Lipidology Trials -
What’s New and What’s in the Pipeline?

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European Society of Cardiology

SUPPORTED BY AN EDUCATIONAL GRANT FROM AMGEN and NOVARTIS
I have the following potential conflict(s) of interest to report

<table>
<thead>
<tr>
<th>Type of affiliation / financial interest</th>
<th>Name of commercial company</th>
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<tbody>
<tr>
<td>Receipt of grants/research support:</td>
<td>AstraZeneca, Bayer Healthcare, MSD, Resverlogix, KOWA, Pfizer</td>
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<tr>
<td>Receipt of honoraria or consultation fees:</td>
<td>Bayer Healthcare, MSD, Pfizer, Novo Nordisk</td>
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<tr>
<td>Participation in a company sponsored speaker’s bureau:</td>
<td>Pfizer, Novo Nordisk</td>
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Challenges in Lipidology Trials

- **What is the pathophysiology?**
  - What are the targets?
    - LDL? HDL? TG? LP(a)?
  - Relation between lipidology, atherosclerosis and CV events?
  - Time discrepancies?

- **What are the end-points?**
  - Can these guide in early/late phases of drug development?
  - Outcome events – This is what matters!

- **What is the comparator?**
  - Keeping pace with a rapidly evolving field
Targets

- **Targeting LDL**
  - PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
  - RNA interference (RNAi) to reduce PCSK9 (ORION)
  - Decreasing LDL synthesis - Bempedoic acid

- **Targeting HDL**
  - CETP inhibitors
  - Epigenetics - BET on MACE program
  - Apo-A1 infusion – AEGIS program

- **Targeting triglycerides**
  - REDUCE-IT
  - PROMINENT

- **New - Targeting ANGPTL3 (inh of lipoprotein lipase)**
IMPROVE-IT - Proves again the LDL Hypothesis

CTT Collaboration.
Lancet 2005; 366:1267-78;
Effects of Evolocumab

- ↓ LDL-C by 59% to a median of 30 mg/dL
- ↓ CV outcomes in patients on statin
- Safe and well-tolerated

**Figure:**
- **LDL Cholesterol (mg/dl) vs. Weeks after randomization**
  - **Placebo:** No significant change in LDL-C levels.
  - **Evolocumab:** Median reduction of 59%, absolute decrease of 56 mg/dl.
  - **KM Rate (%) at 3 Years**
    - CVD, MI, stroke: HR 0.85 (0.79-0.92), P<0.0001
    - CVD, MI, stroke, UA, cor revasc: HR 0.80 (0.73-0.88), P<0.0001

**Source:** Sabatine MS et al. NEJM 2017;376:1713-22
Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm

P<0.0001

Achieved LDL Cholesterol (mg/dl)

Cardiovascular Death, MI or Stroke

Q1 Q2 Q3 Q4

Placebo Evolocumab
From: Effect of the PCSK9 Inhibitor Evolocumab on Total Cardiovascular Events: A Prespecified Analysis From the FOURIER Trial
JAMA Cardiol. Published online May 22, 2019. doi:10.1001/jamacardio.2019.0886

First, Additional, and Total Primary End Point Events During Follow-up by Randomization Group

The first occurrence of the primary end point was significantly reduced in the evolocumab group compared with the placebo group (hazard ratio [HR], 0.85; 95% CI, 0.79-0.92; P < .001), as were additional events (incidence rate ratio [RR], 0.74; 95% CI, 0.65-0.85) and total events (RR, 0.82; 95% CI, 0.75-0.90; P < .001).

