ORION-1
Primary efficacy & safety outcomes

LDL-C reduction from 6 to 9 months following single or second injections of inclisiran, a novel siRNA compound

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On behalf of the ORION-1 investigators
Background

Major progress is being made in ASCVD

PCSK9 inhibition is now a validated target for reducing LDL-C and ASCVD

PCSK9 mAb therapy requires 12-26 injections per year

Adherence data with PCSK9 mAbs show no substantial improvement over statins

Poor adherence and LDL-C variability are associated with poor outcomes

These limitations are most relevant in high risk patients with high LDL-C

1. Sabatine M et al NEJM 2017
2. Hines D et al ACC 2017 abstract #1203-313
Harnessing RNAi offers an alternative treatment for PCSK9 and LDL-C

- Inclisiran, a synthetic siRNA molecule, inhibits PCSK9 synthesis in the liver
- In Phase I, 300 mg inclisiran lowered LDL-C 50-60% for 84 days (n=69)

Objective of ORION-1

- Evaluate optimal dosing regimens in patients with elevated LDL-C and high CV risk

 References:
2. Fitzgerald K et al. Lancet 2013;9911:60-8
### Methods

#### Trial design

- **Screening** (Day -14 to Day -1)
- **Randomization** (Day 1, n=501)

#### One dose starting regimen

- Placebo N=65
- 200 mg N=60
- 300 mg N=61
- 500 mg N=65

#### Randomized (n=501)

- **Treated** (n=497)

#### Two dose starting regimen

- Placebo N=62
- 100 mg N=61
- 200 mg N=62
- 300 mg N=61

- **Day 1** Study drug given
- **Day 14** 1st follow-up visit
- **Day 30** Monthly follow-up visits
- **Day 90**
- **Day 180** Primary evaluation
- **Day 210** End of study visit
- **Day 360** Extended follow-up

- **Day 1** Study drug given
- **Day 14** 1st follow-up visit
- **Day 30** Monthly follow-up visits
- **Day 90** Study drug given
- **Day 180** Primary evaluation
- **Day 210** End of study visit
- **Day 360** Extended follow-up

- **Primary evaluation**
- **Completed** (n=483)
## Patients

### High-risk CV patients, balanced by randomization

<table>
<thead>
<tr>
<th></th>
<th>One dose starting regimen</th>
<th>Two dose starting regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=65)</td>
<td>Placebo (N=62)</td>
</tr>
<tr>
<td></td>
<td>Inclisiran (N=186)</td>
<td>Inclisiran (N=184)</td>
</tr>
<tr>
<td>Age</td>
<td>Mean years</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>Male sex</td>
<td>%</td>
<td>64.6</td>
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<tr>
<td></td>
<td></td>
<td>53.2</td>
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<tr>
<td>Prior ASCVD</td>
<td>%</td>
<td>69.2</td>
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<tr>
<td></td>
<td></td>
<td>74.2</td>
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<tr>
<td>Statin Rx</td>
<td>%</td>
<td>70.3</td>
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<tr>
<td></td>
<td></td>
<td>77.0</td>
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<tr>
<td>LDL-C</td>
<td>Mean mg/dL</td>
<td>128.5</td>
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<tr>
<td></td>
<td></td>
<td>125.2</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>Mean mg/dL</td>
<td>157.8</td>
</tr>
<tr>
<td></td>
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<td>157.1</td>
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<tr>
<td>Apo-B</td>
<td>Mean mg/dL</td>
<td>102.4</td>
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<tr>
<td></td>
<td></td>
<td>104.6</td>
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<tr>
<td>Lipoprotein(a)</td>
<td>Median nmol/L</td>
<td>27.0</td>
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<tr>
<td></td>
<td></td>
<td>50.5</td>
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<tr>
<td>PCSK9</td>
<td>Mean ng/mL</td>
<td>404.7</td>
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<td></td>
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<td>431.3</td>
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</table>
**Safety**

