receipt of research support (personal or institutional), speaking honoraria, and/or consulting fees.

Background

- Lipid-lowering therapies (statins) have greatly reduced cardiovascular (CV) disease burden[1]
- Many patients at high CV risk have elevated low-density lipoprotein cholesterol (LDL-C), despite statin treatment[2-6]
  - Insufficient response to high-intensity statins
  - Inability to take effective doses of statins due to tolerability issues
- Additional oral options that complement maximally tolerated lipid-lowering therapies are needed for patients unable to achieve adequate LDL-C lowering[7]
- Bempedoic acid is a once-daily oral, first-in-class, small-molecule drug being developed for the treatment of hyperlipidemia

1. Boekholdt SM, et al. *J Am Coll Cardiol.* 2014; 64(5):485-494; 2. deGoma EM, et al. *Circ Cardiovasc Genet.* 2016;9(3):240-249; 3. Gitt AK, et al. *Atherosclerosis.* 2016;255:200-209; 4. Menzin J, et al. *J Manag Care Spec Pharm.* 2017;23(12):1270-1276; 5. Perez de Isla, et al. *J Am Coll Cardiol.* 2016;67(11):1278-1285; 6. Lakey WC, et al. *J Clin Lipidol.* 2016;10:870-879; 7. Grundy SM, et al. *J Am Coll Cardiol.* 2018. doi:10.1016/j.jacc.2018.11.003.

Bempedoic Acid Mechanism of Action



- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Bempedoic acid inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Bempedoic acid upregulates LDL receptors and lowers LDL-C
- Activated bempedoic acid is not present in skeletal muscle

For review see: Pinkosky SL, et al. *Nat Commun.* 2016:28;7:13457.
BA, bempedoic acid.

CLEAR Wisdom Study Design

- Aim: Evaluate long-term efficacy and safety of bempedoic acid in high CV-risk patients receiving maximally tolerated statin ± other lipid-lowering therapy
- Phase 3, double-blind, placebo-controlled, parallel-group study conducted in 86 sites in North America and Europe
- Patients randomized 2:1 to treatment with bempedoic acid 180 mg or placebo once daily for 52 weeks in addition to maximally tolerated statin ± other lipid-lowering therapy
  - Key inclusion criteria
    - Pre-existing atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH)
    - Baseline LDL-C ≥ 100 mg/dL (2.6 mmol/L) at screening and ≥ 70 mg/dL (1.8 mmol/L) following placebo run-in while receiving maximally tolerated statins