Figure Legend:

First, Additional, and Total Primary End Point Events During Follow-up by Randomization Group
Total Events During Follow-up by Randomization Group for Components of the Primary End Point

Total events were significantly reduced with evolocumab vs placebo for the component of myocardial infarction (incidence rate ratio [RR], 0.74; 95% CI, 0.65-0.84; P < .001) and stroke (RR, 0.77; 95% CI, 0.64-0.93; P = .007) and coronary revascularizations (RR, 0.78; 95% CI, 0.71-0.87; P < .001). There was no difference between treatment groups in total hospitalization for unstable angina events or in cardiovascular deaths.
VESALIUS: Effect of Evolocumab in Pts without Previous MI or Stroke

- Screening
- Randomization 1:1
- Evolocumab + optimized lipid-lowering therapy 
  ≥ 6500 Subjects
- Placebo + optimized lipid-lowering therapy 
  ≥ 6500 Subjects
- ≥ 4 years
- ≥ 13000 subjects
ORION-1

Inclisiran inhibits PCSK9 synthesis by RNA interference
Planned interim analysis of a multi-center randomized controlled dose-finding trial

Kausik K Ray, Ulf Landmesser, Lawrence A Leiter, David Kallend, Peter Wijngaard
Robert Dufour, Timothy Hall, Mahir Karakas, Traci Turner, Frank LJ Visseren,
R Scott Wright, and John JP Kastelein

On behalf of the ORION-1 investigators
Inclisiran inhibits PCSK9 synthesis by RNA interference.

Inclisiran harnesses a natural catalytic process:

- Synthetic double strand 21-23mer oligonucleotide
- 3x GalNAc at sense 3’ end enables hepatic-specific uptake via ASGP receptor
- Chemically modified to prevent RNAse degradation
- Dicer separates antisense strand – and incorporates it into RISC
- RISC degrades PCSK9 mRNA catalytically to halt PCSK9 protein synthesis in the liver

RISC - RNA induced silencing complex
One dose and two doses of inclisiran up to day 180
Efficacy of 300 mg versus placebo on LDL-C

Percentage change (±95% CI)

Days from first injection

Placebo (N=22) 300mg (N=21)

Placebo (N=23) 300mg (N=28)

Available data as of 25 Oct 2016
ORION-11: Efficacy of Inclisiran for Lowering LDL in pts with ASCVD/Risk

Percent change in LDL-C over time – observed values ITT patients

- Time-averaged Δ 50%
- Δ 54%

P-value for placebo – inclisiran comparison at each time point <0.00001

1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

Ray, ESC, Paris, Aug 2019
Silencing Novel Target Genes: A New Strategy for Lipid Lowering

Advantages of siRNAs
- same molecule can destroy multiple copies of the RNA in a way that provides substantial longevity in terms of duration of effect
- can be targeted directly to the liver

New gene targets – proteins that inhibit the lipoprotein lipase pathway and triglyceride metabolism
- apolipoprotein C-III (APOC3)
- angiopoietin-like 3 (ANGPTL3)

The siRNA molecules targeting these genes are both in development by Arrowhead Pharmaceuticals. ARO-APOC3 is being developed as a potential treatment for patients with severe hypertriglyceridemia and familial chylomicronemia syndrome, and ARO-ANG3 is being developed for the treatment of dyslipidemias such as familial hypercholesterolemia and other metabolic diseases.
MAASTRICHT, The Netherlands — A novel antiprotein convertase subtilisin/kexin type 9 (PCSK9) recombinant fusion protein that offers a more convenient dosing regimen than anti-PCSK9 monoclonal antibodies substantially decreases low-density-lipoprotein (LDL)-cholesterol levels on patients already taking maximally tolerated statins, results of a phase 2 trial show.

LIB003 combines a PCSK9-binding domain with human serum albumin in a recombinant fusion therapeutic agent derived from a mammalian cell line. The binding domain blocks the interaction between PCSK9 and the LDL-cholesterol receptor, and the albumin linkage increases the half-life to 12 to 15 days, allowing low-volume injections to be given every 4 weeks.

Following on from promising phase 1 data, the team conducted a phase 2 study in which 81 patients were randomized to 150 mg, 300 mg, or 350 mg of LIB003 or placebo for 12 weeks.

