State of the Art: The Odyssey Trials

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A Tale of Two “Odysseys”

Odyssey of Homer

~10-year Journey

Odyssey of PCK9

~10-year Journey
Rapid Odyssey of PCSK9

- Adenoviral ↑ expression in mice
- PCSK9 KO mouse ↓ LDL-C
- PCSK9 (NARC-1) discovered
- PCSK9 GOF mutations associated with ADH
- PCSK9 LOF mutations found with 28% ↓ LDL-C and 88% ↓ CHD risk
- Humans null for PCSK9 have LDL-C ~15 mg/dL

First subject treated with PCSK9 mAb
First patients with FH & nonFH treated with PCSK9 mAb
First publication POC in patients


PCSK9 Promotes Degradation of LDLRs

PCSK9 → LDLR protein → LDL-C

Nonsense mutations → Loss-of-function
Loss-of-Function PCSK9 Mutations Are Associated with Low LDL-C and Low Prevalence of CHD Events

28% Lower LDL-C

No PCSK9 Mutation

PCSK9 Mutation

50th Percentile

138 mg/dl

100 mg/dl

88% Reduction in Heart Disease

Impact of an PCSK9 mAb on LDL Receptor Expression
# PCSK9 mAB in Clinical Development

<table>
<thead>
<tr>
<th>Compound</th>
<th>Company</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab (REGN 727/SAR 236553)</td>
<td>Regeneron/Sanofi</td>
<td>Phase III</td>
</tr>
<tr>
<td>Evolocumab (AMG 145)</td>
<td>Amgen</td>
<td>Phase III</td>
</tr>
<tr>
<td>Bococizumab (PF-04950615/RN316)</td>
<td>Pfizer/Rinat</td>
<td>Phase III</td>
</tr>
<tr>
<td>RG7652</td>
<td>Roche/Genentech</td>
<td>Phase II</td>
</tr>
<tr>
<td>LY3015014</td>
<td>Eli Lilly</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

1. Does Alirocumab effectively lower LDL-C?
2. Is this effect persistent (additive?) with statin use (↑LDLR, ↑PCSK9)?
3. What is the optimal dose of Alirocumab?
4. How frequently should it be dosed?
5. Efficacy in patients with defective LDLR (FH)?
6. Is Alirocumab safe over the short term?

Alirocumab Phase II: 12 Week LDL-C Change in Statin Treated Patients with Hypercholesterolemia

LDL-C Mean (±SE) % Change from Baseline

-80
-70
-60
-50
-40
-30
-20
-10
0

BASELINE WEEK 2 WEEK 4 WEEK 6 WEEK 8 WEEK 10 WEEK 12

Placebo
SAR236553 50 mg Q2W
SAR236553 100 mg Q2W
SAR236553 150 mg Q2W

∆ - 64.2%
∆ - 39.6%
∆ - 6.5%
∆ - 72.4%

McKenny et al JACC 2012;59:2344-53
Alirocumab Phase II: 12 Week LDL-C Change in Statin Treated Patients with Hypercholesterolemia

McKenney et al JACC 2012;59:2344-53
Alirocumab Phase II: Combination with Atorvastatin 10mg or 80mg in Patients with Hypercholesterolemia

LDL-C Mean (% Change from Baseline)

- Placebo + A80
- SAR236553 150mg Q2W + A10
- SAR236553 150mg Q2W + A80

Δ - 73%

Δ - 66%

Δ - 17%

* P<0.0001 vs Placebo + A80

Roth et al NEJM 2012; 367:1891-1900
## Safety of Alirocumab: Phase II

<table>
<thead>
<tr>
<th></th>
<th>Atorva 80mg + placebo (n=30)</th>
<th>Atorva 10mg + Alirocumab 150mg Q2W (n=31)</th>
<th>Atorva 80mg + Alirocumab 150mg Q2W (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any AE</strong></td>
<td>19 (61%)</td>
<td>14 (45%)</td>
<td>18 (60%)</td>
</tr>
<tr>
<td><strong>Serious</strong></td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Resulting in Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Permanent discontinuation</td>
<td>4 (13%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>AST&gt;3x ULN</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system</td>
<td>4 (13%)</td>
<td>0</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>7 (23%)</td>
<td>4 (13%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>6 (19%)</td>
<td>2 (6%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>2 (7%)</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Auto antibodies</td>
<td>0/24</td>
<td>3/28</td>
<td>4/28</td>
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Roth et al. NEJM 2012; 367:1891-1900
Alirocumab Phase I/II and Phase III

Phase I/II- What Have we Learned?
1. Alirocumab effectively lowers LDL-C beyond statin reductions
2. 75mg-150mg Q2weeks is the preferred dosing regimen
3. Alirocumab appears safe in short term studies

Phase III- What we Need to Learn
1. Confirm long term efficacy/outcomes with this dosing
2. Long term safety
3. Variety of patients (FH, hypercholesterolemia)
4. Variety of treatments (monotherapy, combination w/statin, alternative to statin)
## ODYSSEY Phase 3 Program

*Fourteen global Phase 3 trials including >23 500 patients across >2000 study centers*

