Lipid-Altering Drug Development and Research Update 2016

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Medical Director / President
L-MARC Research Center
INTRODUCTION:
What is a good resource for lipid-altering drugs in development?
What is the process by which drugs are developed, and how do FDA approval processes affect the clinical use of lipid-altering drugs?
Process of Food and Drug Development Approval
New chemical entity (NCE) or new molecular entity (CME)

• Drug Discovery

• Preclinical Testing

Process of Food and Drug Development Approval
New chemical entity (NCE) or new molecular entity (CME)

- Investigational New Drug (IND) Application
- Clinical Trials (Phase 1 – 4)
- Special Protocol Assessment / Agreement (SPA)
- New Drug Application (NDA)
- Prescription Drug User Fee Act (PDUFA) of 1992
- FDA Advisory Committee


Process of Food and Drug Development Approval
New chemical entity (NCE) or new molecular entity (CME)

- FDA Advisory Committee Meeting

Process of Food and Drug Development Approval
New chemical entity (NCE) or new molecular entity (CME)

- Approval
- Contingency FDA Approval Decision
  - Commitment to outcomes trials
  - Risk Evaluation and Mitigation Strategy
- Post-Approval additional regulatory treatment indications


Legal Relevance of a SPA

Risk awareness in a volatile world
(By Aberdeen Asset Management)

FDA rejects Amarin appeal on Vascepa trial design, shares slump
Legal Relevance of a SPA

A Victory for Amarin Further Erodes FDA Regulation of off-label Promotion

By David C. Gilbert

On Friday, August 7, Judge Paul Engelmayer, U.S. District Court for the Southern District of New York, handed down one of the most significant rulings concerning First Amendment protection for a pharmaceutical manufacturer’s off-label promotion of an otherwise approved drug. Judge Engelmayer granted a motion for preliminary injunction in favor of Amarin Pharma, Inc. (“Amarin” or “the Company”) and did what some believed the court would not do: reach the merits of Amarin’s First Amendment claim.

Legal Relevance of a SPA

Amarin wins lawsuit with FDA over off-label promotion of Vascepa; shares up 9% after hours

Mar 8, 2015, 10:30 ET / About: Amarin Corporation PLC (AMRN) / By: Douglas W. Hoxme, SN News Editor

- Amarin (NASDAQ: AMRN) wins its First Amendment litigation against the FDA [Amarin, Inc. et al. v. FDA et al., No. 15-2588 (S.D.N.Y. May 7, 2015)] concerning off-label promotion of Vascepa (icosapent ethyl) Capsules.
- Under the terms of the settlement, both parties agree to abide by the August 7, 2015 judicial declaration that Amarin may promote the off-label use of Vascepa to healthcare professionals with the proviso that it is done so in a truthful and non-misleading manner. In addition, the FDA agreed to provide the company with an optional preapproval provision through 2020 for new off-label claims. Both parties also agreed to a dispute resolution provision designed to avoid future litigation.
- The dispute arose over Amarin’s desire to inform physicians of the data from the ANCHOR clinical trial which showed a statistically significant treatment benefit in patients with high triglycerides (between 200 mg/dL and 500 mg/dL) who received Vascepa. The FDA cited it as Vascepa’s narrow clearance for patients with triglyceride levels above 500 mg/dL, a much smaller patient population.
Process of Food and Drug Development Approval
New chemical entity (NCE) or new molecular entity (CME)

Ezetimibe Fails to Garner Support for CV- Event Reduction Claim From FDA Advisory Committee

Key Points:
- Ezetimibe currently approved for lowering LDL cholesterol levels
- FDA panel not convinced by IMPROVE-IT data showing that ezetimibe added to statin therapy further reduces CV events in ACS patients

By Michael O’Riordan
Tuesday, December 15, 2015

A US Food and Drug Administration (FDA) advisory committee voted yesterday against approving a claim that adding ezetimibe, marketed as Zetia by Merck/Schering-Plough, to statin therapy reduces the risk of cardiovascular (CV) events in ACS patients.

