PCSK9 for LDL Cholesterol Reduction: What have we learned from clinical trials?

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Dr Evan A Stein MD PhD
Director Emeritus
Metabolic & Atherosclerosis Research Center
Cincinnati, Ohio USA
PCSK9 for LDL Cholesterol Reduction: What have we learned from clinical trials?

Evan A Stein MD PhD
Director Emeritus
Metabolic & Atherosclerosis Research Center
Cincinnati

Disclosure Information:
Consultant to Regeneron, Sanofi, Amgen, Genentech/Roche and Adnexus/BMS for PCSK9 inhibitor development
Part III: PCSK9 monoclonal antibody therapy

Phase II studies

Slide deck kindly supplied by
Dr Evan A Stein MD PhD
Director Emeritus
Metabolic & Atherosclerosis Research Center
Cincinnati, Ohio USA
Hypercholesterolaemic patients on statin therapy
What did we want to learn from Phase 2?

- Will higher doses be more effective?
- Will higher doses produce longer lasting effect?
- Will LDL-C effect be maintained if added to maximal dose atorvastatin?
- Will initial results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH population with additional LDLr defects?
- Will patients with history of muscle related side effects on statins tolerate and respond to PCSK9 mAb?
- Will PCSK9 mAb be effective in Homozygous FH?
- Will PCSK9 mAb reduce Lp(a)
- Will PCSK9 mAb at higher doses, larger patient populations, longer administration and when added to maximal dose statin still be safe and well tolerated?
Safety and Efficacy of a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease, SAR236553/REGN727, in Patients With Primary Hypercholesterolemia Receiving Ongoing Stable Atorvastatin Therapy

James M. McKenney, PHARMd,* Michael J. Koren, MD, CPI,† Dean J. Kereiakes, MD,‡ Corinne Hanotin, MD,‖ Anne-Catherine Ferrand, MSc,‖ Evan A. Stein, MD, PhD§

Clinicaltrials.gov no. NCT01288443
Study Design

**Screening Period** (7 weeks)

- LDL-C ≥ 100 mg/dL at Wk-1 while taking atorva 10, 20, or 40 mg for ≥ 6wks

**Treatment Period (12 weeks)**

- N=31
  - Placebo Q2W

- N=30
  - SAR236553 50mg Q2W

- N=31
  - SAR236553 100mg Q2W

- N=31
  - SAR236553 150mg Q2W

- N=30
  - SAR236553 200mg Q4W w/alt placebo

- N=30
  - SAR236553 300mg Q4W w/alt placebo

**Follow-up Period** (8 weeks)

- Primary Endpoint
  - % Δ calculated LDL-C from baseline to week 12

- Secondary Endpoints
  - % Δ in other lipoproteins and apolipoproteins and % patients reaching pre-specified LDL-C levels

**Diet***

- NCEP ATP-III TLC or equivalent diet

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*McKenney et al JACC 2012;59:2344-53*
Alirocumab Administered 2 weekly (Q2W) SC: Change in Calculated LDL-C from Baseline to Week 12

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

McKenney et al JACC 2012;59:2344-53
Alirocumab Administered 4 weekly (Q4W) SC: Change in Calculated LDL-C from Baseline to Week 12

Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, and 12 in the modified intent-to-treat (mITT) population, by treatment group. Week 12 estimation using LOCF method.

McKenney et al JACC 2012;59:2344-53
Evolocumab (AMG 145) Every 2 Weeks: LDL-C Percentage Change From Baseline

Mean percentage change from baseline in calculated LDL-C.

Stein et al Euro Heart J 2014 (in press)
Evolocumab (AMG 145) Every 4 Weeks: LDL-C Percentage Change From Baseline

Mean percentage change from baseline in calculated LDL-C.

Stein et al Euro Heart J 2014 (in press)
What have we learnt from Phase 2?

