



Endocrinologic and Metabolic Drugs Advisory Committee Meeting  
Gaithersburg, MD  
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## FDA Introductory Remarks

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## History

- February 1987 – EMDAC discussed approvability of lovastatin
- 1994 – Scandinavian Simvastatin Survival Study
- Multiple cardiovascular outcomes trials (CVOTs) investigating the benefits of statins followed suit
- For statins, ~40 mg/dL reduction in LDL-C reduces the risk for major cardiovascular events by ~22%.<sup>1</sup>

<sup>1</sup> Cholesterol Treatment Trialists' Collaboration. *Lancet* 2010;376:1670-81.

# Surrogate Endpoints

- What is a surrogate?

“...a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of therapy.”<sup>1</sup>
- Use depends on the evidence that a drug’s effect on the surrogate predicts clinical benefit.
  - *Known* to predict benefit → “traditional” or “full” approval
  - *Reasonably likely* to predict benefit → accelerated approval
- Risk factor ≠ Surrogate Endpoint

<sup>1</sup> Accelerated Approval Proposed Rule, 57 FR 13235 (15 April 1992).

## Accelerated Approval

- Potential approval pathway based on substantial evidence of a drug's effect on a surrogate endpoint that is *reasonably likely* to predict clinical benefit.
- Post-marketing confirmatory trial to verify clinical benefit
- Has never been used for the approval of lipid-modulating drugs
  - Post-marketing CVOTs have been voluntary

## Controversy

- Last first-in-class drug to lower LDL-C in a broad population was Zetia (ezetimibe) in 2002
- The lack of CV outcomes data became especially controversial when clinical trials published in 2008 raised concerns regarding both the clinical benefits and risks of ezetimibe.<sup>1,2</sup>
- Approval based on a surrogate endpoint always leaves uncertainty regarding true clinical benefit, which can create challenges when safety concerns arise.

## Controversy (2)

- The ezetimibe IMPROVE-IT trial has now completed.<sup>1</sup>
- According to the investigators, adding ezetimibe to simvastatin in the setting of acute coronary syndrome led to a statistically significant reduction in the risk of CV events of a magnitude they expected based on the degree of LDL-C lowering achieved.
- Increasing emphasis on using therapies that have proven clinical benefit, moving away from specific biomarker targets?
  - 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
  - Controversy acknowledged

<sup>1</sup> Cannon CP, et al. *N Engl J Med* 2015.

## Relying on Surrogates Sometimes Fails Us

- Off-target adverse effects can surprise us.
- Sometimes we might get the causal relationship wrong.
- Example: Despite ~25% reduction in LDL-C and ~70% increase in HDL-C, torcetrapib increased risk of CV events by 25% and increased risk of all-cause mortality by 58%.<sup>1</sup>

<sup>1</sup> Barter PJ, et al. *N Engl J Med* 2007;357:2109-22.

## Why not discuss using accelerated approval?

- It's never been used before for a lipid-modulating drug.
- Today is not the forum to discuss the various regulatory considerations that would inform the feasibility of using this approval pathway.
- Focus on whether the demonstrated LDL-C lowering by evolocumab is sufficient to substitute for demonstrating its effect on clinical outcomes in one or more populations.

## Recent Approvals for HoFH

- In Dec 2012 and Jan 2013, we approved Juxtapid (lomitapide) and Kynamro (mipomersen) for HoFH based on their effects on LDL-C
- Reductions in LDL-C were especially compelling as evidence of benefit for this population, in which the phenotype is a direct result of abnormal LDL metabolism
- Our advisors emphasized that the position of LDL-C as a surrogate may be context-dependent

## CVOTs as Post-Marketing Requirements (PMRs)

- FDA can require post-marketing clinical trials to assess serious risks or to identify unexpected serious risks if specific statutory provisions are met.
- It would make little sense to require a *safety trial* to exclude increased CV risk (i.e., accepting non-inferiority to placebo by some margin) for a drug intended for use solely to reduce CV risk.

# Question 1 (Discussion)

1. Discuss the safety of evolocumab as observed in the clinical development program, and in your discussion comment on the following:
  - a. Discuss your interpretation of the safety data with respect to any adverse effects related to diabetes, liver-related safety, muscle, neurological/neurocognitive events, hypersensitivity, as well as any other concerns you may identify.
  - b. Discuss the adequacy of the current clinical database to characterize the safety of evolocumab. Consider the extent of drug exposure (i.e., number of patients and duration of exposure), the strengths/limitations of the study designs themselves, and the generalizability of the trial populations to the target patient population(s), if approved.
  - c. Discuss your level of concern regarding the safety of achieving very low levels of LDL-C induced by evolocumab.

## Question 2 (Discussion)

2. The applicant has proposed two dosage regimens, which were selected to appeal to patient preference considerations (related to the dosing procedure/frequency) rather than to provide doses intended to allow titration with respect to the magnitude of LDL-C lowering. Healthcare providers who are uncomfortable with very low levels of LDL-C would either have to down titrate other lipid-altering drugs (e.g., statin) or discontinue evolocumab. Discuss whether you would have any concerns with evolocumab not being labeled with dosage regimens that provide varying degrees of LDL-C lowering, if approved.

## Question 3 (Discussion)

3. For homozygous familial hypercholesterolemia (HoFH), the applicant has proposed a recommended dose of evolocumab of either 420 mg once monthly or 420 mg every 2 weeks (Q2W). Discuss whether the applicant has provided adequate data to characterize the efficacy and safety of the 420 mg Q2W dosage in this population.