No safety concerns: Adverse events similar to placebo

<table>
<thead>
<tr>
<th>Safety population</th>
<th>One dose starting regimen</th>
<th>Two dose starting regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Inclisiran</td>
</tr>
<tr>
<td></td>
<td>N=65</td>
<td>N=186</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>46 (70.8)</td>
<td>140 (75.3)</td>
</tr>
<tr>
<td>Serious</td>
<td>3 (4.6)</td>
<td>17 (9.1)</td>
</tr>
<tr>
<td>Severe</td>
<td>2 (3.1)</td>
<td>11 (5.9)</td>
</tr>
<tr>
<td>Related</td>
<td>12 (18.5)</td>
<td>39 (21.0)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0</td>
<td>7 (3.8)</td>
</tr>
</tbody>
</table>

**TEAEs (treatment emergent adverse events) - similar incidence placebo vs inclisiran:**

One dose starting regimen: Nasopharyngitis, myalgia, back pain, cough, arthralgia, headache

Two dose starting regimen: Myalgia, headache, diarrhea, nasopharyngitis, arthralgia, back pain
Safety

No safety concerns: Liver and muscle enzymes

No LFT elevations related to drug
• Transient transaminase increases - no differences between randomized groups
  - 0.8% placebo
  - 0.8% inclisiran

No difference in incidence of myalgias or CPK enzyme elevation
• One clinically relevant case of myonecrosis on placebo

No deaths related to drug administration
• Two deaths¹ >100 days beyond injection and clearly related to underlying disease

1: Patient A: History of CHD, MI and PCI died of a fatal MI on Day 104 of the study. (500mg x1 dose)

Patient B: Developed complications of aortic aneurysm surgery including an aorto-esophageal fistula requiring esophagectomy, leading to infection of the prosthesis, sepsis, and stroke, culminating in death on Day 198 of the study. Patient also had AF, chronic renal failure, emphysema, HT and obesity. (200mg x2 doses)
Safety
No safety concerns: Other relevant parameters

No thrombocytopenia
No neuropathy
No immunogenicity (no anti-drug antibodies)
No pro-inflammatory symptoms or elevated markers
Efficacy: One dose starting regimen
Clamped PCSK9 knockdown

Mean percent change (±95% CI)

Days from first injection

End of study if LDL-C back to baseline

P-value for all comparisons to placebo <0.0001

Placebo
200 mg
300 mg
500 mg
Efficacy: Two dose starting regimen
Clamped PCSK9 knockdown

End of study if LDL-C back to baseline

Mean percent change (±95% CI)

Days from first injection

P-value for all comparisons to placebo <0.0001

Placebo

100 mg

200 mg

300 mg
Efficacy: One dose starting regimen
Robust, sustained LDL-C reductions – 300 mg optimal

300 mg
50.9% reduction

300 mg
38.4% reduction

9 months time adjusted
mean 41% reduction

P-value for all comparisons to placebo <0.0001
Efficacy: Two dose starting regimen
Robust, sustained LDL-C reductions – optimal start regimen

- **300 mg x2**
  - 55.5%
  - 52.6%
- 9 months time adjusted mean 50% reduction

P-value for all comparisons to placebo <0.0001

Days from first injection

Mean percent change (±95% CI)

- Placebo
- 100 mg
- 200 mg
- 300 mg
Efficacy: Two dose starting regimen
Individual patient responses (%) at day 180

Placebo
Percent reduction

Inclisiran 300 mg
 Percent reduction

All patients responded

Mean 52.6%
Max 80.9%
Efficacy: Two dose starting regimen
Individual patient responses (mg/dL) at day 180

Mean -64.2 mg/dL
Max -122.0 mg/dL

All patients responded
Conclusions

Two 300 mg starting dose regimen for inclisiran selected

No safety concerns

Optimal dosage 300 mg given twice as starting regimen then Q6 monthly
- All patients responded with significant LDL-C lowering
- At 6 months, mean LDL-C↓ of 52.6% (64 mg/dL), and up to 81% (122 mg/dL)

Unique attributes of inclisiran address multiple unmet needs
- LDL-C variability within individuals is practically eliminated
- Injection burden reduced substantially
- Sustained effect between infrequent injections
- Opportunity to improve patient adherence
In an ORION-1-like population, inclisiran 300 mg delivers sustained LDL-C lowering of 60-65 mg/dL

In a CVOT, this is likely to confer substantial reductions in MACE

ORION-4 will study CV outcomes with inclisiran in high risk primary and secondary prevention patients with average LDL-C ~130 mg/dL
Inclisiran in Patients at High Cardiovascular Risk with Elevated LDL Cholesterol

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