What is/was unique about PCSK9 inhibitor drug development?
PCSK9: rapid progress from discovery to clinic in less than a decade

PCSK9 Inhibitor development programs are unique in their:

- Biology and Safety
- Mechanism
- Efficacy
- Approved indicated use
- Potential concerns of high efficacy
- Administration

References:

What is/was unique about PCSK9 inhibitor drug biology and safety?
Small Molecules

Prodrugs

Pro Drug

Active Drug

drug is inactive before metabolism

drug becomes active after metabolism

drug takes effect directly

Antisense Oligonucleotides (ASO’s)


Medicines in Development Biologics: 2013 Report

Monoclonal Antibodies Nomenclature and Safety Considerations

- Mouse variable
- Mouse constant
- No repeated dosing

- All mouse variable
- Human constant

- Part mouse variable
- Human constant

- Human variable
- Human constant
- Repeated dosing possible

Mouse mAb (-omab) | Chimeric mAb (-ximab) | Humanized mAb (-zumab) | Fully Human mAb (-umab)
---|---|---|---
Mouse variable | All mouse variable | Part mouse variable | Human variable
Mouse constant | Human constant | Human constant | Human constant
No repeated dosing | Repeated dosing possible


What is/was unique about PCSK9 inhibitor drug mechanism?

Lipid-Altering Drug Mechanisms of Action

**BILE ACID SEQUESTRANTS / RESINS**

- BAS $\rightarrow$ ↑HMGCoA $\rightarrow$ ↑LDLR
- $\rightarrow$ ?NPC1L1 $\rightarrow$ ↑SREBP2 $\rightarrow$ ↑LDLR $\rightarrow$ ↑PCSK9 (↑ LDLR)
- Net ↑ LDLR $\rightarrow$ ↓ Circulating LDL-C

**SREBP2 INHIBITORS**

- SREBP2 Inhibitor $\rightarrow$ ↓ HMGCoA (↓ LDLR)
- $\rightarrow$ ↓ NPC1L1 (↑ LDLR)
- $\rightarrow$ ↑ PCSK9 (↑ LDLR)
- $\rightarrow$ ↓ LDLR (↓ LDLR)
- Net ↑ LDLR $\rightarrow$ ↓ Circulating LDL-C

Lipid-Altering Drug Mechanisms of Action

**PCSK9 INHIBITOR MECHANISM OF ACTION**

- PCSK9 Inhibitor $\rightarrow$ ↑LDLR
- (↑ ↑HMGCoA / ↓ LDLR)
- (↑ ?NPC1L1 / ? LDLR)
- (↑ ?SREBP2 / ↓ LDLR)
- Net ↑ LDLR $\rightarrow$ ↓ Circulating LDL-C
Alirocumab 150 mg SC – Dynamic Relationship Between mAb Levels, PCSK9, and LDL-C

What is/was unique about PCSK9 drug approved indications?
Statin Prescribing Information Indicated Use

INDICATIONS AND USAGE
[atorvastatin] is an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct therapy to diet to:
• Reduce the risk of MI, stroke, revascularization procedures, and angina in patients without CHD, but with multiple risk factors
• Reduce the risk of MI and stroke in patients with type 2 diabetes without CHD, but with multiple risk factors
• Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for CHF, and angina in patients with CHD
• Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia
• Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipoproteinemia
• Reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH)
• Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy


PCSK9 Inhibitor European Prescribing Information Indications

[PCSK9 INHIBITOR] is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

• In combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin
• Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

The effect of [PCSK9 INHIBITOR] on cardiovascular morbidity and mortality has not yet been determined

PCSK9 = proprotein convertase subtilisin/kexin type 9.
PCSK9 Inhibitor US
Prescribing Information Indications

• [PCSK9 INHIBITOR] is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C

• The effect of [PCSK9 INHIBITOR] on cardiovascular morbidity and mortality has not been determined

PCSK9 = proprotein convertase subtilisin/kexin type 9.

What is/was unique about PCSK9 inhibitor efficacy?
“Optimal LDL [cholesterol] 50 to 70 mg/dl: Lower is better and physiologically normal”

Mean Total Cholesterol, mg/dL


What is/was unique about PCSK9 inhibitor administration?
NLA Annual Summary 2016: Lipid-Altering Drugs in Development

Table 1 (continued)

<table>
<thead>
<tr>
<th>Class of agent and mechanism of action</th>
<th>Name</th>
<th>Manufacturer</th>
<th>Sample references or Clinical Trials.gov Identifiers</th>
<th>Sentinel, reported safety/tolerability findings</th>
<th>Sentinel, lipid effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual modulator of adenosine triphosphate-citrate lyase (ETC-1002) and adenosine monophosphate-activated kinase</td>
<td>Bempedoic acid (Esketimide)</td>
<td>Esperion</td>
<td>181</td>
<td>Possible increase in myalgia, mild increase in homocysteine and mild decrease in hemoglobin</td>
<td>15%-25% reduction in LDL-C levels, 15%-21% reduction in non-HDL-C levels</td>
</tr>
</tbody>
</table>
### NLA Annual Summary 2016: Lipid-Altering Drugs in Development

**ETC-1002 May Impact Additional CV Risk Factors Via Activation of AMP-Activated Kinase (AMPK)**

ETC-1002 free acid activates AMPK in the liver and could provide beneficial effects on multiple cardiometabolic risk factors.