## Question 4 (Discussion)

4. The goal of LDL-C-lowering therapy is to reduce the risk for cardiovascular (CV) disease. Historically, a change in LDL-C has been considered sufficient to establish the effectiveness of a lipid-altering drug intended for use to reduce cardiovascular risk, without any regulatory requirement to demonstrate evidence for benefit in a CV outcomes trial, provided the reduction is sufficiently robust and the product (or its class) does not have safety issues that raise concern that risk exceeds benefit.

Discuss whether evolocumab-induced LDL-C lowering is sufficient to substitute for demonstrating its effect on clinical outcomes (i.e., to substitute for investigation in a CV outcomes trial) in one or more populations (e.g., different degrees of CV risk, familial vs. non-familial etiologies of hyperlipidemia, use with or without concomitant statins, etc.).

## Question 5 (Vote)

5. Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval in one or more patient populations (excluding HoFH)? We remind you that under the current regulatory pathway, it would not be required to successfully demonstrate an effect of evolocumab on CV outcomes after an approval based on changes in LDL-C.
  - a. If yes, please explain your rationale and describe the patient population(s) for whom you believe that benefit/risk is favorable.
  - b. If no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit/risk to support approval.

## Question 6 (Vote)

6. Has the applicant sufficiently established that the LDL-C-lowering benefit of evolocumab exceeds its risks to support approval for homozygous familial
  - a. If yes, please explain your rationale.
  - b. If no, please describe what further studies you believe the applicant must conduct to establish a favorable benefit/risk to support approval.



Endocrinologic and Metabolic Drugs  
Advisory Committee Meeting  
Gaithersburg, MD  
10 June 2015

**Clinical Review of Efficacy and Safety**  
**BLA 125522**  
**Evolocumab injection**

Eileen Craig, MD

Medical Officer

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# Outline

- Background
- Evolocumab Clinical Program
- Efficacy Findings
- Safety Findings and Concerns
  - Overall findings
  - Diabetes Mellitus
  - Pancreatitis
  - Neurocognitive Findings
  - Safety in Low LDL-C Subgroup
  - Anti-evolocumab Antibody Formation
  - Hypersensitivity
  - Musculoskeletal Issues
  - Hepatic Issues
  - Cardiovascular Events
  - Safety of the 420 mg Q2W dose

## Background and Proposed Dosage

- Evolocumab is a human IgG2 antibody directed to PCSK9.
  - By binding to PCSK9 it inhibits binding to LDLR
  - Prevents PCSK9-mediated LDLR degradation
  - Leads to ↑ in LDLR and ↓ in serum LDL-C
- Proposed Dosage for Primary Hyperlipidemia:
  - 140 mg every 2 weeks or 420 mg once monthly
- Proposed Dosage for HoFH:
  - 420 mg once monthly or 420 mg every 2 weeks
- Administered by pre-filled syringe or auto-injector
  - One injection for 140 mg dose; 3 injections for 420 mg dose

# Pertinent Regulatory Background

## FDA comments at End of Phase 2 Meeting: July 2012

- Monotherapy and superiority to ezetimibe/statin claims would likely require cardiovascular outcomes trial (CVOT) data
- Concerns regarding only taking two dosing regimens (Q2W and Q4W) into phase 3 when both seemed to yield approximately the same degree of LDL-C lowering
- Concerns with some of the proposed study populations who may not be taking the maximum tolerated dose of statin
- Prefer that duration of studies be 24 weeks instead of 12 weeks

## Pertinent Regulatory Background

### FDA comments: Statin-intolerance Trials, May 2013

- LDL-C reduction not likely to be different in statin-tolerant and statin-intolerant populations
- Reminded the company of the division's proposed definition of statin-intolerance but clarified that any clinical definition of statin intolerance must have intolerance to at least 2 statins
- Recommended, again, important trial design elements
  - randomized, double-blind, controlled, parallel-group design
  - blinded placebo run-in period
  - blinded statin re-challenge arm
  - sufficient duration to assess safety/tolerability-6 months minimum

## Primary Hyperlipidemia Indication

- Adults with primary hyperlipidemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), TC/HDL-C, ApoB/apolipoprotein A1 (ApoA1), very low density lipoprotein cholesterol (VLDL-C), triglycerides (TG) and lipoprotein (a) (Lp[a]), and to increase HDL-C and ApoA1:
  - in combination with a statin or statin with other lipid lowering therapies (e.g., ezetimibe), or
  - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or
  - alone or in combination with other lipid-lowering therapies in patients for whom a statin is not considered clinically appropriate.