- Will higher doses be more effective? **No**
- Will higher doses produce longer lasting effect? **The higher the dose the longer the effect**
- Will LDL-C effect be maintained if added to maximal dose atorvastatin?
- Will initial results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH population with additional LDLr defects?
- Will patients with history of muscle related side effects on statins tolerate and respond to PCSK9 mAb?
- Will PCSK9 mAb be effective in Homozygous FH?
- Will PCSK9 mAb reduce Lp(a)
- Will PCSK9 mAb at higher doses, longer administration and when added to maximal dose statin still be safe and well tolerated?
Atorvastatin with or without an Antibody to PCSK9 in Primary Hypercholesterolemia

Eli M. Roth, M.D., James M. McKenney, Pharm.D., Corinne Hanotin, M.D., Gaelle Asset, M.Sc., and Evan A. Stein, M.D., Ph.D.
Study Design

Screening and Run-in Period

W-7 D-49
W-1 D-7
W0 D1

Diet*

N=214
Atorvastatin 10mg

Screening Visit

N=31
SAR236553 Placebo + Atorvastatin 80mg

N=31
SAR236553 150mg Q2W + Atorvastatin 80mg

N=31
SAR236553 150mg Q2W + Atorvastatin 10mg (maintenance dose)

W2 D15
W4 D29
W6 D43
W8 D57
W12 D85
W16 D113

SAR 150mg SQ Q2W

Safety Population N=92

Efficacy Population mITT [LOCF] N=88

W8 D57
W12 D85
W16 D113

N=30
SAR236553 150mg Q2W + Atorvastatin 80mg

Treatment Period (8 weeks)

Follow-up Period (8 weeks)

* NCEP ATP-III TLC or equivalent diet

Roth et al NEJM 2012; 367:1891-1900
Change in Calculated LDL-C
2-Week Intervals from Baseline to Week 8

Roth et al. NEJM 2012; 367:1891-1900

* P<0.0001 vs Placebo + A80

*P<0.0001 vs PL + A80mg
What have we learnt from Phase 2?

- Will higher doses be more effective? No
- Will higher doses produce longer lasting effect? The higher the dose the longer the effect
- Will LDL-C effect be maintained if added to maximal dose atorvastatin? Yes – but appears to maximum to LDLr upregulation
- Will initial results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH population with additional LDLr defects?
- Will patients with history of muscle related side effects on statins tolerate and respond to PCSK9 mAb?
- Will PCSK9 mAb be effective in Homozygous FH?
- Will PCSK9 mAb reduce Lp(a)

What have we learnt from Phase 2?
Heterozygous familial hypercholesterolaemia
Low-Density Lipoprotein Cholesterol–Lowering Effects of AMG 145, a Monoclonal Antibody to Proprotein Convertase Subtilisin/Kexin Type 9 Serine Protease in Patients With Heterozygous Familial Hypercholesterolemia

The Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) Randomized Trial

Frederick Raal, MB, BCh, MMed, PhD; Rob Scott, MD; Ransi Somaratne, MD; Ian Bridges, MSc; Gang Li, PhD; Scott M. Wasserman, MD; Evan A. Stein, MD, PhD
**RUTHERFORD: Study Design**

**Population**

- Global trial with ~55 pts per group
- 18–75 years, with a diagnosis of HeFH by Simon Broome criteria
- LDL-C > 100 mg/dL and triglycerides ≤ 400 mg/dL
- At least 4 weeks of stable lipid-lowering therapy (eg, statin, ezetimibe, bile-acid sequestants, niacin)

**Primary endpoint:**

% change in LDL-C, measured by ultracentrifugation, from baseline at 12 weeks

Raal et al Circulation 2012;126:2408-17
RUTHERFORD: LDLc Changes During Treatment

LDL-C Percentage Change from Baseline (SE)

Placebo (N = 56) 350 mg (N = 55) 420 mg (N = 56)

LDL-C based on Friedewald calculation

Investigational product administration

Raal et al Circulation 2012;126:2408-17
RUTHERFORD: % of Patients Achieving LDL-C, by UC, Targets at Week 12

Percentage Achieving LDL-C

- LDL-C < 100 mg/dL
  - Placebo: 2%
  - 350 mg Q4W: 70%
  - 420 mg Q4W: 89%

- LDL-C < 70 mg/dL
  - Placebo: 0%
  - 350 mg Q4W: 44%
  - 420 mg Q4W: 65%

UC, ultracentrifugation
What have we learnt from Phase 2?