### Lipid Lowering

<table>
<thead>
<tr>
<th>Category</th>
<th>Study Name</th>
<th>n</th>
<th>Duration</th>
</tr>
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<tbody>
<tr>
<td>Monotherapy</td>
<td>ODYSSEY MONO</td>
<td>103</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>ODYSSEY ALTERNATIVE</td>
<td>314</td>
<td>6 months</td>
</tr>
<tr>
<td>Statin Intolerance</td>
<td>ODYSSEY MONO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ODYSSEY ALTERNATIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High LDL-C</td>
<td>ODYSSEY OPTIONS I</td>
<td>347</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>ODYSSEY OPTIONS II</td>
<td>300</td>
<td>6 months</td>
</tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>FH</td>
<td>ODYSSEY FH I</td>
<td>471</td>
<td>18 months</td>
</tr>
<tr>
<td></td>
<td>ODYSSEY FH II</td>
<td>250</td>
<td>18 months</td>
</tr>
<tr>
<td>FH</td>
<td>ODYSSEY HIGH FH</td>
<td>105</td>
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### Safety

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<tr>
<td>High LDL-C</td>
<td>ODYSSEY LONG TERM</td>
<td>2100</td>
<td>18 months</td>
</tr>
<tr>
<td>FH</td>
<td>ODYSSEY OLE</td>
<td>1200</td>
<td>30 months</td>
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### Outcomes

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<th>Duration</th>
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</thead>
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<td>ACS</td>
<td>ODYSSEY OUTCOMES</td>
<td>18000</td>
<td>5-6 years</td>
</tr>
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Modified from Dadu RT and Ballantyne CM. Nat Rev Card. 2014;11:563-575
Duration of Exposure to Alirocumab: Phase III

Double-blinded efficacy and safety evaluation

Primary endpoint Evaluation at Week 24

- **MONO** (n=103)
  - OPTIONS I (n=355)
  - OPTIONS II (n=305)
  - ALTERNATIVE (n=314)
  - 24 Weeks

- **COMBO I** (n=316)
  - 52 Weeks

- **FH I** (n=486)
  - FH II (n=249)
  - HIGH FH (n=107)
  - LONG TERM (n=2,341)
  - 78 Weeks

- **COMBO II** (n=720)
  - 104 Weeks

≥4,400 patient years at completion of studies
ODYSSEY Phase 3 Program: ESC

Fourteen global Phase 3 trials including >23 500 patients across >2000 study centers

Lipid Lowering

- Monotherapy
  - ODYSSEY MONO
    - n=103
    - 6 months
  - ODYSSEY ALTERNATIVE
    - n=314
    - 6 months

- Statin Intolerance
  - ODYSSEY OPTIONS I
    - n=347
    - 6 months
  - ODYSSEY OPTIONS II
    - n=300
    - 6 months

- High LDL-C
  - ODYSSEY COMBO I
    - n=306
    - 12 months
  - ODYSSEY COMBO II
    - n=660
    - 24 months

- High LDL-C
  - ODYSSEY CHOICE I
    - n=700
    - 12 months
  - ODYSSEY CHOICE II
    - n=660
    - 6 months

- FH
  - ODYSSEY FH I
    - n=471
    - 18 months
  - ODYSSEY FH II
    - n=250
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- FH
  - ODYSSEY HIGH FH
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Safety

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  - ODYSSEY OLE
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Outcomes

- ACS
  - ODYSSEY OUTCOMES
    - n=18,000
    - 5-6 years

Modified from Dadu RT and Ballantyne CM. Nat Rev Card. 2014;11:563-575
**ODYSSEY Phase 3 Program: ESC**

*Fourteen global Phase 3 trials including >23 500 patients across >2000 study centers*

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**Lipid Lowering**

- **Monotherapy**
- **Statin**
- **High LDL-C**
- **FH**

### ODYSSEY FHI/II
- 735 pts HeFH
- LDL-C >70/100 on max tx
- Atilorcumab 75mg-150mg Q2wks or placebo
- LDL goal achieved:
  - 72% vs. 2% FHI
  - 81% vs. 11% FHII
- p<0.0001 each

### ODYSSEY COMBO II
- 720 pts CV Risk
- LDL-C >70/100 on statin
- Atilorcumab 75mg-150mg Q2wks vs ezetimibe + placebos
- LDL change:
  - -51% vs. -21%
  - p<0.0001

### ODYSSEY LONGTERM
- 2341 pts HeFH or CV Risk
- LDL-C >70 on statin
- Atilorcumab 150mg Q2wks or placebo + current therapy
- LDL <70mg/dl:
  - 79% vs. 8%
  - p<0.0001

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ODYSSEY Phase 3 Program: Today

Fourteen global Phase 3 trials including >23,500 patients across >2000 study centers

**Lipid Lowering**

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**Safety**

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- **FH**
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**Outcomes**

- **ACS**
  - ODYSSEY OUTCOMES
    - n=18,000
    - 5-6 years

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Conclusions

• **PCSK9 inhibition** has rapidly emerged as a major target for LDL-C lowering

• **Odyssey Phase III program** will inform the safety and efficacy of Alirocumab across a spectrum of conditions and background treatments

• **Ultimate validation of PCSK9** as a therapeutic target awaits clinical outcomes trials (**ODYSSEY OUTCOMES**)

• **IMPROVE IT results** support the potential of non-statin agents and lower LDL-C targets to further lower CVD risk