## HoFH Indication

- Indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C, TC, ApoB, and non-HDL-C in combination with other lipid lowering therapies (e.g., statins, LDL apheresis).
- The following drugs are currently approved for reduction of elevated LDL-C in HoFH populations
  - Statins: rosuvastatin, atorvastatin, simvastatin
  - Statin combo: atorvastatin/ezetimibe and simvastatin/ezetimibe
  - Ezetimibe
  - Lomitapide
  - Mipomersen

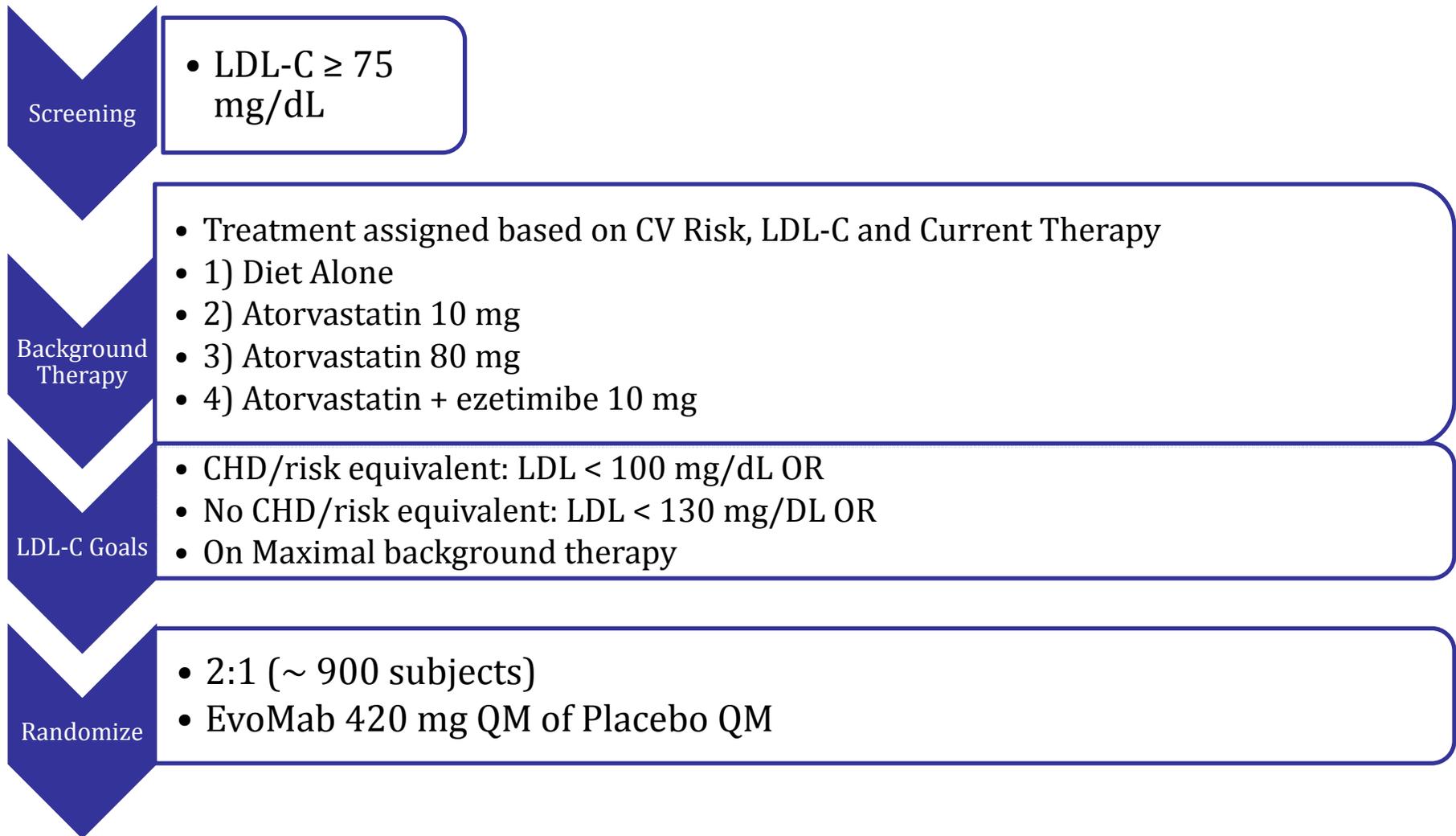
# Evolocumab Database for Primary Hyperlipidemia Efficacy Evaluation

	20110114 Monotherapy	20110115 Combo w/ statin	20110116 Statin- intolerant	20110117 HeFH
Duration	12-weeks	12-weeks	12-weeks	12-weeks
# Subjects	614	1896	307	329
Dose	140 Q2W or 420 QM	140 Q2W or 420 QM	140 Q2W or 420 QM	140 Q2W or 420 QM
Control Group	Placebo and ezetimibe	Placebo and ezetimibe	Ezetimibe	Placebo
Background LLT	Diet alone	Rosuva. 5 or 40 mg; Atorva.10 or 80 mg; or Simva. 40 mg	Diet alone; or Atypical or low-dose statin	Statin ± ezetimibe

# Key Inclusion/Exclusion Criteria in 12-week Phase 3 Trials

	<b>20110114 Monotherapy</b>	<b>20110115 Statin Combo</b>	<b>20110116 Statin-intolerant</b>	<b>20110117 HeFH</b>
Diagnosis	Low CV risk: 10-year Framingham risk score of 10% or less	Combination with statin therapy	Statin-intolerance to $\geq 2$ statins at dose > lowest tablet size	HeFH dx by Simon Broome Register Group criteria
Screening Lipid Levels	Fasting LDL-C 100-190 mg/dL; TG $\leq 400$ mg/dL	LDL-C $\geq 80$ , $\geq 100$ , or $\geq 150$ mg/dL for pts on intensive, non-intensive, and no statin, at screening, respectively; TG $\leq 400$ mg/dL	LDL-C >NCEP/ATP III goals; TG $\leq 400$ mg/dL	Fasting LDL-C $\geq 100$ mg/dL; TG $\leq 400$ mg/dL
Select Key Exclusion Criteria	Myocardial Infarction (MI), unstable angina, PCI, CABG or stroke within 3 months Chronic heart failure (CHF)- NYHA Class III or IV (II - IV for -114) or last LVEF < 30%, Uncontrolled hypertension (HTN), hypo/hyperthyroidism Type 1 diabetes; newly diagnosed or poorly controlled type 2 diabetes mellitus (T2DM), Creatine kinase (CK) > 3 x upper limit of normal (ULN); Aspartate transaminase (AST) or Alanine transaminase (ALT) > 2x ULN; eGFR < 30 ml/min/1.73m <sup>2</sup>			