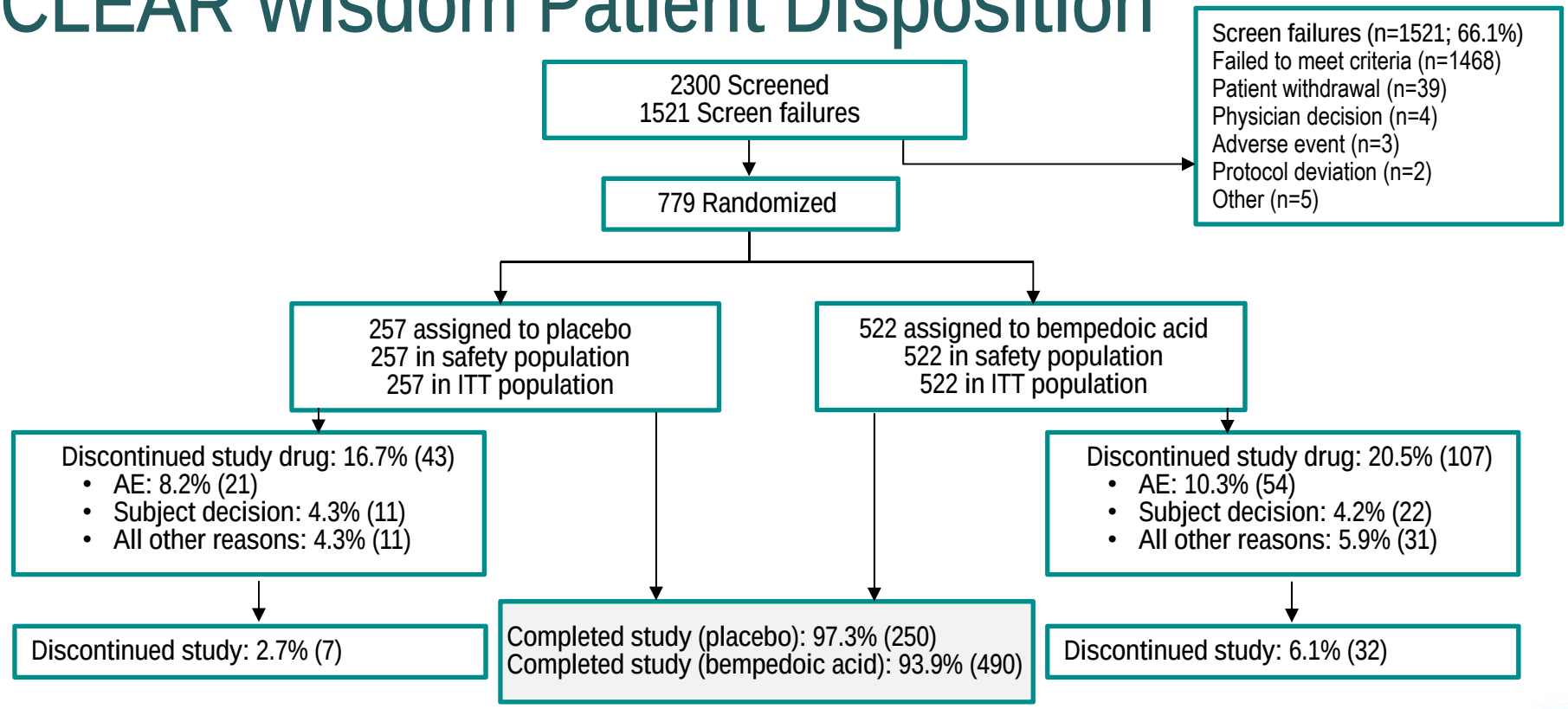
CLEAR Wisdom Clinicaltrials.gov identifier NCT02991118.

CLEAR Wisdom Study Design: Endpoints

- Primary endpoint: Percent change in LDL-C from baseline to week 12
- Key secondary endpoints:
  - Percent change in LDL-C from baseline to week 24
  - Percent change from baseline to week 12 in non–high-density lipoprotein cholesterol (non–HDL-C), total cholesterol (TC), apolipoprotein B (apoB), and high-sensitivity C-reactive protein (hsCRP)
- Key tertiary endpoint: Percent change in LDL-C at week 52
- Key tertiary objective: 52-week safety and tolerability of bempedoic acid compared to placebo

CLEAR Wisdom Clinicaltrials.gov identifier NCT02991118.

CLEAR Wisdom Patient Disposition



CLEAR Wisdom Baseline Characteristics

Characteristic	Placebo n = 257	Bempedoic Acid n = 522
Age, years[a]	64.7 ± 8.7	64.1 ± 8.8
Gender (% male)	65.4	62.8
Race (% white)	94.9	94.1
BMI, kg/m^2[a]	30.6 ± 5.0	30.0 ± 5.2
ASCVD alone, %	93.8	94.8
HeFH (with or without ASCVD), %	6.2	5.2
Diabetes, %	31.5	29.7
Hypertension, %	87.2	83.9

[a]Data are mean ± standard deviation.