- Will higher doses be more effective? No
- Will higher doses produce longer lasting effect? The higher the dose the longer the effect
- Will LDL-C effect be maintained if added to maximal dose atorvastatin? Yes – but appears to maximum to LDLr upregulation
- Will initial results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH population with additional LDLr defects? Yes
- Will patients with history of muscle related side effects on statins tolerate and respond to PCSK9 mAb?
- Will PCSK9 mAb be effective in Homozygous FH?
- Will PCSK9 mAb reduce Lp(a)
- Will PCSK9 mAb at higher doses, longer administration and when added to maximal dose statin still be safe and well tolerated?
Statin-intolerant patients
Effect of a Monoclonal Antibody to PCSK9 on Low-Density Lipoprotein Cholesterol Levels in Statin-Intolerant Patients: The GAUSS Randomized Trial

Published online November 5, 2012

Available at www.jama.com
GAUSS: Study Design & Entry Criteria

Primary endpoint: Percentage change in LDL-C, by ultracentrifugation, from baseline at 12 weeks

NCEP, National Cholesterol Education Program

Sullivan et al JAMA 2012;126:2408-17
## GAUSS: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AMG 145 Q4W</th>
<th>Placebo Q4W + Ezetimibe</th>
<th>Placebo Q4W + Ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 30</td>
<td>N = 32</td>
<td>N = 30</td>
<td>N = 32</td>
</tr>
<tr>
<td><strong>Sex, female, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 (56)</td>
<td>21 (68)</td>
<td>20 (63)</td>
<td>23 (77)</td>
</tr>
<tr>
<td>18 (56)</td>
<td>18 (56)</td>
<td>21 (68)</td>
<td>20 (63)</td>
</tr>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>62 (10)</td>
<td>62 (9)</td>
<td>60 (9)</td>
</tr>
<tr>
<td><strong>LDL-C, mg/dL, mean (SD)</strong>*</td>
<td>195 (48)</td>
<td>190 (48)</td>
<td>204 (60)</td>
</tr>
<tr>
<td><strong>Free PCSK9, ng/mL, mean (SD)</strong></td>
<td>383 (98)</td>
<td>396 (129)</td>
<td>372 (87)</td>
</tr>
<tr>
<td><strong>NCEP high-risk, n (%)</strong></td>
<td>14 (44)</td>
<td>12 (39)</td>
<td>11 (34)</td>
</tr>
<tr>
<td><strong>Coronary artery disease, n (%)</strong></td>
<td>3 (9)</td>
<td>5 (16)</td>
<td>3 (9)</td>
</tr>
<tr>
<td><strong>Statins failed (muscle-related events)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 1, n (%)</td>
<td>32 (100)</td>
<td>31 (100)</td>
<td>32 (100)</td>
</tr>
<tr>
<td>≥ 2, n (%)</td>
<td>28 (53)</td>
<td>24 (77)</td>
<td>23 (72)</td>
</tr>
<tr>
<td>≥ 3, n (%)</td>
<td>11 (34)</td>
<td>11 (35)</td>
<td>12 (38)</td>
</tr>
<tr>
<td><strong>Worst statin-related events, any statin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia, n (%)</td>
<td>31 (97)</td>
<td>30 (97)</td>
<td>29 (91)</td>
</tr>
<tr>
<td>Myositis, n (%)</td>
<td>3 (9)</td>
<td>3 (10)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Rhabdomyolysis, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

* LDL-C measured by ultracentrifugation.
SD, standard deviation; NCEP, National Cholesterol Education Program

Sullivan et al JAMA 2012;126:2408-17
GAUSS: % Change from Baseline in Calculated LDL-C* At All Visits

* Calculated LDL-C values.
Q4W, every 4 weeks; QD, daily, CI, confidence intervals

Sullivan et al JAMA 2012;126:2408-17
## GAUSS: Safety and Tolerability

<table>
<thead>
<tr>
<th>Adverse Events, Patient Incidence, n (%)</th>
<th>AMG 145 280 mg N = 32</th>
<th>AMG 145 350 mg N = 31</th>
<th>AMG 145 420 mg + Ezetimibe 10 mg N = 32</th>
<th>Placebo Q4W + Ezetimibe N = 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-emergent AEs</td>
<td>22 (68.8)</td>
<td>15 (48.4)</td>
<td>18 (56.3)</td>
<td>20 (66.7)</td>
</tr>
<tr>
<td>Serious AEs*</td>
<td>2 (6.3)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>8 (25.0)</td>
<td>3 (9.7)</td>
<td>6 (18.8)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Muscle-related AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (15.6)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>6 (20.0)</td>
</tr>
<tr>
<td>Muscle fatigue</td>
<td>2 (6.3)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1 (3.1)</td>
<td>2 (6.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0 (0.0)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>1 (3.3)</td>
</tr>
<tr>
<td>Other most commonly reported AEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>2 (6.3)</td>
<td>2 (6.5)</td>
<td>1 (3.1)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (6.3)</td>
<td>1 (3.2)</td>
<td>1 (3.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (12.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (6.3)</td>
</tr>
</tbody>
</table>