# Design Elements of Trial 20110109



# Demographics of the Four 12-week Efficacy Trials

	20110114 Monotherapy N=614	20110115 Statin Combo N = 1896	20110116 Statin-intolerant N=307	20110117 HeFH N=329
LDL-C, mean, mg/dL	143	109	193	156
Female, %	66	46	46	42
Age, years, mean	55	60	62	51
Age ≥ 65 years, %	18	35	41	15
High CHD risk, %	1	39	56	43
Mod-High CHD risk, %	5	11	15	6
Coronary artery dis, %	<1	23	29	31
Cerebrovasc or PAD, %	<1	10	16	17
Type 2 diabetes, %	<1	16	20	7
Hypertension, %	29	57	59	33
North America, %	57	39	37	23

# Demographics of 52-week Trial -109

	Diet Only N=111	Atorva. 10 mg N = 383	Atorva. 80 mg N=218	Atorva. 80 /Ez 10 N=189	TOTAL N=901
LDL-C, mean mg/dL	112	100	95	118	104
Female, %	56	56	51	46	52
White, %	68	86	87	71	80
Age, years, mean	52	57	58	55	56
Age ≥ 65 years, %	18	26	25	16	21
High CHD risk, %	5	11	31	64	26
Mod-Hi CHD risk, %	13	11	9	5	9
CAD, %	2	3	16	48	15
Cerebro. or PAD, %	0	1	6	10	4
T2DM, %	3	7	15	22	12
Hypertension, %	42	42	57	56	49
North America, %	74	64	61	33	58

## Evolocumab Database for HoFH

### Phase 3 Trial

- 20110233: Combo with lipid-lowering therapies (LLT), no apheresis; 420 mg QM; 12-weeks, N=49
  - Primary endpoint: percent change from baseline in (UC) LDL-C at week 12

### Phase 2/3 Trial

- 20110271: HoFH and “severe” HeFH; Combo with LLT, apheresis allowed; 420 mg QM or 420 mg Q2W; ongoing, N=238 but only 96 HoFH

## Demographics of the HoFH Trials

	20110233 Non-apheresis		20110271 Non-apheresis	20110271 Apheresis
	EvoMab 420 QM N=33	Placebo N=16	EvoMab 420 QM N=65	EvoMab 420 Q2W N=33
LDL-C, mean mg/dL	356	336	339	283
Female	49%	50%	49%	42%
Age, years, mean	30	32	33	35
Age < 18, n (%)	7 (21)	3 (19)	10 (15)	3 (10)
Coronary artery disease	45%	38%	43%	52%
Cerebrovascular or PAD	12%	0%	8%	32%
Type 2 diabetes mellitus	6%	6%	5%	0%
Hypertension	12%	6%	14%	16%



# EFFICACY

## Primary Endpoint: LDL-C Mean % Change from Baseline to Week 12 in Trials -114, -116 and -117

Trial	EvoMab 140 Q2W	EvoMab 420 QM
Treatment difference from placebo (95% CI)		
-114 (Monotherapy):	-57% (-61, -53)	-55% (-59, -51)
-117 (HeFH):	-59% (-61, -53)	-61% (-69, -54)
Treatment difference from ezetimibe (95% CI)		
-114 (Monotherapy):	-39% (-43, -35)	-38% (-41, -34)
-116 (Statin intolerant):	-38% (-44, -32)	-38% (-42, -33)

High-intensity statins: LDL-C reductions ranging from 48% to 64%

## Primary Endpoint: LDL-C Mean % Change from Baseline to Week 12 in Trial 20110115 (Statin Combination)

Treatment Arm	EvoMab 140 Q2W	EvoMab 420 QM
Treatment difference from placebo (95% CI)		
Atorvastatin 10 mg	-71% (-78, -65)	-59% (-66, -52)
Atorvastatin 80 mg:	-76% (-87, -66)	-71% (-80, -61)
Rosuvastatin 5 mg:	-68% (-75, -62)	-65% (-71, -58)
Rosuvastatin 40 mg:	-68% (-77, -60)	-55% (-65, -45)
Simvastatin 40 mg:	-71% (-77, -64)	-60% (-69, -52)
Treatment difference from ezetimibe (95% CI)		
Atorvastatin 10 mg:	-40% (-46, -33)	-41% (-48, -34)
Atorvastatin 80 mg:	-47% (-58, -37)	-39% (-48, -30)

