Reduction of Lipoprotein(a) With Small Interfering RNA

Results of the OCEAN(a)-DOSE (TIMI 67) Trial

Michelle L. O’Donoghue MD MPH, Baris Gencer MD, J. Antonio G. López MD, Beat Knusel PhD, Julia F. Kuder MA, Xinhui Ran MS, Sabina A. Murphy MPH, Huei Wang PhD, You Wu PhD, Helina Kassahun MD and Marc S. Sabatine MD MPH, on Behalf of the OCEAN(a)-DOSE Trial Investigators

Clinicaltrials.gov: NCT04270760
The study was funded by Amgen
Lipoprotein(a)
Lp(a) and Coronary Heart Disease Risk

Lp(a) distribution in individuals with established atherosclerotic cardiovascular disease

Lp(a) is associated with atherosclerotic cardiovascular disease risk independent of traditional risk factors

Mendelian randomization data support a causal role for Lp(a) in coronary heart disease (CHD) risk.

Burgess et al., JAMA Cardiol 2018;3(7):619-627.
Olpasiran: Mechanism of Action

**Mechanism of action**

- Small interfering RNA directed to the liver.
- The antisense strand is loaded into an RNA-induced silencing complex (RISC) in the hepatocyte.
- The complex then binds to apo(a) mRNA, leading to its degradation and preventing protein translation.
Patients aged 18-80 years with atherosclerotic disease & Lp(a) >150 nmol/L

N=281

RANDOMIZE 1:1:1:1:1

Olpasiran 10mg Q12W

Olpasiran 75mg Q12W

Olpasiran 225mg Q12W

Olpasiran 225mg Q24W

Placebo

Primary Endpoint: % Change in Lp(a) from Baseline to Week 36
Key Secondary Endpoint: % Change in Lp(a) from Baseline to Week 48

Clinicaltrials.gov: NCT04270760

O'Donoghue ML et al., Am Heart J 2022;251:61-69
Investigative Sites

34 sites
7 countries

D. Gaudet
J. Bergeron,
H. Bajaj
R. Goldenberg
G. Thanassoulis

United States

Canada

Iceland

Denmark

Netherlands

Japan

Australia

34 sites
7 countries

R. Rosenson
N. Lepor
S. Baum
E. Stout
T. Leucker
C. Ballantyne,
H. Ginsberg,
P. Moriarty
L. Laffin
R. Strzinek
H. Weintraub
A. Carlisle

R. Troquay
E. Stroes
J. Westerink
A. Mairuhiu
H. Monajemi

B. Bordestgaard
I.C. Klausen

K. Kostner,
D. Sullivan
G. Watts
D. Colquhoun
S. Nicholls

Y. Ishii
J. Kanda
K. Kajirami
I. Inoue

K. Kajinami
I. Inoue

An Academic Research Organization of
Brigham and Women’s Hospital and Harvard Medical School
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Olpasiran Pooled Dose Arms (N=227)</th>
<th>Placebo Q12W SC (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in years, mean (SD)</strong></td>
<td>61.6 (9.6)</td>
<td>63.4 (8.9)</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>88%</td>
<td>89%</td>
</tr>
<tr>
<td><strong>Region / Country</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>58%</td>
<td>69%</td>
</tr>
<tr>
<td>Europe</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Australia</td>
<td>16%</td>
<td>11%</td>
</tr>
<tr>
<td>Japan</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td><strong>Coronary Artery Disease</strong></td>
<td>91%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Myocardial Infarction</strong></td>
<td>27%</td>
<td>37%</td>
</tr>
<tr>
<td><strong>Peripheral Artery Disease</strong></td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Cerebrovascular Disease</strong></td>
<td>20%</td>
<td>22%</td>
</tr>
</tbody>
</table>
## Baseline Lipids & Background Therapies

<table>
<thead>
<tr>
<th></th>
<th>Olpasiran Pooled Dose Arms (N=227)</th>
<th>Placebo Q12W SC (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected lipid lowering therapy use at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td>89%</td>
<td>83%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>55%</td>
<td>41%</td>
</tr>
<tr>
<td>PCSK9 inhibitor</td>
<td>24%</td>
<td>22%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>3.1%</td>
<td>3.7%</td>
</tr>
<tr>
<td><strong>Baseline laboratory values, median (IQR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipoprotein(a), (nmol/L)</td>
<td>261 (197, 360)</td>
<td>246 (200, 343)</td>
</tr>
<tr>
<td>LDL-C, (mg/dl)</td>
<td>68 (52, 87)</td>
<td>65 (48, 81)</td>
</tr>
<tr>
<td>Apolipoprotein B, (mg/dl)</td>
<td>68 (56, 82)</td>
<td>63 (49, 76)</td>
</tr>
</tbody>
</table>
Changes in Lp(a) Through Follow-Up

