## Inhibition of PCSK9: The Birth of a New Therapy

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## Disclosures

Dr. Kastelein consults with and speaks for biotechnological as well as pharmaceutical companies that develop molecules that influence lipoprotein metabolism and / or inflammation to prevend CVD, including Regeneron, Sanofi, Amgen, Roche, Pfizer, and Eli Lilly

## Novel Approaches to Modify Lipids and Lipoproteins

- Low Density Lipoprotein
- > High Density Lipoprotein
- Triglyceride Rich Lipoproteins
- Inflammation
- Lipoprotein a

## **New Approaches to LDL Reduction**

## What is in development?

- Cholesterol Absorption Inhibitors
- Squalene Synthase (SSI) inhibitors
- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- Thyroxin Receptor Agonists
- PCSK9 Inhibitors

## LDL-Receptor Function and Life Cycle



# The Role of PCSK9 in the Regulation of LDL Receptor Expression



## **LDL-C Reduction and Coronary Events**

Lancet 2005; 366: 1267-78



### **PCSK9 LOF Mutations**



Adapted from Cohen JC. N Engl J Med 2006;354:1264-72; ARIC=Atherosclerosis Risk in the Community

## Loss of Function PCSK9 Mutations

Only a small number of patients who are homozygous (or compound heterozygotes) for PCSK9 have been discovered and studied.

These patients appear to have:

- Very low LDL-C levels (~10-20 mg/dL)
- Relatively low TG levels
- Normal HDL-C levels
- These patients have no other health problems

## Familial Hypercholesterolemia



## Familial Hypercholesterolemia

Age of onset of coronary atherosclerosis in FH heterozygotes as assessed by angiography



#### FH in the Netherlands:

#### Screening between January 1994 and December 2010



#### FH in the Netherlands:

#### Screening between January 1994 and December 2010



## FH Patients at LDL Goal



## Impact of a SAR236553/REGN727 on LDL Receptor Expression



A Randomized, Double-Blind, Placebo-Controlled Trial of the Safety and Efficacy of a Monoclonal Antibody to PCSK9, REGN727/SAR236553, in Patients with Heterozygous Familial Hypercholesterolemia on Stable Statin Dose With or Without Ezetimibe Therapy

Evan A. Stein, Dan Gipe, Jean Bergeron, Daniel Gaudet, Robert Weiss, Robert Dufour, Richard Wu, Robert Pordy. Lancet, May 2012

- The goal of this Phase II trial was to evaluate the LDL-C efficacy and safety of REGN727/SAR236553 in:
  - A larger population
  - More diverse HeFH population in terms of LDLr defects
  - More severely affected and aggressively treated group of HeFH patients, including those with CAD
  - Assess multiple and higher doses combined with different dosing regimens of REGN727/SAR236553



Number of randomized patients	77		
Age, mean	53.4 years		
Female	39.0%		
White race	94.8%		
BMI, kg/m²	<b>29.1</b>		
Coronary artery disease	41.6%		
Type 2 diabetes	3.9%		
'High-dose' statin treatment*	76.6%		
Ezetimibe treatment	71.4%		

\*atorvastatin 40 mg/80 mg; rosuvastatin 20 mg/40 mg; simvastatin 80 mg.

Intervention	Baseline LDL-C mg/dL [mmol/L]			% Change LDL-C <sup>1</sup>		
Placebo		150.8	[3.9]	-10.7 (5.0)		
REGN727 150 mg Q4W		166.7	[4.3]	–28.9 (5.1)*		
REGN727 200 mg Q4W		169.8	[4.4]	-31.5 (4.9)*		
REGN727 300 mg Q4W		139.6	[3.6]	-42.5 (5.1)*		
REGN727 150 mg Q2W		147.2	[3.8]	-67.9 (4. <sup>9</sup> )*		
*P<0.0001 for % change REGN727 vs. Placebo. <sup>1</sup> LS mean (SE), using LOCF method.		$\bigcirc$				

Stein EA et al. Lancet on-line May 26, 2012



## The Use of a PCSK9 Monoclonal AB in heFH Patients: Goal Attainment



Stein EA et al. Lancet on-line May 26, 2012

## The Use of a PCSK9 Monoclonal AB in heFH Patients: Secondary Results



	PBO (n=15)	150 mg Q4W (n=15)	200 mg Q4W (n=16)	300 mg Q4W (n=15)	150 mg Q2W (n=16)
<u>Creatinine, mg/dL (Mean [SD])</u> Baseline Week 12	0.7 (0.1) 0.7 (0.1)	0.9 (0.1) 0.8 (0.1)	0.8 (0.2) 0.8 (0.2)	0.8 (0.2) 0.8 (0.2)	1.0 (0.2) 0.9 (0.2)
<u>Glucose, mg/dL (Mean [SD])</u> Baseline Week 12	98.7 (10.7) 98.7 (7.7)	98.5 (8.5) 95.6 (9.2)	102.6 (18.2) 98.4 (18.9)	95.1 (6.9) 95.9 (11.8)	104.1 (15.1) 101.8 (11.7)
<u>ALT, IU/L</u> >3x ULN, n	0	0	0	0	0
<u>AST, IU/L</u> >3x ULN, n	0	0	0	0	0
Creatinine kinase, IU/L >3x ULN, n	0	0	0	0	0
hsCRP mg/L, (Median [Q1;Q3]) Baseline Week 12	0.9 (0.4; 1.6) 0.7 (0.4; 1.2)	0.6 (0.3; 1.4) 0.4 (0.3; 1.4)	0.7 (0.5; 2.5) 0.7 (0.5; 1.3)	0.7 (0.5; 1.3) 0.6 (0.4; 1.7)	1.4 (0.6; 3.4) 1.0 (0.7; 3.7)

hsCRP=high sensitivity C-reactive protein; PBO=Placebo.

The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients

## LAPLACE-TIMI 57 Primary Results

A Double-blind, Randomized, Placebo-controlled, Dose-ranging Study to Evaluate the Efficacy, Safety, and Tolerability of a Monoclonal Antibody to PCSK9 in Combination with a Statin in Patients with Hypercholesterolemia

> Robert P. Giugliano, MD, SM, FAHA, FACC TIMI Study Group, Cardiovascular Division Brigham and Women's Hospital Harvard Medical School, Boston, MA

> > Supported by research grant from Amgen, Inc.

### The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients

- A global, randomized, double-blind, phase 2 trial
- Patients
  - 18-80 years
  - On stable dose of statin ± ezetimibe
  - LDL-C ≥ 85 mg/dL



#### The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients: Results



#### The Use of a PCSK9 Monoclonal AB in Hypercholesterolemic Patients: Results





### In the next five years, we will prove or disprove that additional LDL lowering with other agents than statins is effective

and

we will show or not show that the HDL hypothesis is true.