## Primary Endpoint Results in Trial 20110109 at Week 52

	Diet Only		Atorva. 10 mg		Atorva. 80 mg		Atorva. 80 mg + Eze. 10 mg		TOTAL	
	Pbo	Evo	Pbo	Evo	Pbo	EvoMab	Pbo	Evo	Pbo	EvoMab
LS Mean, %	4.2	-51.5	6.9	-54.7	10.1	-46.7	1.7	-46.8	6.8	-50.1
Trt diff. from placebo, %		-55.7		-61.6		-56.8		-48.5		-57.0
95% CI	(-64.1, -47.3)		(-66.8, -56.4)		(-67.3, -46.3)		(-58.2, -38.2)		(-61.1, -52.9)	
P-value	<0.001		<0.001		<0.001		<0.001		<0.001	

Consistency of Treatment Effect: Week 12: -58 (-61, -55); Week 52: -57 (-61, -53)

LS: least squares; Pbo: placebo; Trt: treatment

# Forest Plot of % Change in LDL

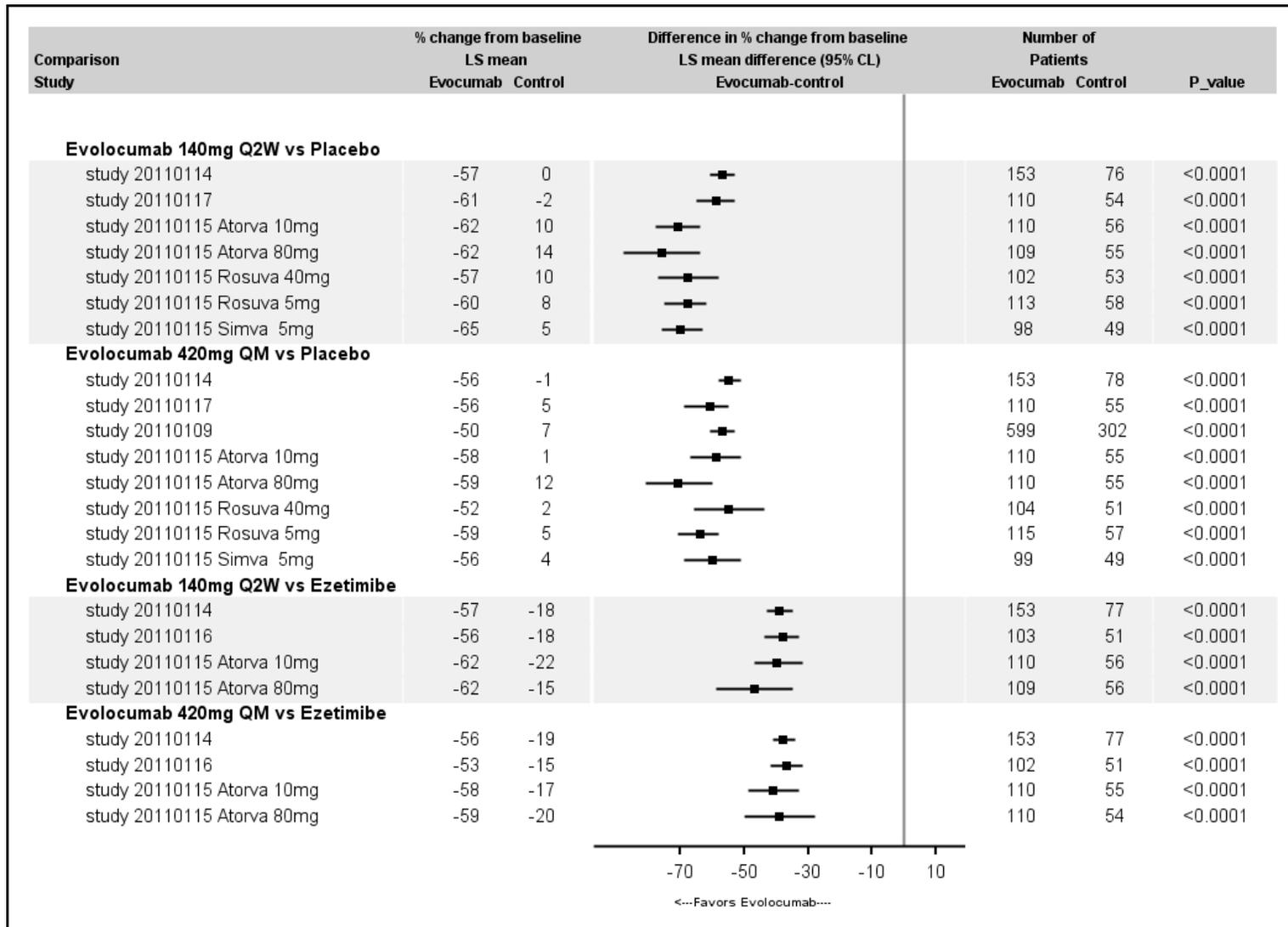


Figure courtesy of FDA statistician, Dr. Shuxian Sinks; Rosuva: rosuvastatin; Simva: simvastatin

# Secondary Efficacy Endpoints: Treatment Difference Compared with Placebo

	Monotherapy -114		Statin Combo -115		HeFH -117		-109
	140 Q2W at Wk 12	420 QM at Wk 12	140 Q2W at Wk 12	420 QM at Wk 12	140 Q2W at Wk 12	420 QM at Wk 12	420 QM at Wk 52
Non-HDL	-50%	-51%	-62%	-56%	-55%	-55%	-50%
ApoB	-48%	-48%	-57%	-51%	-49%	-49%	-44%
TC/HDL	-40%	-45%	-45%	-42%	-46%	-45%	-37%
ApoB/ ApoA1	-50%	-53%	-56%	-53%	-54%	-50%	-46%
Lp(a)	-20%	-18%	-32%	-27%	-32%	-28%	-22%
TG	-6%*	-18%	-17%	-22%	-20%	-12%	-12%
HDL-C	6%	9%	6%	7%	9%	9%	5%
VLDL-C	-8%*	-16%	-18%	-22%	-21%	-9%	-29%

