Cost-Effectiveness of Alirocumab Based on Evidence From a Large Multinational Outcome Trial: The ODYSSEY OUTCOMES Economics Study

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On behalf of the ODYSSEY OUTCOMES Investigators and Committees

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Disclosures

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- This presentation includes off-label and/or investigational uses of drugs
- ODYSSEY OUTCOMES was sponsored by Sanofi Aventis and Regeneron
Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome


Patients with ACS

High-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin

At least one lipid entry criterion met:
- LDL-C ≥70 mg/dL
- Non-HDL-C ≥100 mg/dL
- ApoB ≥80 mg/dL

Double-blind randomization
1-12 months after ACS
N=18,924

Primary endpoint: Time to first occurrence of CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization. All-cause and cardiovascular death were secondary endpoints, analyzed in a hierarchy of secondary endpoints

*Blinded adjustment of alirocumab dose to target achieved LDL-C 25-50 mg/dL and avoid sustained levels <15 mg/dL
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

To prevent one primary endpoint event would require 49 (95% CI 28 to 164) patients to be treated for 4 years

HR 0.85
(95% CI 0.78, 0.93)
P<0.001

All-Cause Death

Placebo vs Alirocumab

Number at risk

Years Since Randomization

Placebo 9462
Alirocumab 9462

Placebo 9219
Alirocumab 9217

Placebo 8888
Alirocumab 8919

Placebo 3898
Alirocumab 3946

Placebo 737
Alirocumab 746

HR 0.85
(95% CI 0.73, 0.98)

**Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)**

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>Alirocumab (N=2814)</th>
<th>Placebo (N=2815)</th>
<th>Absolute risk reduction (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>324 (11.5)</td>
<td>420 (14.9)</td>
<td>3.4</td>
<td>0.76 (0.65, 0.87)</td>
</tr>
<tr>
<td>CHD death</td>
<td>69 (2.5)</td>
<td>96 (3.4)</td>
<td>1.0</td>
<td>0.72 (0.53, 0.98)</td>
</tr>
<tr>
<td>CV death</td>
<td>81 (2.9)</td>
<td>117 (4.2)</td>
<td>1.3</td>
<td>0.69 (0.52, 0.92)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>114 (4.1)</td>
<td>161 (5.7)</td>
<td>1.7</td>
<td>0.71 (0.56, 0.90)</td>
</tr>
</tbody>
</table>
Study Objective

To conduct a trial-based cost effectiveness analysis of alirocumab in patients with elevated LDL-C despite a background of high-intensity or maximally tolerated statin therapy from the perspective of a US payer.
Methods: Cost Data

• Diagnosis-related group (DRG) cost based on Medicare
  • Weighted by national frequency for each CV event type
  • Adjusted rates published by the Centers for Medicare and Medicaid Services (CMS) were assumed for the study
  • Adjusted for commercial rates to account for those <65 years of age
• Cost was applied to CV death and recurrent non-fatal events: MI, ischemic stroke, coronary revascularization, and unstable angina requiring hospitalization
• Follow-up costs after acute events were not included in this analysis
### Costs From Reimbursement Rates

<table>
<thead>
<tr>
<th>Events</th>
<th>CV Event Costs†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death</td>
<td>$20,225</td>
</tr>
<tr>
<td>Non-fatal MI (without revascularization)</td>
<td>$18,862</td>
</tr>
<tr>
<td>Non-fatal ischemic stroke</td>
<td>$12,617</td>
</tr>
<tr>
<td>Ischemia-driven coronary revascularization or unstable angina</td>
<td>$39,531</td>
</tr>
</tbody>
</table>

* Cost of concomitant medications (e.g., statins) not included

† Cost from Medicare reimbursement rates were adjusted to 2018 dollars and to account for subjects <65 years of age, an adjustment factor (1.88x) was used to reflect a commercial reimbursement rate (73.5% of ODYSSEY OUTCOMES patients were ≤65 years of age). All CV event costs were defined with ICD-10 and DRG costs based on the ODYSSEY OUTCOMES protocol definitions and validated by external coding experts.

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**CMS:** [https://data.cms.gov/Medicare-Inpatient/National-Summary-of-Inpatient-Charge-Data-by-Medic/efwk-h4x3/data](https://data.cms.gov/Medicare-Inpatient/National-Summary-of-Inpatient-Charge-Data-by-Medic/efwk-h4x3/data);


Methods

• Extrapolated long-term survival probability, as is standard in C-E analyses
  • Estimates were based on Nelson et al,1 where survival is extrapolated based on age-based mortality rates observed in the placebo arm of the trial
  • We applied observed hazard ratio (HR) to the extrapolated survival curve for placebo arm to estimate long-term survival for the alirocumab arm

• Health-related quality of life (QOL)
  • Baseline utility and CV event disutility weights were estimated from within the trial using EQ-5D

• Treatment effect
  • HRs for all-cause death
  • Event rates for non-fatal recurrent events

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Analyses

• Base case
  • Overall intention-to-treat (ITT) population

• Subgroup analyses
  • Patients with LDL-C $\geq 100$ mg/dL at baseline
  • Patients with LDL-C $< 100$ mg/dL at baseline
## All-Cause Mortality Rates and Hazard Ratios

