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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Individual disclosures*

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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

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

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

2300 Screened
1521 Screen failures

779 Randomized

257 assigned to placebo
257 in safety population
257 in ITT population

Discontinued study drug: 16.7% (43)
• AE: 8.2% (21)
• Subject decision: 4.3% (11)
• All other reasons: 4.3% (11)

Discontinued study: 2.7% (7)

Completed study (placebo): 97.3% (250)

522 assigned to bempedoic acid
522 in safety population
522 in ITT population

Discontinued study drug: 20.5% (107)
• AE: 10.3% (54)
• Subject decision: 4.2% (22)
• All other reasons: 5.9% (31)

Discontinued study: 6.1% (32)

Completed study (bempedoic acid): 93.9% (490)

Screen failures (n=1521; 66.1%)
Failed to meet criteria (n=1468)
Patient withdrawal (n=39)
Physician decision (n=4)
Adverse event (n=3)
Protocol deviation (n=2)
Other (n=5)
### CLEAR Wisdom Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n = 257</th>
<th>Bempedoic Acid n = 522</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years&lt;sup&gt;a&lt;/sup&gt;</td>
<td>64.7 ± 8.7</td>
<td>64.1 ± 8.8</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>65.4</td>
<td>62.8</td>
</tr>
<tr>
<td>Race (% white)</td>
<td>94.9</td>
<td>94.1</td>
</tr>
<tr>
<td>BMI, kg/m&lt;sup&gt;2&lt;/sup&gt;&lt;sup&gt;a&lt;/sup&gt;</td>
<td>30.6 ± 5.0</td>
<td>30.0 ± 5.2</td>
</tr>
<tr>
<td>ASCVD alone, %</td>
<td>93.8</td>
<td>94.8</td>
</tr>
<tr>
<td>HeFH (with or without ASCVD), %</td>
<td>6.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31.5</td>
<td>29.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>87.2</td>
<td>83.9</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are mean ± standard deviation.
## CLEAR Wisdom Baseline Characteristics

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</thead>
<tbody>
<tr>
<td></td>
<td>n = 257</td>
<td>n = 522</td>
</tr>
<tr>
<td>LDL-C, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>122 ± 38.3</td>
<td>119 ± 37.7</td>
</tr>
<tr>
<td>non–HDL-C, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>154 ± 44.4</td>
<td>151 ± 42.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>205 ± 46.1</td>
<td>202 ± 42.7</td>
</tr>
<tr>
<td>apoB, mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>119 ± 30.5</td>
<td>116 ± 29.6</td>
</tr>
<tr>
<td>hsCRP, mg/L&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.9 (0.92, 3.79)</td>
<td>1.6 (0.87, 3.46)</td>
</tr>
<tr>
<td>High-intensity statin, %</td>
<td>52.5</td>
<td>53.3</td>
</tr>
<tr>
<td>Moderate-intensity statin, %</td>
<td>31.9</td>
<td>31.8</td>
</tr>
<tr>
<td>Low-intensity/no statin, %</td>
<td>15.6</td>
<td>14.9</td>
</tr>
</tbody>
</table>

<sup>a</sup>Data are mean ± standard deviation; <sup>b</sup>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 % Change from Baseline

Placebo  Bempedoic Acid
n = 253  n = 498

2.4%  -15.1%

*P < .001 for comparison

17.4% placebo-corrected difference

Mean = least squares mean (standard error).
CLEAR Wisdom Efficacy

Observed LDL-C

<table>
<thead>
<tr>
<th></th>
<th>Baseline&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Week 12</th>
<th>Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample Size (n)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>257</td>
<td>253</td>
<td>237</td>
</tr>
<tr>
<td>Bempedoic Acid</td>
<td>522</td>
<td>498</td>
<td>467</td>
</tr>
<tr>
<td><strong>Observed LDL-C (mg/dL, mean ± SD)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>122.4 ± 38.3</td>
<td>122.8 ± 41.0</td>
<td>116.9 ± 40.3</td>
</tr>
<tr>
<td>Bempedoic Acid</td>
<td>119.4 ± 37.8</td>
<td>97.6 ± 33.8</td>
<td>99.6 ± 36.3</td>
</tr>
</tbody>
</table>

<sup>a</sup>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)

Mean % Change from Baseline

*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

 Mean % Change from Baseline

- LDL-C
- Total Cholesterol
- ApoB
- non-HDL-C

*P < .001 for all comparisons

Mean = least squares mean (standard error).
CLEAR Wisdom Efficacy
Percent Change from Baseline to Week 12 in hsCRP

Median % Change from Baseline

Placebo: n = 240
Bempedoic Acid: n = 467

-9.4% (Placebo)
-18.7% (Bempedoic Acid)

P = .039
(Wilcoxon rank sum test)
### CLEAR Wisdom Safety and Tolerability

**Incidence of Adverse Events**

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>% of Patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overview of AEs in All Patients (patient incidence)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo n = 257</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bempedoic Acid n = 522</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse events</td>
<td>70.8</td>
<td>70.1</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>18.7</td>
<td>20.3</td>
</tr>
<tr>
<td>Study drug discontinuation due to adverse events</td>
<td>8.6</td>
<td>10.9</td>
</tr>
<tr>
<td>Fatal adverse events</td>
<td>0.8</td>
<td>1.1</td>
</tr>
</tbody>
</table>

AE, adverse event; TEAE, treatment emergent adverse event.
## CLEAR Wisdom Safety and Tolerability

### Positively Adjudicated Cardiovascular Events

<table>
<thead>
<tr>
<th>Event</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Positively Adjudicated Treatment-Emergent Clinical Endpoints</td>
<td>10.1</td>
</tr>
<tr>
<td>3-point MACE Clinical Endpoints</td>
<td>4.7</td>
</tr>
<tr>
<td>4-point MACE Clinical Endpoints</td>
<td>7.8</td>
</tr>
<tr>
<td>5-point MACE Clinical Endpoints</td>
<td>8.2</td>
</tr>
<tr>
<td>CV death</td>
<td>0.8</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>3.5</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.8</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>5.8</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>1.6</td>
</tr>
</tbody>
</table>
### CLEAR Wisdom Safety and Tolerability

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

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

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 \(\geq 5\%\) 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