\* failed to achieve statistical significance according to the applicant's testing strategy

## Efficacy Endpoints in HoFH Trial -233: Primary: Mean % Change in LDL-C

<b>20110233 Week 12 420 mg QM</b>	<b>Placebo (n=16)</b>	<b>EvoMab N=33)</b>	<b>Treatment difference (n=49)</b>	<b>P-value</b>
Baseline LDL, mg/dL	336	356		
UC <sup>1</sup> LDL-C, %	8	-23	-31 (-44, -18)	<0.001

<sup>1</sup> directly measured LDL by ultracentrifugation

## Efficacy Endpoints in HoFH Trial -233:

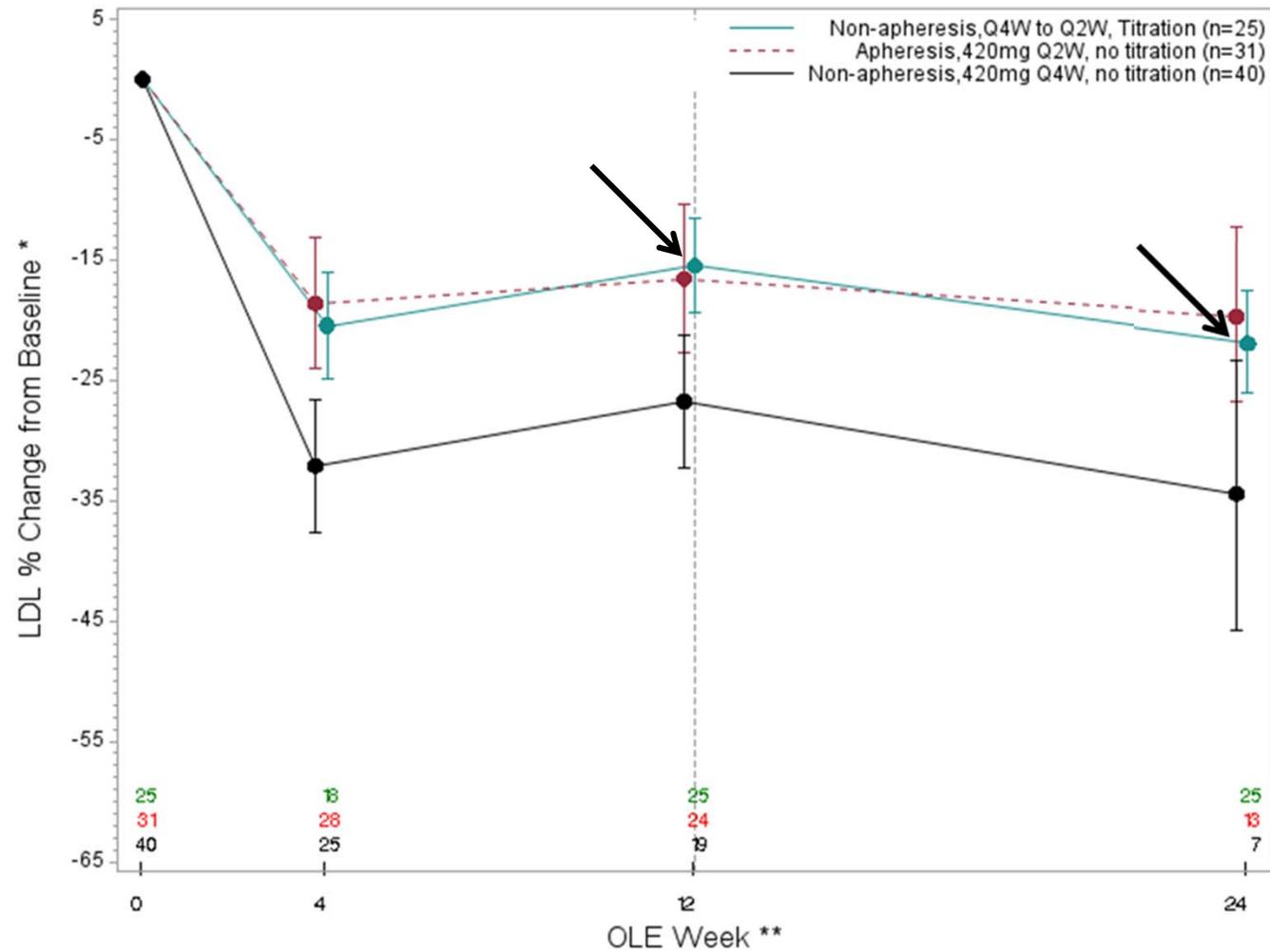
20110233 Week 12 420 mg QM	Placebo (n=16)	EvoMab N=33)	Trt difference (n=49)	P-value
<b>Secondary Endpoints</b>				
ApoB, %	4	-19	-23 (-35, -11)	<0.001
Lp(a), %	2	-9	-12 (-25, 2)	0.088
<b>Exploratory Endpoints</b>				
Non-HDL-C, %	8	-22	-30 (-42, -18)	<0.001
Total Cholesterol, %	8	-19	-27 (-38, -16)	<0.001
ApoB/ApoA1, %	5	-23	-28 (-39, -17)	<0.001
TC/HDL, %	4	-22	-26 (-38, -14)	<0.001
HDL-C, %	4	4	0 (-9, 9)	0.98
TG, %	-2	-1	0 (-15, 16)	0.97
VLDL, %	63	19	-44 (-128, 40)	0.30