* Four serious adverse events were reported for AMG 145: acute pancreatitis, coronary artery disease, hip fracture, and syncope. **None were considered treatment related.**

AE: Adverse event. Some patients experienced more than 1 AE.
Two patients with CK elevations > 10 x ULN:

- One patient (AMG 145, 350 mg) had an isolated CK elevation of 2773 U/L at week 4 the day after an intense weight-lifting workout.
  - Resolved spontaneously without treatment interruption by the next study visit
  - Adjudicated not to be a muscle-related event by the Clinical Events Committee

- One patient (AMG 145, 350 mg) had an isolated CK elevation of 2030 U/L accompanied by generalized muscular pain at week 2, following strenuous exercise.
  - Rosuvastatin and AMG 145 were discontinued, and subsequent CK values were normal.
  - Muscle biopsy showed a normal pattern.
  - Adjudicated positively as a myopathy event
What have we learnt from Phase 2?

- Will higher doses be more effective? No
- Will higher doses produce longer lasting effect? The higher the dose the longer the effect
- Will LDL-C effect be maintained if added to maximal dose atorvastatin? Yes – but appears to maximum to LDLr upregulation
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- Will PCSK9 mAb be effective in Homozygous FH?
- Will PCSK9 mAb reduce Lp(a)
- Will PCSK9 mAb at higher doses, longer administration and when added to maximal dose statin still be safe and well tolerated?
Homozygous familial hypercholesterolaemia
Effect of the Proprotein Convertase Subtilisin/Kexin 9 Monoclonal Antibody, AMG 145, in Homozygous Familial Hypercholesterolemia

Evan A. Stein, MD, PhD; Narimon Honarpour, MD, PhD; Scott M. Wasserman, MD; Feng Xu, MS; Rob Scott, MD; Frederick J. Raal, MB, BCh, PhD
Evolocumab (AMG 145) 420 mg SC Q4W for 12 weeks (NCT01588496), maintained for an additional 12 weeks of treatment at 4-week intervals, and then 12 weeks with AMG 145 420 mg SC Q2W (NCT01624142).

* Week 2 and week 10 study visits are optional. Red rectangles indicate prespecified cutoff dates for efficacy and safety analyses.

SC = subcutaneous; Q4W = every 4 weeks; Q2W = every 2 weeks; LDL-C = low-density lipoprotein cholesterol

**TESLA: Patient Genotype and LDLR Activity**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mutation Allele 1 (Estimated LDLR Function)</th>
<th>Mutation Allele 2 (Estimated LDLR Function)</th>
<th>Overall LDLR Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Asp266Glu (15%-30%)</td>
<td>Asp266Glu (15%-30%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 2</td>
<td>1187-10 G&gt;A† (Not determined)</td>
<td>Asp266Glu (15%-30%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Asp224Asn (&lt;2% )</td>
<td>Cys296Tyr (Not determined)</td>
<td>Negative#</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Deletion Exon 4-18 (Not determined)</td>
<td>Cys197Gly (Not determined)</td>
<td>Negative#</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Asp221Gly (&lt;2%)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 6*</td>
<td>Asp227Glu (5%-15%)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 7*</td>
<td>Asp227Glu (5%-15%)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Asp175Asn (Not determined)</td>
<td>Asp227Glu (5%-15%)</td>
<td>Receptor defective</td>
</tr>
</tbody>
</table>

*Confirmed by fibroblast culture
†Mutation at splice acceptor site 10 nucleotides upstream of the first nucleotide of exon 9, 1187
*True homozygous patient; patients share the same genotype