<table>
<thead>
<tr>
<th>ITT</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab (per 100 patient years)</td>
<td>1.24</td>
</tr>
<tr>
<td>Placebo (per 100 patient years)</td>
<td>1.46</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.85</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LDL-C ≥100 mg/dL</th>
<th>Overall</th>
</tr>
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<tbody>
<tr>
<td>Alirocumab (per 100 patient years)</td>
<td>1.41</td>
</tr>
<tr>
<td>Placebo (per 100 patient years)</td>
<td>2.02</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.71</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>LDL-C &lt;100 mg/dL</th>
<th>Overall</th>
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<tr>
<td>Alirocumab (per 100 patient years)</td>
<td>1.16</td>
</tr>
<tr>
<td>Placebo (per 100 patient years)</td>
<td>1.22</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.95</td>
</tr>
</tbody>
</table>
## Cardiovascular Event Rates for ITT Population

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Annual event rate for alirocumab per 100 patient-years</th>
<th>Annual event rate for placebo per 100 patient-years</th>
</tr>
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<tbody>
<tr>
<td>CV death</td>
<td>0.89</td>
<td>1.01</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>3.20</td>
<td>3.69</td>
</tr>
<tr>
<td>Non-fatal ischemic stroke</td>
<td>0.44</td>
<td>0.62</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>0.14</td>
<td>0.24</td>
</tr>
<tr>
<td>Ischemia-driven coronary revascularization</td>
<td>3.19</td>
<td>3.70</td>
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## Value-Based Price

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<th>Population</th>
<th>Annual price of alirocumab to be cost effective</th>
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<tr>
<td>Base case</td>
<td>ITT</td>
<td>$100,000/QALY</td>
</tr>
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<td>$6,319</td>
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<td>ITT</td>
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<tr>
<td>Baseline LDL-C</td>
<td>≥100 mg/dL</td>
<td>$13,357</td>
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<td></td>
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</tr>
<tr>
<td>Baseline LDL-C</td>
<td>&lt;100 mg/dL</td>
<td>$2,083</td>
</tr>
</tbody>
</table>
Varying the Cost of Alirocumab

Willingness to pay/QALY

Annual cost of Alirocumab

$0 $2,000 $4,000 $6,000 $8,000 $10,000 $12,000 $14,000 $16,000

$0 $50,000 $100,000 $150,000 $200,000 $250,000

$6,300 at $100k/WTP Threshold

All patients

Bhatt et al, AHA 18
At any level of willingness to pay, cost-effectiveness is greater in patients with baseline LDL-C values \( \geq 100 \) mg/dL relative to the overall ITT population.

**Varying the Cost of Alirocumab**

- $6,300 at $100k/WTP Threshold
- $13,400 at $100k/WTP Threshold

All patients

\( \geq 100 \) mg/dL
At any level of willingness to pay, cost-effectiveness is lesser in patients with baseline LDL-C values <100 mg/dL relative to the overall ITT population.
Strengths

• **Trial-based economic model** that leverages patient-level data from ODYSSEY OUTCOMES to inform the analysis with fewer assumptions compared with cohort-based Markov models

• All-cause death and total events data from the trial were used
Limitations

• Modeling done with all-cause mortality, which was nominally significant, i.e., not by the prespecified hierarchical testing of secondary endpoints

• Country-specific costs were not used – US costs were applied to the global population

• Cost only includes event cost based on US reimbursement rates – no follow-up costs were included (results are conservative, in this regard)

• Factors other than high LDL-C, e.g., diabetes, may identify additional patients for whom treatment with alirocumab has favorable cost effectiveness
Conclusion

• In the overall ODYSSEY OUTCOMES population, alirocumab was cost effective at a price up to $6,319 per year at the $100,000 willingness to pay threshold.

• The higher the baseline LDL-C, the higher the value of alirocumab appeared to be.

• Based on both absolute clinical benefit and cost-effectiveness, alirocumab may offer good value in patients with a history of ACS and LDL-C ≥100 mg/dL despite maximally tolerated statin therapy.
Back up
Cost/QALY Calculation

- Lifetime cost and quality adjusted life years (QALYs) accrued for each treatment group were estimated.
- Cost effectiveness was measured as the incremental cost effectiveness ratio (ICER), defined as:
  \[
  \text{ICER} = \frac{\text{Cost}_{\text{alirocumab}} - \text{Cost}_{\text{placebo}}}{\text{QALYs}_{\text{alirocumab}} - \text{QALYs}_{\text{placebo}}}
  \]
- We estimated the annual cost of alirocumab to be cost effective across commonly used willingness to pay thresholds.
- Cost and QALYs were discounted at 3% per year.
Survival Curves (95% Confidence Bands) in Placebo Group*

Interpreting Extrapolated Survival Curve

• The observed survival represents
  • Varying follow-up from 5 days to 4 years

• The extrapolated survival for the first 4 years
  • Followed-up all subjects for 4 years
    • Resulting in a more aged population
  • Higher risk of mortality in older subjects
    • Resulting in higher cumulative mortality rate

• The separation of the extrapolated and observed survival curves
  • Due to aged population as a result of continuing following-up
## Value-Based Price

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Population</th>
<th>Annual price of alirocumab to be cost effective at varying willingness to pay thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>ITT</td>
<td>$3,293</td>
</tr>
<tr>
<td>Baseline LDL-C ≥100 mg/dL</td>
<td>ITT</td>
<td>$6,910</td>
</tr>
<tr>
<td>Baseline LDL-C &lt;100 mg/dL</td>
<td>ITT</td>
<td>$1,139</td>
</tr>
<tr>
<td>Stratified HR (&lt;1 year/ ≥ 1 year)</td>
<td>ITT</td>
<td>$4,483</td>
</tr>
</tbody>
</table>