Oppenheimer 29th Annual Healthcare Conference

Mark Timney, Chief Executive Officer

New York City • 20th March 2019
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Introduction
Mark Timney, Chief Executive Officer

25 years experience leading US and global organizations most with Merck, including a focus on primary care

Broad and deep track record building leading cardiovascular brands

Commitment to all strategic options to maximize value of inclisiran

Focused on driving and unlocking shareholder value
2019 is a defining year for MDCO
The countdown to data has begun

Fully aligned and committed to maximizing the value of inclisiran

Full commercial rights to inclisiran in all markets and market exclusivity to 2034, with anticipated extensions through 2035

Secured cash to fund clinical and pre-commercial activities into 2020

Inclisiran is anticipated to address the world’s leading cause of death
Topics for today
Setting the agenda for 2019

– The unsolved problem of cardiovascular disease for patients globally

– Inclisiran as a potential game changer

– Progress update

– Anticipated news flow
Globally, 34 people died of CVD as I walked to this podium.

Another 49,000 will be dead by this time tomorrow.
CVD is responsible for 1 in 3 deaths worldwide
America’s #1 Killer

>17 million die from CVD annually\(^1\)
6.3 million are <70 year olds\(^1\)

854,000 die from CVD annually\(^2\)
160,000 <65 year olds\(^2\)

Majority of premature deaths are preventable

1. WHO, CVD Facts, 17 May 2017; 2. CDC Wonder Database 2018
LDL Cholesterol
America’s #1 modifiable risk factor

LDL-C is the leading cause of cardiovascular disease

50% of premature CV deaths could be prevented with better LDL-C management

2018 AHA/ACC guidelines and PCSK9 trials support the principle that lowering LDL-C levels to very low levels reduces ASCVD events across a spectrum of CV risk
Unmet needs

Lack of adherence

LDL-C not at goal despite statins

Prevention of second event

Under-treated cholesterol population
Unmet needs
AHA declares urgent challenges in CVD

Inclisiran could be the potential solution

1. McClellan et al, Circulation. 2019;139:00/e1-e11
43 to 67% of patients are non-adherent to statins after one year\(^1\)

- 40% of high risk patients discontinue by 6 months\(^2\)
- Only 5% maintain treatment for 5 years or longer\(^3\)

Non-adherence is a major driver of CV death

- 2X increased risk of CV death\(^4\)
- 4X increased risk of CV events

Unmet needs

80% of patients with ASCVD are not at LDL-C goal

Available therapies are not optimized in many patients, but even when they are…

- 14% high-intensity statins with ezetimibe is not enough
- 10% don’t tolerate high intensity statins
- >50% are non-adherent

Unmet needs
Statins are falling short of reducing second event and mortality

CV RRR accrues with time on therapy
14% with one year of treatment
31% with 3 years of treatment

Statin adherence is defined by the medication possession ratio (MPR)

# Unmet needs

12.7 million Americans could potentially benefit from inclisiran

<table>
<thead>
<tr>
<th>Highest risk hypercholesterolemia population (Millions of patients)</th>
<th>US¹</th>
<th>EU5²</th>
<th>Japan³</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed FH or ASCVD</td>
<td>27.5</td>
<td>19.7</td>
<td>10.3</td>
<td>57.4</td>
</tr>
<tr>
<td>Treated with oral LLTs</td>
<td>15.1</td>
<td>12.2</td>
<td>4.7</td>
<td>32.0</td>
</tr>
<tr>
<td>Failing to reach LDL-C goal</td>
<td>12.7</td>
<td>9.5</td>
<td>2.4</td>
<td>24.7</td>
</tr>
</tbody>
</table>

1. 1 US National Health and Nutrition Examination Survey (CDC); NHANES FH definition includes all patients with baseline LDL-C > 190 mg/dl
## Unmet needs

**Inclisiran uniquely suited to be a preferred solution**

<table>
<thead>
<tr>
<th>Unmet needs</th>
<th>Inclisiran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of adherence</td>
<td>Built in patient adherence</td>
</tr>
<tr>
<td>LDL-C not at goal despite LLT</td>
<td>Potent, durable, and consistent efficacy – mean LDL-C &gt;50%</td>
</tr>
<tr>
<td>Prevention of second CV event</td>
<td>Potential for a 25% CV risk benefit</td>
</tr>
<tr>
<td>Under-treated population eligible for LLT</td>
<td>Potential for primary, and secondary prevention</td>
</tr>
</tbody>
</table>
# Inclisiran

**A new class of lipid lowering therapy**

<table>
<thead>
<tr>
<th>Therapeutic profile</th>
<th>Inclisiran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>Twice a year</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Inhibits the synthesis of PCSK9</td>
</tr>
<tr>
<td>Current lipid treatment paradigm</td>
<td>Aligns with current treatment pathways</td>
</tr>
<tr>
<td>Adherence</td>
<td>HCP administration provides adherence reassurance</td>
</tr>
<tr>
<td>Efficacy</td>
<td>Long and durable</td>
</tr>
<tr>
<td>Cold chain</td>
<td>Not required</td>
</tr>
<tr>
<td>LDL-C Variability</td>
<td>Minimal</td>
</tr>
<tr>
<td>Potential for better CV outcomes</td>
<td>High</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Synthetic and easily scalable</td>
</tr>
</tbody>
</table>
Inclisiran: Ph. II results