<table>
<thead>
<tr>
<th>Mutation Status</th>
<th>Percentage Change from Baseline, %, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 12 Q4W Dosing</td>
</tr>
<tr>
<td></td>
<td>UC LDL-C</td>
</tr>
<tr>
<td>Defective LDLR (n=6)</td>
<td>-22.9 (17.5)</td>
</tr>
<tr>
<td></td>
<td>-23.6 (7.6)</td>
</tr>
<tr>
<td>Negative LDLR (n=2)</td>
<td>2.6 (3.7)</td>
</tr>
<tr>
<td></td>
<td>15.3 (34.7)</td>
</tr>
<tr>
<td><strong>Average of Week 4, 8, and 12 Q4W Dosing</strong></td>
<td></td>
</tr>
<tr>
<td>Defective LDLR (n=6)</td>
<td>-19.3 (15.5)</td>
</tr>
<tr>
<td></td>
<td><strong>-26.3 (20.4)</strong></td>
</tr>
<tr>
<td>Negative LDLR (n=2)</td>
<td>4.4 (10.3)</td>
</tr>
<tr>
<td></td>
<td>11.0 (23.6)</td>
</tr>
</tbody>
</table>

† Signed-rank test; * Lipoprotein (a) was only collected at week 12 for every-4-week dosing.
UC = ultracentrifugation; Q4W = every 4 weeks; Q2W = every 2 weeks; LDLR = low-density lipoprotein receptor

Comparison of absolute (mg/dL) LDL-C reductions in HoFH: Apo B antisense\textsuperscript{1}, MTP inhibitor\textsuperscript{2} and PCSK9 inhibition\textsuperscript{3}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\end{figure}

- Mipomersen\textsuperscript{*}: wk 26: \(-115\), wk 26: \(-170\), wk 52: \(-147\), wk 72: \(-127\), wk 36: \(-115\)
- Lomitapide\textsuperscript{*}: wk 26: \(-115\), wk 52: \(-147\), wk 72: \(-127\), wk 36: \(-115\)
- AMG 145\textsuperscript{#}: wk 36: \(-115\)

\textsuperscript{*}34 pts LOCF, \textsuperscript{*}23 of 26 completers, \textsuperscript{#}6 LDLr defective

## TESLA: CK Elevations and Liver Enzymes

<table>
<thead>
<tr>
<th>Adverse events, no. of patients (%)</th>
<th>AMG 145 (N = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Test Data</td>
<td></td>
</tr>
<tr>
<td>ALT or AST &gt;3 x ULN any post-baseline visit</td>
<td>0 (0)</td>
</tr>
<tr>
<td>CK &gt;5 x ULN any post-baseline visit</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Stein et al *Circulation*. 2013;128:2113-2120
TESLA: Conclusions

- This study demonstrated, for the first time, that significant LDLC lowering is achievable with a PCSK9 monoclonal antibody in HoFH patients with defective LDLr activity.

- AMG 145, even at a dose of 420 mg Q2W, was well tolerated and was not associated with any notable side effects or increased hepatic transaminases.

- Based on the results of this proof-of-concept trial, a larger, double-blind, randomized and placebo-controlled trial of evolocumab in HoFH has commenced and is fully recruited.
What have we learnt from Phase 2?

- Will higher doses be more effective? No
- Will higher doses produce longer lasting effect? The higher the dose the longer the effect
- Will LDL-C effect be maintained if added to maximal dose atorvastatin? Yes – but appears to maximum to LDLr upregulation
- Will initial results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH population with additional LDLr defects? Yes
- Will patients with history of muscle related side effects on statins tolerate and respond to PCSK9 mAb? Yes
- Will PCSK9 mAb be effective in Homozygous FH? Yes - in LDL receptor defective patients
- Will PCSK9 mAb reduce Lp(a)
- Will PCSK9 mAb at higher doses, longer administration and when added to maximal dose statin still be safe and well tolerated?
Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145): A Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials

Error bars represent standard error.

* P < 0.001

Raal et al JACC 2014;(). doi:10.1016/j.jacc.2014.01.006 Online First
### Evolocumab Pooled analysis >1300 patients: Clinical Adverse Effects

<table>
<thead>
<tr>
<th>AMG 145 – by dose and dose frequency</th>
<th>Placebo</th>
<th>All AMG 145</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg Q2W (n=124)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105 mg Q2W (n=125)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>140 mg Q2W (n=123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>280 mg Q4W (n=156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg Q4W (n=210)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>420 mg Q4W (n=213)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>280 mg Q4W (n=156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg Q4W (n=210)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>420 mg Q4W (n=213)</td>
<td></td>
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</tr>
<tr>
<td>(n=333) (n=981)</td>
<td></td>
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</tr>
</tbody>
</table>