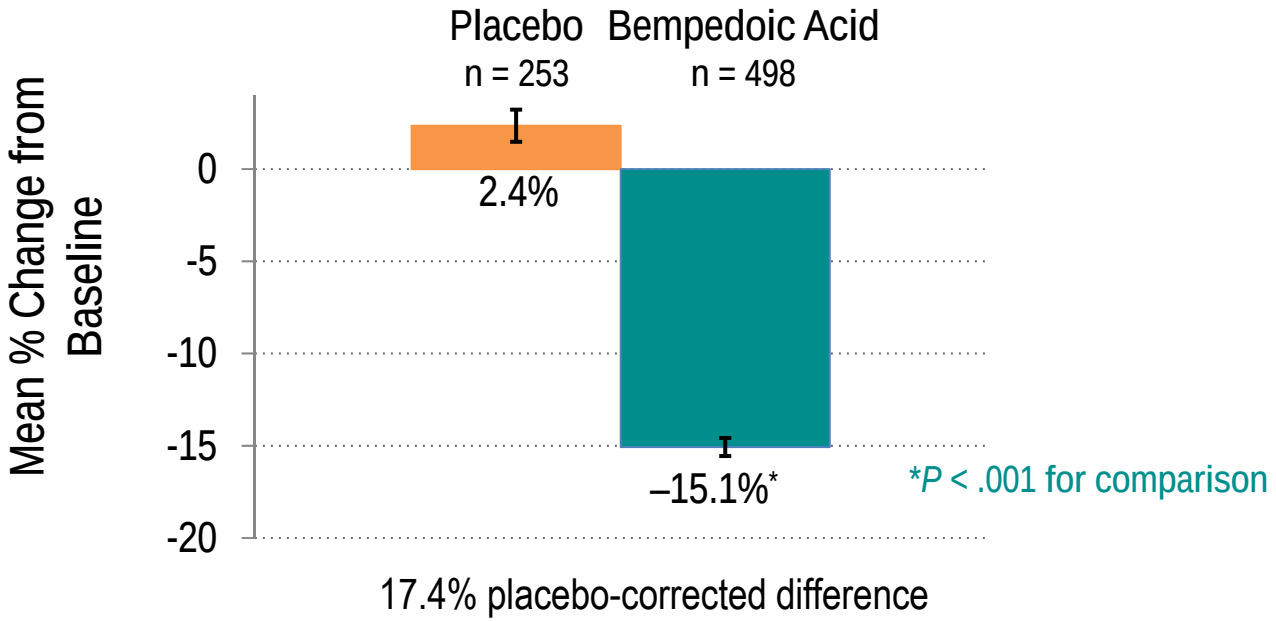
CLEAR Wisdom Baseline Characteristics

Characteristic	Placebo n = 257	Bempedoic Acid n = 522
LDL-C, mg/dL[a]	122 ± 38.3	119 ± 37.7
non–HDL-C, mg/dL[a]	154 ± 44.4	151 ± 42.7
Total cholesterol, mg/dL[a]	205 ± 46.1	202 ± 42.7
apoB, mg/dL[a]	119 ± 30.5	116 ± 29.6
hsCRP, mg/L[b]	1.9 (0.92, 3.79)	1.6 (0.87, 3.46)
High-intensity statin, %	52.5	53.3
Moderate-intensity statin, %	31.9	31.8
Low-intensity/no statin, %	15.6	14.9

[a]Data are mean ± standard deviation; [b]Data are median (Q1, Q3).
Statin intensity adapted from Stone NJ, et al. *J Am Coll Cardiol.* 2014;63(25 PtB):2889-2934.

CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in LDL-C (Primary Endpoint)



Mean = least squares mean (standard error).

