ORION-1 Trial

Inclisiran lowers LDL-C and PCSK9 irrespective of diabetes status without worsening glycemia

Lawrence A Leiter, MD, FRCPC, FACP, FACE, FAHA
St Michael’s Hospital, Toronto
ORION-1: Diabetes status subgroups  
Presented on behalf of the Steering Committee

<table>
<thead>
<tr>
<th>Role</th>
<th>Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead authors</td>
<td>Lawrence A Leiter, MD, FRCPC, FACP, FACE, FAHA</td>
</tr>
<tr>
<td></td>
<td>Hwee Teoh, PhD</td>
</tr>
<tr>
<td>Principal investigator</td>
<td>Kausik K Ray, MBChB, MD, MPhil</td>
</tr>
<tr>
<td>Chairman</td>
<td>John JP Kastelein, MD, PhD, FESC</td>
</tr>
<tr>
<td>Members and national</td>
<td>Ulf Landmesser, MD, FESC</td>
</tr>
<tr>
<td>investigators</td>
<td>Lawrence A Leiter, MD, FRCPC, FACP, FACE, FAHA</td>
</tr>
<tr>
<td></td>
<td>R Scott Wright, MD, FACC, FESC, FAHA</td>
</tr>
<tr>
<td>Members</td>
<td>David Kallend, MBBS</td>
</tr>
<tr>
<td></td>
<td>Peter Wijngaard, PhD</td>
</tr>
</tbody>
</table>
ORION-1: Diabetes status subgroups
Disclosures for Lawrence A Leiter, MD

Research grants
- Astra Zeneca, Amgen, Esperion, Kowa, Merck, Sanofi/Regeneron, The Medicines Company

Advisory panels
- Astra Zeneca, Amgen, Merck, Sanofi/Regeneron
**ORION-1: Diabetes status subgroups**

**Major progress in ASCVD - but challenges remain**

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

- mAb therapy requires 12-26 injections per year
- Adherence with PCSK9 mAbs is not substantially better than that with statins

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

- Approximately 9% of ASCVD risk is attributable to poor adherence
- Limitations are most relevant in high risk patients

---

4. Chowdhury R et al. EHJ 2013;34:2940-8
RNAi harnessing

Viable option to inhibit PCSK9 and lower LDL-C

Inclisiran

Synthetic siRNA that inhibits PCSK9 synthesis in the liver

Phase I trial

300 mg inclisiran lowered LDL-C 50-60% for 84 days


2. Fitzgerald K et al. Lancet. 2014;383:60-68

ORION-1: Diabetes status subgroups
RNAi – A natural process for inhibiting mRNA
ORION-1: Diabetes status subgroups
GalNAc-siRNA conjugate facilitates hepatic uptake

Asialoglycoprotein receptor
- Expressed only by hepatocytes
- High rate of ligand uptake

Inclisiran
- siRNA conjugated to N-acetylgalactosamine
- Subcutaneous administration
- Targeted delivery to hepatocytes

GalNAc-siRNA inclisiran conjugate
ORION-1: Diabetes status subgroups
Trial entry criteria

### Phase II dose-finding trial

<table>
<thead>
<tr>
<th>≥18 years old</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ASCVD</th>
<th>ASCVD risk equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>all patients on maximally tolerated statin ± other lipid-lowering Rx</td>
<td>LDL-C &gt;100 mg/dL (2.6 mmol/L)</td>
</tr>
<tr>
<td>LDL-C &gt;70 mg/dL (1.8 mmol/L)</td>
<td></td>
</tr>
</tbody>
</table>

ASCVD = atherosclerotic cardiovascular disease
ORION-1: Diabetes status subgroups
Overall trial design

Screening (Day -14 to Day -1)

Day 1
Stratified by country | Rx
Randomized (n=501)

One dose starting regimen
Given on day 1

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

Two dose starting regimen
Given on days 1 and 90

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

Primary evaluation: day 180
End of study visit: day 210
Extended evaluation: day 360

ORION-1: Diabetes status subgroups
Overall trial results have been published

Safety data
- No concerns

Efficacy data
- All patients responded at 300 mg dose given 2x with significant LDL-C lowering
  - Mean LDL-C↓ at 6 months: 53% (absolute reduction 64 mg/dL)
  - Maximum LDL-C↓ at 6 months: 81%

Future studies will have dosing at Day 1, Day 90 and every 180 days thereafter
ORION-1: Diabetes status subgroups
Analysis of patients without versus with diabetes