Evan Stein, MD, founder, LIB Therapeutics, and Metabolic & Atherosclerosis Research Center, Cincinnati, presented the results here at the European Atherosclerosis Society 2019 Congress. LIB Therapeutics funded the study.
Targeting LDL: Novel Suppression of Cholesterol Synthesis - Bempedoic acid

- **Bempedoic acid** - directly inhibits ATP citrate lyase (ACL), a key enzyme that supplies substrate for cholesterol and fatty acid synthesis; upregulates LDL receptors

- **Esperion therapeutics** - 12,604 patients, 1000 sites, approximately 30 countries
Efficacy and safety of bempedoic acid added to ezetimibe in statin-intolerant patients with hypercholesterolemia: A randomized, placebo-controlled study

Christie M. Ballantyne a, *, Maciej Banach b, G.B. John Mancini c, Norman E. Lepor d, e, Jeffrey C. Hanselman f, Xin Zhao f, Lawrence A. Leiter g
Targets

• **Targeting LDL**
  - Role of PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
  - RNA interference (RNAi) to reduce PCSK9 (ORION)
  - Decreasing LDL synthesis - Bempedoic acid

• **Targeting HDL**
  - CETP inhibitors
  - Epigenetics - BET on MACE program
  - Apo-A1 infusion – AEGIS program

• **Targeting triglycerides**
  - REDUCE-IT
  - PROMINENT

• **Other - Targeting ANGPTL3 (inh of lipoprotein lipase)**
Cholesteryl Ester Transfer Protein (CETP) Inhibition

Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes transfer of cholesteryl ester (CE) from HDL to apoB-containing lipoproteins (VLDL and LDL-C) in exchange for triglycerides.

Free Cholesterol (FC) in Extrahepatic tissues
LDL / VLDL

<table>
<thead>
<tr>
<th>Drug</th>
<th>HDL</th>
<th>LDL</th>
<th>Clinical Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Torcetrapib (60 mg/d)</td>
<td>+61%</td>
<td>-24%</td>
<td>↑ Mortality</td>
</tr>
<tr>
<td>Dalcetrapib (600 mg/d)</td>
<td>+25%</td>
<td>-4%</td>
<td>Ø Benefit</td>
</tr>
<tr>
<td>Anacetrapib (100 mg/d)</td>
<td>+140%</td>
<td>~ -30%</td>
<td>REVEAL +</td>
</tr>
<tr>
<td>Evacetrapib (130 mg/d)</td>
<td>? +130%</td>
<td>? -30%</td>
<td>Abandoned</td>
</tr>
</tbody>
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Adapted from Rosenson RS et al. Circulation 2012;125:1905
RVX-208 (Apabetalone) is a first-in-class, orally active, small-molecule stimulator of apolipoprotein (APO)A1 gene expression.

Bromodomain and Extra-Terminal (BET) Inhibitor

RVX-208 increases total HDL as well as the alpha- and pre-beta HDL fractions.
BET on MACE – Phase 3 Outcome Study

Primary Efficacy End Point: CV Death, Non-Fatal MI and Stroke (N=274)

Hazard ratio, 0.82 (95% CI, 0.65–1.04), P=0.11

Median follow-up 26 months

Primary Endpoint: Placebo 12.4% Apabetalone 10.3%

No. at Risk
Placebo  1206  1135  1102  937  641  383  108
Apabetalone 1212  1151  1114  950  672  397  107

Ray et al, AHA, Nov 2019
Single 80 mg/kg Infusion of Reconstituted ApoA-I Reduced Human Femoral Plaque Lipid & Macrophage Size > 50% in 5-7 Days

Gibson et al. AHA 2016
AEGIS-II: Study Design

A Phase 3, Multicenter, Double-blind, Randomized, Placebo-controlled, Parallel-group Study

- 17,400 AMI patients
- Stratification by:
  - STEMI/NSTEMI
  - PCI/medical mgt
  - Region

6 g CSL112 (n=8700)

Placebo (n=8700)