Least square means % change in Lp(a) vs Weeks

- Placebo
- Olpasiran 10mg Q12W
- Olpasiran 75mg Q12W
- Olpasiran 225mg Q12W

Last injection
Changes in Lp(a) Through Follow-Up

Least square means % change in Lp(a)

Weeks

Placebo

Olpasiran 225mg Q24W

Last active drug injection

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Primary Endpoint:
% Change in Lp(a) at 36 weeks

Olpasiran Doses

Placebo-adjusted least square means % change in Lp(a)

-101.1%
-97.4%
-70.5%
-100.5%
% Achieving Lp(a) Concentration <125 nmol/L

Week 36

- Placebo: 0%
- 10 mg Q12W: 66.7%
- 75 mg Q12W: 100%
- 225 mg Q12W: 100%
- 225 mg Q24W: 98.1%
Interindividual Variability in Lp(a) Response at Week 36
Lp(a) Reduction by Subgroups

Placebo-adjusted least square means % change in Lp(a) for olpasiran 225 mg every 12 weeks at week 36
Changes in LDL-C and Apolipoprotein B

Week 36

Placebo-adjusted least squares means % change

10 mg q12 weeks: -23.7%  LDL-C  -18.9%  Apolipoprotein B

75 mg q12 weeks: -22.6%  LDL-C  -16.7%  Apolipoprotein B

225 mg q12 weeks: -23.1%  LDL-C  -17.6%  Apolipoprotein B

225 mg q24 weeks: -24.8%  LDL-C  -18.8%  Apolipoprotein B
## Safety & Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Olpasiran 10 mg Q12W SC (N=58)</th>
<th>Olpasiran 75 mg Q12W SC (N=58)</th>
<th>Olpasiran 225 mg Q12W SC (N=56)</th>
<th>Olpasiran 225 mg Q24W SC (N=55)</th>
<th>Placebo Q12W SC (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Emergent Adverse Events</td>
<td>78%</td>
<td>79%</td>
<td>84%</td>
<td>85%</td>
<td>83%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5.2%</td>
<td>5.2%</td>
<td>11%</td>
<td>7.3%</td>
<td>15%</td>
</tr>
<tr>
<td>Reported as related to study drug</td>
<td>12%</td>
<td>22%</td>
<td>29%</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Leading to discontinuation of study drug</td>
<td>1.7%</td>
<td>1.7%</td>
<td>1.8%</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5.2%</td>
<td>1.7%</td>
<td>7.1%</td>
<td>7.3%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Liver-related adverse events</td>
<td>1.7%</td>
<td>3.4%</td>
<td>1.8%</td>
<td>1.8%</td>
<td>3.7%</td>
</tr>
<tr>
<td>Hyperglycemia, new-onset or worsening diabetes mellitus</td>
<td>8.6%</td>
<td>5.2%</td>
<td>8.9%</td>
<td>5.5%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Injection site reactions*</td>
<td>5.2%</td>
<td>19%</td>
<td>21%</td>
<td>24%</td>
<td>11%</td>
</tr>
<tr>
<td>Hypersensitivity reactions**</td>
<td>1.7%</td>
<td>6.9%</td>
<td>5.4%</td>
<td>9.1%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

*Injection site reactions were generally mild
**Hypersensitivity reactions were generally described as mild injection site pain
Conclusions

• Olpasiran, an siRNA, dosed 75 mg or higher every 12 weeks, reduces Lp(a) concentration by more than 95% in patients with established atherosclerotic cardiovascular disease.

• To date, the drug appears both safe and well-tolerated.

• Injection site and related hypersensitivity reactions were more common with olpasiran. These were described as mild in severity and resolved without treatment.

• These findings set the foundation for phase 3 testing scheduled to commence later this year (NCT05581303).
Small Interfering RNA to Reduce Lipoprotein(a) in Cardiovascular Disease

Michelle L. O'Donoghue, M.D., M.P.H., Robert S. Rosenson, M.D.,
Baris Gencer, M.D., J. Antonio G. López, M.D., Norman E. Lepor, M.D.,
Seth J. Baum, M.D., Elmer Stout, M.D., Daniel Gaudet, M.D., Ph.D.,
Beat Knusel, Ph.D., Julia F. Kuder, M.A., Xinhui Ran, M.S.,
Sabina A. Murphy, M.P.H., Huei Wang, Ph.D., You Wu, Ph.D.,
Helina Kassahun, M.D., and Marc S. Sabatine, M.D., M.P.H.,
for the OCEAN(a)-DOSE Trial Investigators*