#### AEs\(^a\)

| \(n\) | \(|\%|\) |
|--------|-------|
| Nasopharyngitis | 65 (52.4) | 74 (59.2) | 69 (56.1) | 89 (57.1) | 118 (56.2) | 122 (57.3) | 164 (49.2) | 557 (56.8) |
| Headache | 4 (3.2) | 3 (2.4) | 6 (4.9) | 1 (0.6) | 6 (2.9) | 6 (2.8) | 11 (3.3) | 32 (3.3) |
| Diarrhoea | 3 (2.4) | 4 (3.2) | 4 (3.3) | 2 (1.3) | 6 (2.9) | 8 (3.8) | 11 (3.3) | 28 (2.9) |
| Myalgia | 4 (3.2) | 2 (1.6) | 3 (2.4) | 7 (4.5) | 7 (3.3) | 3 (1.4) | 4 (1.2) | 32 (3.3) |
| Nausea | 0 (0.0) | 1 (0.8) | 6 (4.9) | 7 (4.5) | 5 (2.4) | 7 (3.3) | 6 (1.8) | 26 (2.7) |
| Fatigue | 0 (0.0) | 2 (1.6) | 4 (3.3) | 4 (2.6) | 4 (1.9) | 8 (3.8) | 7 (2.1) | 22 (2.2) |
| Treatment-related AEs | 8 (6.5) | 16 (12.8) | 13 (10.6) | 19 (12.2) | 27 (12.9) | 25 (11.7) | 32 (9.6) | 113 (11.5) |
| AEs leading to discont | 0 (0.0) | 0 (0.0) | 2 (1.6) | 0 (0.0) | 2 (1.0) | 2 (0.9) | 5 (1.5) | 7 (0.7) |
| SAEs | 0 (0.0) | 2 (1.6) | 5 (4.1) | 4 (2.6) | 4 (1.9) | 5 (2.3) | 4 (1.2) | 20 (2.0) |
| Treatment-related SAEs | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Stein et al EHJ 2014 (in press)
# Evolocumab Pooled analysis >1300 patients: Lab of Interest

<table>
<thead>
<tr>
<th>AMG 145 – by dose and dose frequency</th>
<th>Placebo (n=333)</th>
<th>All AMG 145 (n=981)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 mg Q2W (n=124)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>105 mg Q2W (n=125)</td>
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<td></td>
</tr>
<tr>
<td>140 mg Q2W (n=123)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>280 mg Q4W (n=156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>350 mg Q4W (n=210)</td>
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<td></td>
</tr>
<tr>
<td>420 mg Q4W (n=213)</td>
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<td></td>
</tr>
</tbody>
</table>

## AEs and labs of interest

- **Injection-site reaction**: 2 (1.6) 7 (5.6) 2 (1.6) 9 (5.8) 13 (6.2) 5 (2.3) 11 (3.3) 40 (4.1)
- **Muscle-related AEs**: 7 (5.6) 5 (4.0) 4 (3.3) 13 (8.3) 11 (5.2) 13 (6.1) 13 (3.9) 59 (6.0)
- **CK > 5 x ULN**: 3 (2.4) 2 (1.6) 1 (0.8) 0 (0.0) 3 (1.4) 5 (2.3) 3 (0.9) 14 (1.4)
- **ALT or AST >3 x ULN**: 1 (0.8) 0 (0.0) 0 (0.0) 0 (0.0) 2 (1.0) 1 (0.5) 2 (0.6) 4 (0.4)
- **Binding antibodies**: 0 (0.0) 1 (0.8) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 1 (0.3) 1 (0.1)
- **Neutralizing antibodies**: 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)

5 patients in the AMG 145 treatment group had creatine kinase >10 x ULN, all of which were resolved at follow-up blood test.

Stein et al EHJ 2014 (in press)
Conclusions
What have we learnt from Phase 2?