Pre-specified protocol objective and methods

To compare the impact of inclisiran in patients with and without diabetes at baseline on:

- PCSK9 levels
- Lipid profile
- Glycemic control
## ORION-1: Diabetes status subgroups
### Patient baseline characteristics

<table>
<thead>
<tr>
<th>ITT</th>
<th>One starting dose</th>
<th>Two starting doses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without diabetes</td>
<td>With diabetes</td>
</tr>
<tr>
<td></td>
<td>(n=223)</td>
<td>(n=27)</td>
</tr>
<tr>
<td>Placebo</td>
<td>(n=57)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Inclisiran</td>
<td>(n=166)</td>
<td>Inclisiran</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as % or median for the intention-to-treat population, which consisted of all participants who underwent randomization.
ORION-1: Diabetes status subgroups
PCSK9 levels – similar lowering from Day 1-180

One starting dose

- Without diabetes (218)
- With diabetes (25)

Placebo  200 mg  300 mg  500 mg

LS mean % change in PCSK9 levels

0  19*  -48  -46  -55  -65  -59  -66

Two starting doses

- Without diabetes (197)
- With diabetes (42)

Placebo  100 mg  200 mg  300 mg

LS mean % change in PCSK9 levels

0  -7  -51  -65  -66  -69  -71

*P = 0.0116 vs. group without diabetes; all others, P > 0.05 for the difference between participants with and without diabetes within each treatment arm at Day 180.
ORION-1: Diabetes status subgroups
LDL-C levels – similar lowering from Day 1-180

One starting dose
- Without diabetes (218)  - With diabetes (25)
Placebo  200 mg  300 mg  500 mg
LS mean % change in LDL-C levels
- 3  -5  -28  -28
- -37  -41  -53  -46

Two starting doses
- Without diabetes (197)  - With diabetes (42)
Placebo  100 mg  200 mg  300 mg
LS mean % change in LDL-C levels
- 2  -1.2  -35  -37.2  -43  -48.3  -52  -55

Primary endpoint evaluation. P > 0.05 for the difference between participants with and without diabetes within each treatment arm at Day 180.
ORION-1: Diabetes status subgroups
LDL-C lowering similar without versus with diabetes

Placebo or inclisiran 300 mg given Day-1
One starting dose

Placebo or inclisiran 300 mg given Day-1 and -90
Two starting doses
ORION-1: Diabetes status subgroups
HbA1c levels – no differential change from Day 1-180

One starting dose

- Without diabetes (218)
- With diabetes (25)

Placebo 200 mg 300 mg 500 mg

LS mean % change in A1c levels

0.0 0.0 0.0 0.1
-0.3 -0.4 -0.2 -0.6

Two starting doses

- Without diabetes (197)
- With diabetes (42)

Placebo 100 mg 200 mg 300 mg

LS mean % change in A1c levels

0.1 0.0 0.1 0.1 0.0 0.0
0.1 -0.3 -0.3

P > 0.05 for the difference between participants with and without diabetes within each treatment arm at Day 180.
ORION-1: Diabetes status subgroups
AE profile was similar in both groups

<table>
<thead>
<tr>
<th>Pre-specified safety population</th>
<th>Without diabetes</th>
<th>With diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>≥1 AE</td>
</tr>
<tr>
<td>Doses</td>
<td>Treatment group</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Placebo</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Inclisiran (200 to 500 mg)</td>
<td>166</td>
</tr>
<tr>
<td>2</td>
<td>Placebo</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>Inclisiran (100 to 300 mg)</td>
<td>150</td>
</tr>
</tbody>
</table>

No unexplained or persistent elevations in any liver parameter considered related to inclisiran
No symptomatic/clinically significant elevations of creatinine kinase in any inclisiran-treated group
For the primary efficacy endpoint at 180 days, 300 mg inclisiran given at Day 1 and 90

- Lowered LDL-C by >50% in persons with ASCVD or ASCVD-risk equivalents, regardless of whether they had diabetes or not
- Had no effect on glycemia
- Displayed no clinically important safety signals
Inclisiran may represent an excellent alternative to monoclonal antibodies to PCSK9 in individuals both with and without diabetes.

Inclisiran is characterized by a much lower injection frequency and a clean safety profile to date, attributes that could help with therapeutic adherence and clinical efficacy for cardiovascular risk reduction.