Dec 2019: >7000 pts enrolled

Visit: 1 2 3 4 5 6 7 8 9 10 11 12
Infusion: 1 2 3 4 D 180 D 365

Interim analysis for efficacy at 70% of targeted MACE
Interim analyses for futility will be conducted at 30 & 50% of targeted MACE

- Enriched Study Population: Multi-vessel disease and one of the following: ≥65 years of age, previous MI, peripheral artery disease, or diabetes mellitus
- Primary endpoint: Time-to-first occurrence of CVD, MI or stroke through day 90
- Follow up: All subjects followed for at least 365 days
 Targets

• **Targeting LDL**
  - PCSK9 Inhibitors (FOURIER, SPIRE, ODYSSEY)
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• **Targeting HDL**
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• **Targeting triglycerides**
  - REDUCE-IT
  - STRENGTH
  - PROMINENT

• **Other - Targeting ANGPTL3 (inh of lipoprotein lipase)**
Increased residual CV risk in patients with Diabetes and High (200-499mg%) vs Normal (<150mg%) TG despite statin-controlled LDL cholesterol

Gregory Nichols et al, Diabetes Obes Metab. 2018;1–6
REDUCE IT: CV Risk Reduction with Icosapent Ethyl (Vascepa) For Hypertriglyceridemia (N=8179)

- **Targeted pts with high TG** (mean 216; range 150-499mg%)
- **High dose (2G bid) purified** product
- 71% sec prevention, 40% DM, Baseline LDL-C 75 mg%
REDUCE-IT

Total (First and Subsequent) Events
Key Secondary: CV Death, MI, Stroke

Key Secondary Composite Endpoint

RR, 0.72
(95% CI, 0.63–0.82)
P=0.00000071

HR, 0.74
(95% CI, 0.65–0.83)
P=0.0000006

ACC 2019
STRENGTH (Statin Residual Risk Reduction With Epanova in High CV Risk Patients with Hypertriglyceridemia)

- Double-blind, placebo-controlled (corn oil), parallel group design using Epanova (AZ; n-3 fatty acid)
- 13,000 patients with hypertriglyceridemia, low HDL and high risk for CVD
- Randomized 1:1 to corn oil + statin or Epanova + statin, once daily
- Approximately 3-5 years follow up - MACE outcomes driven trial

Results expected – 2020
**PROMINENT**

- Test Product: K-877 (pemafibrate) 0.2 mg
- Dose: One tablet twice daily
- Mode of Administration: Oral
- Mechanism of action: new generation selective PPAR-α modulator (SPPARM-α)
- Storage: Room temperature

### Benefit-Risk Profile

<table>
<thead>
<tr>
<th>Benefit-Risk Profile</th>
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<tbody>
<tr>
<td><em>greater potency and PPAR-α selectivity than fenofibrate</em></td>
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<tr>
<td>greater TG-lowering efficacy</td>
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<tr>
<td>improved safety and tolerability</td>
</tr>
<tr>
<td>minimal inhibitory effects on major drug-metabolizing enzymes and transporters</td>
</tr>
<tr>
<td>no impact of renal function on maximum total exposure</td>
</tr>
<tr>
<td>no evidence of QTc prolongation</td>
</tr>
<tr>
<td>less frequent elevation of liver enzymes than fenofibrate</td>
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Triglycerides: PROMINENT Study (N=10,000)

Patient population
- Adults with T2D with moderate hypertriglyceridemia and low HDL
- Stable background therapy with statins (or statin intolerant within LDL targets)
  2/3 subjects: with documented CVD
  1/3 subjects: primary prevention (M≥50y or F≥55y)

Pre-Screening Based on medical records

Screening procedures

Randomization
1:1 Ratio

Visit 0 1 1.1 2 3 4 5 6 7 8 9
Week/Month -6W -3W 0 1W M2 M4 M6 M8 M10 M12 CSED FU

Arm 1: Pemafibrate 0.2 mg BID

Arm 2: Placebo BID

Alternate bi-monthly calls and in person visits

Key randomization criteria
- A1c ≤9.5%
- Fasting TG >200<500 mg/dL
- HDL<40 mg/dL