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**Cholesteryl ester transfer protein (CETP) inhibitor**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anacetrapib</td>
<td>Merck</td>
<td>Generally well tolerated with no increase in blood pressure; drug concentration still detectable 2–4 years after last dosing.</td>
</tr>
<tr>
<td>TA-8995</td>
<td>Amgen (Dezima)</td>
<td>As much as 40% reduction in LDL-C, 27 - 45% reduction in LDL-C, 76 - 179% increase in HDL-C</td>
</tr>
</tbody>
</table>
INDIANAPOLIS, July 27, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) has accepted the recommendation of the ACCELERATE study data monitoring committee to continue the Phase 3 trial of the investigational medicine evacetrapib, based on data from an interim futility analysis.

Last patient visit in ACCELERATE - which is evaluating evacetrapib in approximately 12,000 patients with high-risk atherosclerotic cardiovascular disease (ASCVD) - is expected in July 2016.
Amgen to buy Dezima Pharma for $300 million in cash

Amgen Inc (AMGN.O) said it will buy biotechnology company Dezima Pharma B.V., adding another cholesterol drug to its expanding portfolio of treatments for cardiovascular diseases.

Amgen said it will pay $300 million in cash for the Netherlands-based company and up to $1.25 billion on meeting certain development and sales milestones.

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Lilly to Discontinue Development of Evacetrapib for High-Risk Atherosclerotic Cardiovascular Disease

INDIANAPOLIS, Oct. 12, 2015 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and the ACCELERATE study’s academic leadership have accepted the recommendation of the independent data monitoring committee to terminate the Phase 3 trial of the investigational medicine evacetrapib, due to insufficient efficacy. Lilly will discontinue development of evacetrapib for the treatment of high-risk atherosclerotic cardiovascular disease and will now conclude other studies in the program.
Merck Provides Update on REVEAL Outcomes Study

Friday, November 13, 2015 8:00 am EST

KENILWORTH, N.J. --(BUSINESS WIRE)--Merck (NYSE:MRK), known as MSD outside the United States and Canada, today announced that the Data Monitoring Committee (DMC) of the REVEAL outcomes study for anacetrapib has completed its planned review of unblinded study data and recommended the study continue with no changes. The DMC reviewed safety and efficacy data from the study, which included an assessment of futility. Merck remains blinded to the actual results of this analysis and to other REVEAL safety and efficacy data.

REVEAL is a 30,000 patient, event-driven study sponsored by Oxford University, which is projected to conclude in early 2017. The REVEAL Steering Committee and Merck will continue to monitor the progress of the study. No additional interim efficacy analyses are planned.

DGAT1 = Small intestine, liver, and adipose tissue
DGAT2 = Liver and adipose tissue
The process of dietary lipid digestion and absorption.

A

Emulsion

B

MAG
FA
CL

Lymph

Yuguang Shi, and Dong Cheng Am J Physiol Endocrinol Metab 2009;297:E10-E18

Proposed mechanistic insights into how cardiovascular disease (CVD)-predicting signature lipids may promote the pathogenesis of atherosclerosis.

Diet and de novo Lipogenesis


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NLA Annual Summary 2016: Lipid-Altering Drugs in Development

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Targets/Pharmacodynamics</th>
</tr>
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<tbody>
<tr>
<td>Antisense Apo C3 inhibitor</td>
<td>Volanesoren: Ionis Pharamaceuticals</td>
</tr>
<tr>
<td>Antisense inhibitor of lipoprotein (a)</td>
<td>ISIS-APO(a)Rx Ionis</td>
</tr>
</tbody>
</table>

- Injection site reactions: Up to 77% reduction in triglyceride levels
- Injection site reactions: Dose dependent reduction in lipoprotein (a) up to 78%
SAN FRANCISCO -- Ionis Pharmaceuticals has reclaimed rights to its cardiovascular drug Kynamro, which it had partnered to Genzyme in 2008.