## Efficacy Endpoint in HoFH Trial -271: Mean (SE)% LDL-C Change

20110271	Overall HoFH N=96	Non- apheresis N=65	Apheresis N=31	EvoMab 420 mg Titration (Non-apheresis)	
				QM	Q2W
Week 12	N=68	N=44	N=24	N=25	
LDL-C, % (SE)	-19 (3)	-20 (3)	-17 (6)	-16 (4)	
Week 24	N=45	N=32	N=13	N=25	
LDL-C, % (SE)	-23 (4)	-25 (4)	-20 (7)		-22 (4)

QM ⇒ Q2W associated with ~ 6% greater reduction in LDL-C.

# LDL % Change Among HoFH Patients in OLE Study



\* Baseline refers to previous study baseline or OLE baseline for new enrollees

\*\* Does not correspond to # of weeks on treatment with study medication

## Efficacy Conclusions

- Evolocumab provided robust decreases in LDL-C and other lipid parameters across the four 12-week trials.
- Evolocumab 140 mg Q2W dose and the 420 mg QM dose yield similar LDL-C reductions.
- Persistence of efficacy of the 420 mg monthly dose was demonstrated in the 52-week trial -109.
  - Evolocumab was effective across all subgroups .
- HoFH trial -233: evolocumab, compared to placebo, significantly reduced LDL-C from baseline to Week 12 by 31%.
  - Mean change from BL to Week 12 within EvoMab arm alone was -23%.
- Open-label HoFH extension trial -271: Evolocumab resulted in LDL-C reductions of 19% at Week 12 and 23% at Week 24.
  - Increasing the frequency of dosing from 420 mg QM to 420 mg Q2W associated with modest reduction of LDL-C.