CLEAR Wisdom Efficacy

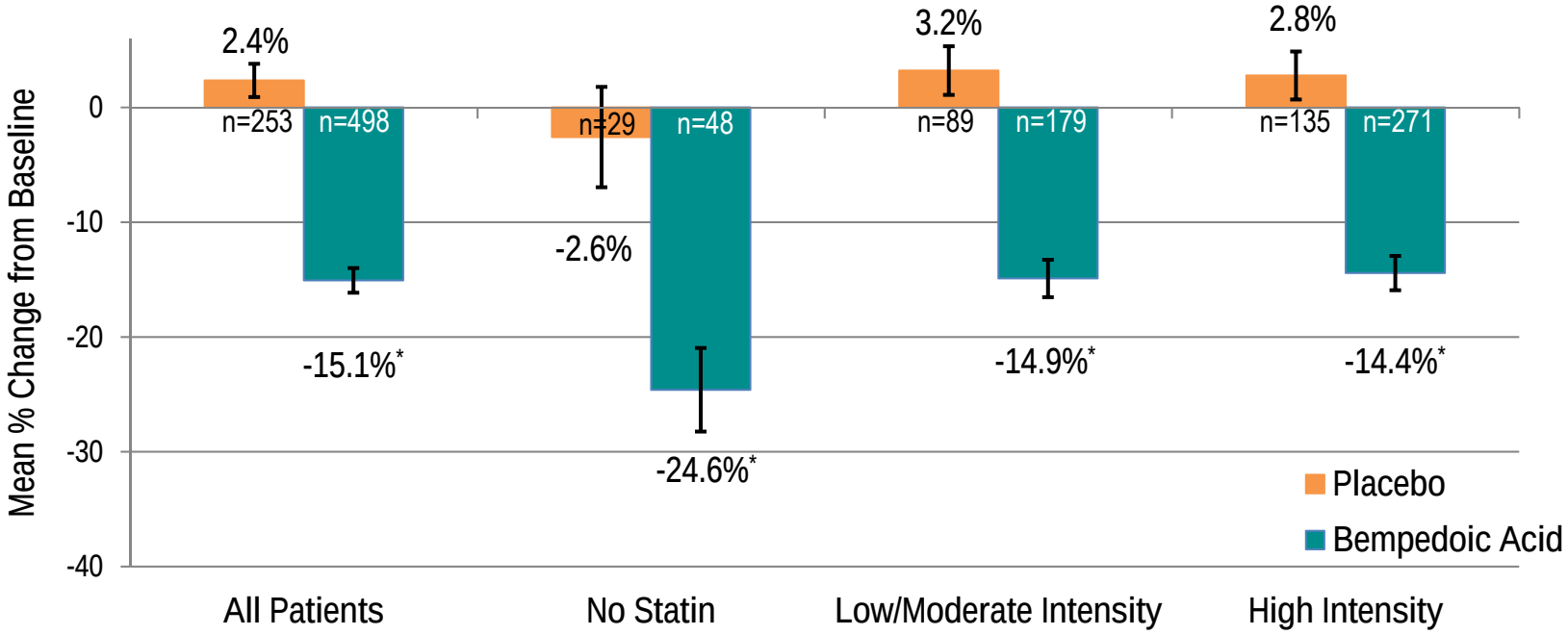
Observed LDL-C

	Baseline[a]	Week 12	Week 52
Sample Size (n)			
Placebo	257	253	237
Bempedoic Acid	522	498	467
Observed LDL-C (mg/dL, mean ± SD)			
Placebo	122.4 ± 38.3	122.8 ± 41.0	116.9 ± 40.3
Bempedoic Acid	119.4 ± 37.8	97.6 ± 33.8	99.6 ± 36.3

[a]Baseline is defined as the mean of the last 2 non-missing values on or prior to the first dose on day 1.

CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in LDL-C (Background Statin Intensity)