56% peak LDL-C reduction with 300mg dose

Mean percent change (±95% CI)

Days from first injection

p-value for all comparisons to placebo <0.0001

Starting

Maintenance

56% 53%

Placebo 100 mg 200 mg 300 mg

Inclisiran: Ph. II results
51% time-averaged LDL-C reduction over 6 months

6-months time-averaged LDL-C reduction = 51%

Inclisiran: Ph. III design
Twice-a-year dosing regimen targeting >50% average LDL-C reduction

Simulation results (LDL-C from simultaneous model):
Different dosing schedules for the 300 mg dose

- 300 mg dose on days 1, 90, and every 180 days

Average LDL-C reduction 55%
Update on progress
Countdown to Phase III results

- Phase III trials continue to progress according to plan
- No material safety observations to date
- Cardiovascular outcomes trial (ORION-4) enrollment ongoing
- Manufacturing efficiency enables pricing flexibility
- Critical pre-commercialization activities underway
Phase III programs for NDA / MAA in LDL-lowering
18-months treatment trials have completed enrollment (March 2018)

<table>
<thead>
<tr>
<th>Study</th>
<th>Countries</th>
<th>Main inclusion criteria</th>
<th>Baseline LDL-C</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-9</td>
<td>US, EU, SA</td>
<td>Heterozygous FH</td>
<td></td>
<td>482</td>
</tr>
<tr>
<td>ORION-10</td>
<td>US</td>
<td>ASCVD secondary prev.</td>
<td>&gt;70 mg/dL</td>
<td>1,561</td>
</tr>
<tr>
<td>ORION-11</td>
<td>EU, SA</td>
<td>ASCVD secondary prev. High risk primary prev.</td>
<td>&gt;70 mg/dL, &gt;100 mg/dL</td>
<td>1,617</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>Total</strong> 3,660</td>
</tr>
</tbody>
</table>
Inclisiran: Safety profile
No material adverse events to date

Five positive DSMB reviews of 3,660 patients in Phase III trials to date
Substantially all patients who had received their third dose of study medication have completed a 60-day follow up visit

To date > 2,850 patient-years of inclisiran safety data have been collected in the ORION program, with no material safety observations as we enter the final months of these trials.

Ongoing review of blinded data
- Very low incidence of reported mild, transient injection site reactions
- No reports of study-medication-related LFT elevations
- Emerging data at least as favorable as published Phase II ORION-1 trial
ORION-4
A streamlined secondary prevention CVOT study

- 15,000 patients – enrollment underway
- Target baseline LDL-C ≥100 mg/dL
- Patients will be treated with 300 mg of inclisiran or matching placebo, given on Day-1, Day-90 and every six months thereafter.
- Median follow-up 4 or 5 years
- Primary endpoint CHD death, MI, fatal or non-fatal ischemic stroke, urgent revascularization
- Key secondary endpoints include 1) CHD death/MI and 2) CV death
ORION-4

Designed to demonstrate 25% or greater risk reduction

<table>
<thead>
<tr>
<th>LDL-C levels (mg/dL)</th>
<th>Potential CV outcomes annualized risk reduction¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
</tr>
<tr>
<td>150</td>
<td>44%</td>
</tr>
<tr>
<td>125</td>
<td>37%</td>
</tr>
<tr>
<td>100</td>
<td>29%</td>
</tr>
<tr>
<td>75</td>
<td>22%</td>
</tr>
<tr>
<td>50</td>
<td>15%</td>
</tr>
<tr>
<td>Typical baseline in clinical trials</td>
<td></td>
</tr>
<tr>
<td>63</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

¹: Assumes 5 years median observation
## ORION-4
Statistically powered to show mortality benefit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Assumed annual event rate for placebo</th>
<th>Power (2P&lt;0.01)</th>
<th>Power (2P&lt;0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>2.7%</td>
<td>&gt;99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>CHD death or MI</td>
<td>1.7%</td>
<td>99%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>CV death</td>
<td>0.9%</td>
<td>90%</td>
<td>97%</td>
</tr>
</tbody>
</table>
Inclisiran: unique effectiveness
Potent, durable, and consistent LDL-C reductions – 300 mg optimal

<table>
<thead>
<tr>
<th>Days from first injection</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>180</th>
<th>210</th>
<th>240</th>
<th>270</th>
<th>300</th>
<th>330</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean percent change (±95% CI)</td>
<td>300 mg</td>
<td>50.9% reduction</td>
<td>300 mg</td>
<td>38.6% reduction</td>
<td>300 mg</td>
<td>19.0% reduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Time adjusted LDL-C reduction from Day 1 to Day 360 = 37%

P-value for all comparisons to placebo <0.0001
## Development to NDA and MAA

### Anticipated news flow over next 12 months

<table>
<thead>
<tr>
<th>Potential event</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sixth DSMB review of phase III data</td>
<td>2Q 2019</td>
</tr>
<tr>
<td>Validation of manufacturing batches</td>
<td>3Q 2019</td>
</tr>
<tr>
<td>Phase III data from pivotal trials</td>
<td>3Q 2019</td>
</tr>
<tr>
<td>Potential NDA submission</td>
<td>4Q 2019</td>
</tr>
<tr>
<td>Potential MAA submission</td>
<td>1Q 2020</td>
</tr>
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Q&A