Primary endpoint: MACE+
- MI
- Ischemic Stroke
- CVD death
- Unstable angina requiring unplanned revascularization

Nov 2019 – 8455 recruited
Targets

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- **New - Targeting ANGPTL3 (inh of lipoprotein lipase)**
Association of Genetically Enhanced Lipoprotein Lipase–Mediated Lipolysis and LDL Cholesterol–Lowering Alleles With Risk of CAD and Type 2 Diabetes

Lotta et al, JAMA Cardiology 2018;3(10):957-966
ANGPTL3 and Protection from CAD

CENTRAL ILLUSTRATION: ANGPTL3 Deficiency and Protection From Coronary Artery Disease

A
Deep Phenotyping in a Mendelian Family with Complete ANGPTL3 Deficiency
Complete ANGPTL3 Deficiency
First-degree Related Controls
No Coronary Atherosclerosis Detected in Complete ANGPTL3 Deficiency

Quantify Atherosclerotic Plaque

B
Large-scale Association of Heterozygous ANGPTL3 Deficiency
Loss of Function Mutations
Test for Association with CAD
Functional Analysis of Missense Mutations in Mouse Models

C
Circulating ANGPTL3 Levels and Risk of MI
Cases with MI
Control
Measure Plasma ANGPTL3 Protein Concentration

35% Decreased Risk of Myocardial Infarction in Lowest Tertile of ANGPTL3 Concentration

Evinacumab – “FDA Grants Breakthrough Designation”

- Evinacumab is a **monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3)** - an **inhibitor of lipoprotein lipase (LPL)** (which is responsible for breakdown of triglycerides and other lipids)

- In Phase I, **evinacumab reduced TG levels by 64-73%**, far outperforming current treatments such as fish oils or fibrates which typically reduce TG by 20% to 50%

- In **Homozygous familial hypercholesterolemia (HoFH)** -
  - adding the drug to standard cholesterol treatment such as statins improved LDL-cholesterol reduction
Evinacumab – ELIPSE HoFH Trial

ANGPTL3 antibody halves LDL-c levels in HoFH patients in phase 3 trial

NEWS - AUG. 15, 2019

Positive phase 3 results of the ELIPSE HoFH trial have been announced for evinacumab, an investigational angiopoietin-like 3 (ANGPTL3) antibody, in patients with homozygous familial hypercholesterolemia (HoFH). ANGPTL3 acts as an inhibitor of lipoprotein lipase (LPL) and endothelial lipase, and appears to play a central role in lipoprotein metabolism.

On average, patients entered the trial with LDL-c levels of 255 mg/dL, despite treatment with other lipid-lowering therapies, including maximally-tolerated statins, PCSK9 inhibitors, ezetimibe, LDL apheresis and lomitapide. The trial met its primary endpoint, showing that adding evinacumab to other lipid-lowering therapies decreased LDL-c by 49% on average, compared to lipid-lowering therapies alone.

ELIPSE HoFH is an ongoing phase 3 randomized, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of evinacumab 15 mg/kg administered intravenously every four weeks in 65 patients aged 12 years or older with HoFH (43 evinacumab, 22 placebo). In the evinacumab treatment group, 98% of patients were on statins, 81% were on PCSK9 inhibitors, 75% were on ezetimibe, 33% were on LDL apheresis and 26% were on lomitapide. In addition, 35% of evinacumab patients had the most severe, "null/null" form of HoFH.

The phase 3 trial was designed to assess the effect of evinacumab on LDL-c and other lipid-related endpoints. Results from the evinacumab group at week 24 included:

- 49% reduction in LDL-c from baseline, compared to placebo (47% reduction for evinacumab vs. 2% increase for placebo, P<0.0001), the primary endpoint. LDL-c reductions were observed from the first assessment at week 2, and were maintained throughout the 24-week double-blind treatment period.

- 132 mg/dL absolute change in LDL-c from baseline, compared to placebo (135 mg/dL reduction...