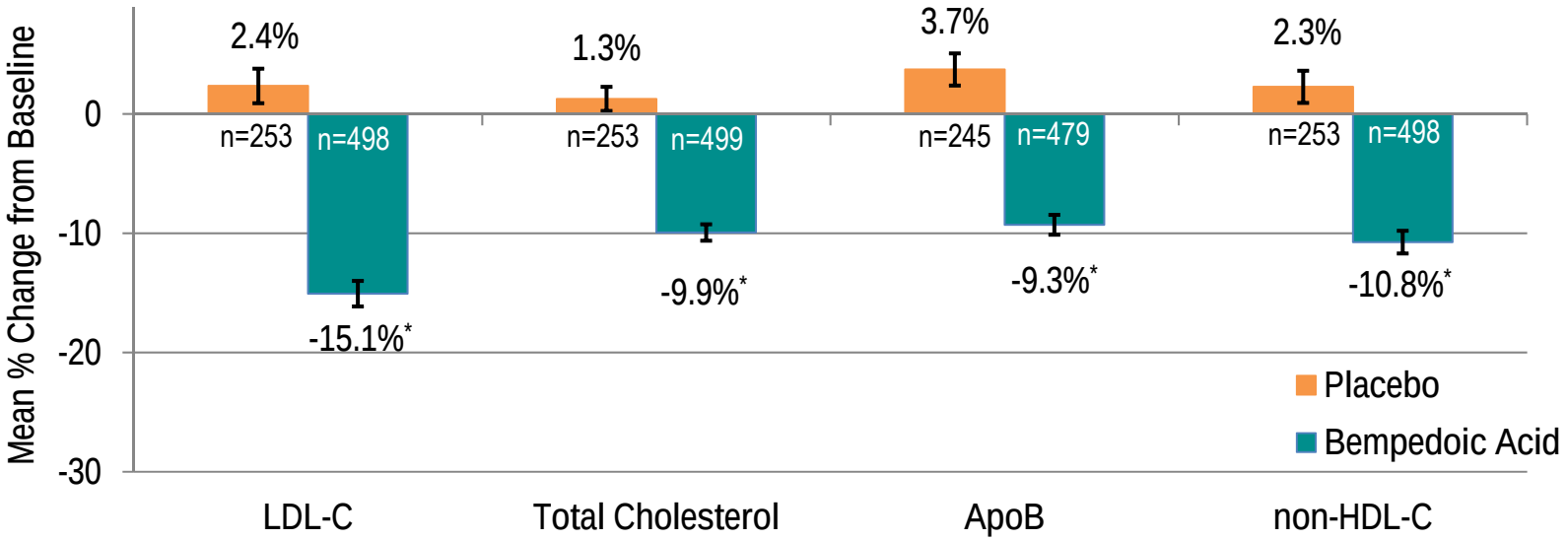


*$P < .001$ for all comparisons

Mean = least squares mean (standard error).

CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in Lipids and Lipoproteins

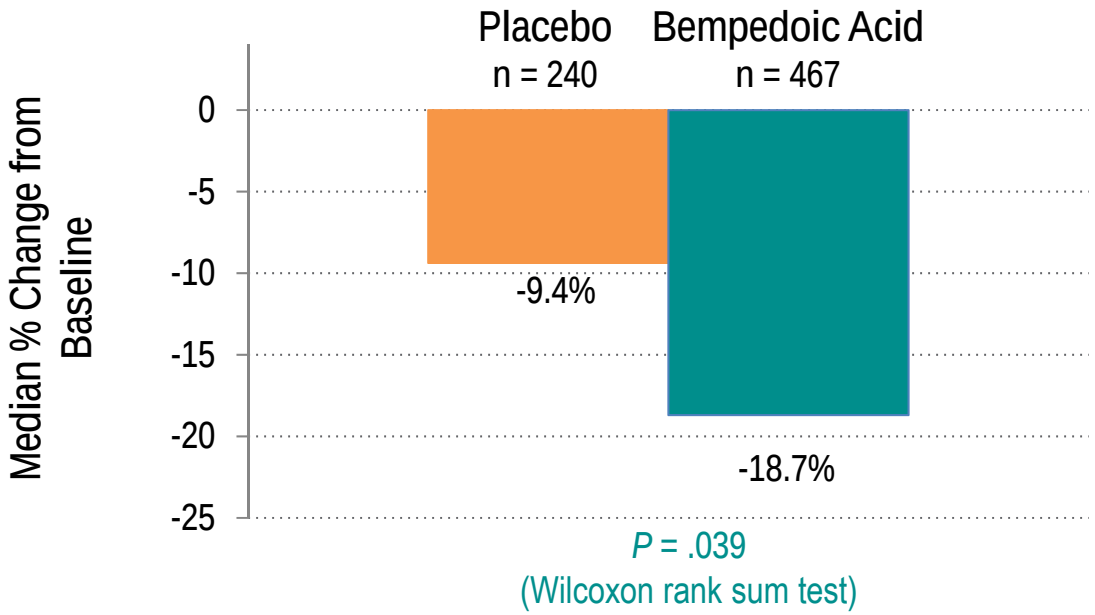


*$P < .001$ for all comparisons

Mean = least squares mean (standard error).

CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in hsCRP



CLEAR Wisdom Safety and Tolerability

Incidence of Adverse Events

TEAEs *Overview of AEs in All Patients (patient incidence)*	% of Patients Placebo n = 257	 Bempedoic Acid n = 522	 *P* value
Any adverse events	70.8	70.1	0.87
Serious adverse events	18.7	20.3	0.63
Study drug discontinuation due to adverse events	8.6	10.9	0.38
Fatal adverse events	0.8	1.1	1.00

AE, adverse event; TEAE, treatment emergent adverse event.

CLEAR Wisdom Safety and Tolerability

Positively Adjudicated Cardiovascular Events

Event	% of Patients	
	Placebo n = 257	Bempedoic Acid n = 522
All Positively Adjudicated Treatment-Emergent Clinical Endpoints	10.1	8.2
3-point MACE Clinical Endpoints	4.7	2.7
4-point MACE Clinical Endpoints	7.8	5.7
5-point MACE Clinical Endpoints	8.2	6.1
CV death	0.8	0.8
Nonfatal myocardial infarction	3.5	1.1
Nonfatal stroke	0.8	0.8
Coronary revascularization	5.8	3.8
Hospitalization for unstable angina	1.6	1.9

CLEAR Wisdom Safety and Tolerability

No Worsening of Glycemic Measurements in Patients With a History of Diabetes

Glycemic Measurement	Placebo n = 81	Bempedoic Acid n = 155
Patients (%) experiencing on-treatment blood glucose ≥ 126 mg/dL	75.3	69.7
12-week change in fasting blood glucose (mg/dL)	7.6 (34.7)	–0.5 (30.8)
12-week change in hemoglobin A1C (%)	0.13 (0.78)	–0.08 (0.51)

Fasting blood glucose and hemoglobin A1C absolute change from baseline at week 12 values are observed as mean ± standard deviation.

CLEAR Wisdom Safety and Tolerability

Summary of Adverse Events

- No statistically significant difference between placebo and bempedoic acid treatment arms in incidence of total AEs, SAEs, study drug discontinuations due to AEs, or fatal AEs
- There was an equal incidence of fatal TEAEs positively adjudicated as a CV death in placebo (n = 2, 0.8%) and bempedoic acid (n = 4, 0.8%) arms
- Two additional fatal TEAEs in bempedoic acid arm were due to gas poisoning and septic shock
- All fatal adverse events and serious adverse events were assessed as unrelated to study medication

AE, adverse event; SAE, serious adverse event; TEAE, treatment emergent adverse event.

CLEAR Wisdom Safety and Tolerability

Summary of Adverse Events

- All patients with fatal AEs had a medical history of ASCVD
- Most common adverse events[a] were nasopharyngitis and urinary tract infection

[a]Most common adverse events are those occurring in ≥ 5% of patients in either treatment arm.

CLEAR Wisdom Summary: Efficacy

- CLEAR Wisdom provides additional evidence that bempedoic acid is efficacious in patients at high CV risk with hypercholesterolemia, despite receiving maximally tolerated statin therapy
  - Bempedoic acid reduced LDL-C at week 12 by 17.4%
  - Reductions in LDL-C were maintained for 52 weeks
  - Bempedoic acid also significantly lowered non–HDL-C, apoB, total cholesterol, and hsCRP

CLEAR Wisdom Summary: Safety

- Bempedoic acid was safe and well tolerated when given as an adjunct to maximally tolerated statins
  - AE profile of bempedoic acid was generally similar to that of placebo
  - Adjudicated major adverse CV events were 2% lower than placebo with bempedoic acid
  - No worsening of 12-week glycemic measurements in patients with a history of diabetes compared to placebo

CLEAR Wisdom: Conclusion

- Bempedoic acid may provide an additional therapeutic option to safely lower LDL-C in high CV risk patients with elevated LDL-C treated with maximally tolerated statins and other lipid-modifying therapies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