- Will higher doses be more effective? No
- Will higher doses produce longer lasting effect? The higher the dose the longer the effect
- Will LDL-C effect be maintained if added to maximal dose atorvastatin? Yes – but appears to maximum to LDLr upregulation
- Will initial results seen in small group of HeFH from one center be maintained in larger and more diverse HeFH population with additional LDLr defects? Yes
- Will patients with history of muscle related side effects on statins tolerate and respond to PCSK9 mAb? Yes
- Will PCSK9 mAb be effective in Homozygous FH? Yes - in LDL receptor defective patients
- Will PCSK9 mAb reduce Lp(a) Yes
- Will PCSK9 mAb at higher doses, longer administration and when added to maximal dose statin still be safe and well tolerated? Over 1200 patients have received mAb to PCSK9, and safety continues to be encouraging.
mAbs Targeted to PCSK9 in Development:

Conclusion

• Inhibition of PCSK9 with fully human mAbs is a very promising, and potentially the most effective, approach to reducing LDL-C including patients:
  – With nonFH, HeFH and LDLr defective HoFH
  – On statins or diet alone and
  – Those unable to tolerate statins, or effective doses of statins.
  – Additive to all existing therapy
  – SC delivery every 2 or 4 weeks

• In large phase 2 program of 2 agents of over 1200 patients no significant adverse effects have emerged so far

• Phase 3 programs including 2 large CVD outcome trials are already underway with the Amgen (evolocumab) and Sanofi (alirocumab) fully human monoclonal antibodies
# PCSK9 Inhibitors in Development

<table>
<thead>
<tr>
<th>Investigational Product</th>
<th>Company</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
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<tr>
<td>Alirocumab (SAR236553, REGN727)</td>
<td>Sanofi (Regeneron)</td>
<td>Phase III</td>
</tr>
<tr>
<td>Evolocumab (AMG 145)</td>
<td>Amgen</td>
<td>Phase III</td>
</tr>
<tr>
<td>Bococizumab (PF-0490615 /RN316)</td>
<td>Pfizer (Rinat)</td>
<td>Phase III</td>
</tr>
<tr>
<td>MPSK 3169A (RG7652)</td>
<td>Genentech (Roche)</td>
<td>Phase II</td>
</tr>
<tr>
<td>LY3015014</td>
<td>Lilly</td>
<td>Phase II</td>
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<tr>
<td><strong>PCSK9 protein binding fragment</strong></td>
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<tr>
<td>Bristol Myers Squibb/Adnexus</td>
<td>BMS-962476 (Adnectin)</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>PCSK9 synthesis inhibitor/siRNA</strong></td>
<td></td>
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<tr>
<td>Alnylam/The Medicines Co</td>
<td>ALN-PCS02</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>Small molecule</strong></td>
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<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

Updated from Stein et al Curr Atheroscler Rep 2013; 15: 310
Overview of ODYSSEY Phase 3 clinical trial program

12 global phase 3 trials
Including more than 23,500 patients across more than 2,000 study centers

HeFH population
Add-on to max tolerated statin (+ other LMT)

- ODYSSEY FH I (EFC12492) N=471
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  18 months

- ODYSSEY FH II (CL1112) N=250
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  18 months

- ODYSSEY HIGH FH (EFC12732) N=105
  LDL-C ≥ 160 mg/dL
  18 months

HC in high CV risk population
Add-on to max tolerated statin (+ other LMT)

- ODYSSEY COMBO I (EFC11568) N=306
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  12 months

- ODYSSEY CHOICE I (CL1308) N=700
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  12 months

- ODYSSEY OPTIONS I (CL1110) N=350
  Patients not at goal on moderate dose atorvastatin
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  6 months

- ODYSSEY COMBO II (EFC11569) N=660
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  24 months

Additional populations

- ODYSSEY MONO (EFC11716) N=100
  Patients on no background LMTs
  LDL-C ≥ 100 mg/dL
  6 months

- ODYSSEY ALTERNATIVE (CL1119) N=250
  Patients with defined statin intolerance
  LDL-C ≥ 70 mg/dL OR LDL-C ≥ 100 mg/dL
  6 months

- ODYSSEY COMBO II (EFC11569)
  *For the ODYSSEY COMBO II other LMT not allowed at entry

- ODYSSEY OUTCOMES (EFC11570)
  N=18,000
  LDL-C ≥ 70 mg/dL

HC = hypercholesterolemia; LMT = lipid-modifying therapy

*For the ODYSSEY COMBO II other LMT not allowed at entry
PROFICIO

Program to Reduce LDL-C and Cardiovascular Outcomes Following Inhibition of PCSK9 In Different Populations


*Subjects completed a qualifying Phase 2 study. †Subjects completed a qualifying Phase 3 study.