ApoCIII

- Apolipoprotein C-III (ApoC-III) is a small protein that resides on various lipoproteins
- Inhibits lipoprotein/hepatic lipases
- Impairs hepatic uptake of triglyceride (TG)-rich lipoproteins (such as lipoprotein remnants)
- Generally promotes hypertriglyceridemia.
- May contribute to insulin resistance
- May contribute to atherosclerosis.
Gemcabene (CI-1027)
Acetyl CoA Carboxylase Inhibitor

300, 600, and 900 mg daily LDL-C reductions compared to placebo 17.0, 25.5, and 28.7%.

Acquired by Gemphire to develop as orphan drug in HoFH.
Effectiveness and tolerability of a new lipid-altering agent, *gemcabene*, in patients with low levels of high-density lipoprotein cholesterol

Harold E. Boys, MD, James M. McKenney, PharmD, Carlos A. Dujevina, MD, Helmut G. Schrott, MD, Michael J. Zema, MD, Jack Nyberg, MS, Diane E. MacDougall, MS, Gemcabene Study Group

NLA Annual Summary 2016: Lipid-Altering Drugs in Development

<table>
<thead>
<tr>
<th>Peroxisome proliferator activated receptor (PPAR) delta agonist</th>
<th>MBX-8025</th>
<th>Gynamay</th>
<th>Possible Increase in creatine kinase, mild decrease in hemoglobin, and increase in platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 - 43% reduction in LDL-C levels, 18 - 41% reduction in non-HDL-C, 26 - 30% reduction in triglycerides, reduction in apoB and small LDL particles</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MBX-8025, A Novel Peroxisome Proliferator Receptor-δ Agonist: Lipid and Other Metabolic Effects in Dyslipidemic Overweight Patients Treated with and without Atorvastatin

Harold E. Bays, Sherwyn Schwartz, Thomas Littlejohn, III, Boris Kerzner, Ronald M. Krauss, David B. Karpf, Yun-Jung Choi, Xiaoyan Wang, Sue Naim, and Brian K. Roberts

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*TL approved the original manuscript but was deceased on March 30, 2011, before final manuscript.

DOI: http://dx.doi.org/10.1210/jc.2011-1061
Received: March 22, 2011
Accepted: June 27, 2011
First Published Online: July 13, 2011

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<tr>
<th>Cholesterol absorption inhibitor</th>
<th>HS-25</th>
<th>Hisun</th>
<th>NCT02087917 Not reported</th>
<th>Not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botanic extract from red yeast Chinese rice</td>
<td>ZueZhiKang</td>
<td>Beijing Peking University WBL Biotech Co. (WPLU)</td>
<td>18/5.1.90</td>
<td>Lowers LDL cholesterol</td>
</tr>
</tbody>
</table>
Effects of Xuezhikang in patients with dyslipidemia: A multicenter, randomized, placebo-controlled study

Patrick M. Moriarty, MD, Eli M. Roth, MD, Adam Karns, MD, Ping Ye, MD, PhD, Shui-Ping Zhao, MD, PhD, Yuhua Liao, MD, David M. Capuzzi, MD, Harold E. Bays, MD, Fumin Zhang, MD, Shaowen Liu, MD, Alan J. Reichman, MD, Osvaldo A. Brusco, MD, Guoping Lu, MD, Sam Lerman, MD, Zhenwen Duan, PhD, Shuren Guo, MD, Ping Lan Liu, MD, Junxian Zhao, MD, Yan Zhang, MD, Simon Li, MD, PhD*
Original Article

Icosabutate for the treatment of very high triglycerides: A placebo-controlled, randomized, double-blind, 12-week clinical trial

Harold E. Bays, MD, Jonas Hallén, MD, PhD, Runar Vige, MSc, David Fraser, PhD, Rong Zhou, PhD, Svein Olaf Hustvedt, PhD, David G. Orloff, MD, John J. P. Kastelein, MD, PhD*

NLA Annual Summary 2016: Lipid-Altering Drugs in Development
SUMMARY:
Take Home Message:
What is a good resource for lipid-altering drugs in development?

Journal of Clinical Lipidology (2016) 10, S1-S37

Original Contribution

National Lipid Association Annual Summary of Clinical Lipidology 2016

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Lipid-Altering Drug Development and Research Update 2016