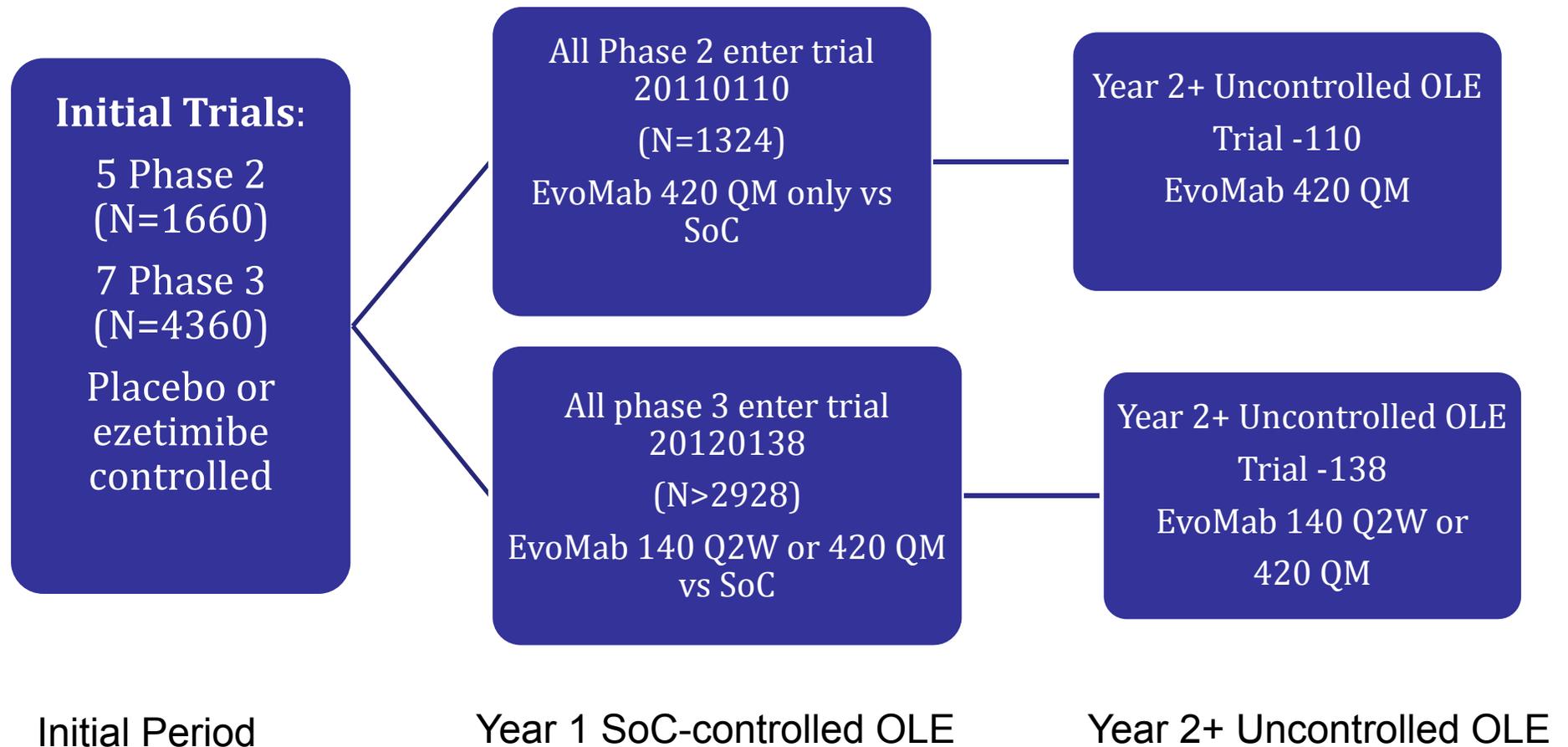


# SAFETY

# Outline

- Evolocumab Exposure in Safety Database
- Adverse Events Overview
- Safety Concerns
  - Diabetes Mellitus
  - Pancreatitis
  - Neurocognitive Findings
  - Safety in Low LDL-C Subgroup
  - Anti-evolocumab Antibody Formation
  - Hypersensitivity
  - Musculoskeletal Issues
  - Hepatic Issues
  - Cardiovascular Events
  - Safety of the 420 mg Q2W dose

# Datasets for Primary Hyperlipidemia Safety Analysis



# Evolocumab Exposure in Primary Hyperlipidemia Safety Database

	Any Placebo	Any Control <sup>a</sup>	EvoMab 140 mg Q2W or 420 mg QM
# of Subjects	1526	3027	4783
≥ 3 months	1501	2988	4654
≥ 6 months	294	1444	3276
≥ 12 months	287	718	1760
≥ 24 months	0	1	598

Approximate # of participants treated with evolocumab for ≥ 1 year:

- 350 with CVD
- 500 at high and 150 at mod-hi CVD risk
- 180 with diabetes
- 460 on high- and 560 on moderate-intensity concomitant statin
- 440 ≥ 65 years old

a: Includes placebo, ezetimibe or standard of care

## Duration of Study Drug Exposure During Initial Trials

	CONTROL			EVOMAB		
Duration in months	Placebo Q2W (N = 586)	Placebo QM (N = 940)	Ezetimibe (N = 554)	140 mg Q2W (N=1245)	420 mg QM (N=1956)	420 mg QM + Eze. (N = 30)
Mean	2.7	5.5	2.7	2.6	5.3	2.8
Median	2.8	2.8	2.8	2.8	2.8	2.8
Min, Max	0.3, 3.4	0.1, 12.3	0.5, 3.4	0, 3.3	0.4, 12.3	1.9, 2.9

### Safety Population:

- Mean age: 58 years, 30% ≥ 65 years of age, 51% female, 83% white
- 19% CAD, 2% stroke, 13% T2DM, 51% HTN
- 34% at high and 10% at moderately-high CHD risk by ATP III
- 30% on concomitant high-intensity statin
- 38% on concomitant moderate-intensity statin
- Baseline LDL-C: 127 mg/dL (range 119-194 mg/dL)

## Duration of Study Drug Exposure during the Year 1 SoC-Controlled Period of the Open-label Extension Studies

- The median duration of exposure to control or evolocumab for the year 1 SoC-controlled period: 7.4 months.
- Some of the limitations of these OLE studies include:
  - Reporting bias by either patients or investigators
  - Represents a select and smaller group of patients who tolerated therapy in the randomized trial and agreed to participate in the OLE study

## Key Exclusion Criteria in Phase 2/3 Trials for Safety

- MI, unstable angina, PCI, CABG or stroke within 3 months
- Uncontrolled serious cardiac arrhythmia
- CHF- NYHA Class III or IV (II - IV for -114) or last LVEF < 30%
- Uncontrolled HTN, hypo/hyperthyroidism
- Type 1 diabetes; newly diagnosed or poorly controlled T2DM
- CK > 3 x ULN
- Significant hepatic disease (AST or ALT > 2x ULN)
- Significant renal disease (eGFR < 30 ml/min/1.73m<sup>2</sup>)
- Diagnosis of DVT or PE within 3 months
- Malignancy within last 5 years (except for non-melanoma skin cancer, etc)

## Evolocumab Exposure in Trial -271: HoFH Safety Database

<b>Duration of Exposure</b>	<b>EvoMab 420 mg QM or 420 mg Q2W</b>
Total # of Subjects	96
≥ 8 weeks	84 (88%)
≥ 12 weeks	69 (72%)
≥ 24 weeks	47 (49 %)
<b>Evolocumab Exposure (months)</b>	
Mean	6.4
Median	5.1
Min, Max	0.1, 21.1

Trial 233: 11 adolescents with HoFH; Trial 271: 14 adolescents with HoFH

## # of Subjects Exposed to the Evolocumab 420 mg Q2W Dose in HoFH Safety Database

	Any 420 mg Q2W		
	Q2W Only <sup>a</sup>	QM and Q2W <sup>b</sup>	Total
HoFH Subjects	27	34	61
<i>Non-apheresis subjects (began on QM)</i>	0	30	30
<i>Apheresis subjects (began on Q2W)</i>	27	4	31

a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.

b Apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM, or non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W.

## Exposure Duration for Evolocumab 420 mg Q2W Dose in Trial -271 (120-day Safety Update; 01 July 2014)

	20110271: HoFH		
	Q2W Only <sup>a</sup>	QM and Q2W <sup>b</sup>	QM Only <sup>c</sup>
HoFH Subjects	28	47	25
Median Exposure (months)	7.1	12.5	5.5
Mean Exposure (months)	6.7	11.5	6.3

a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.

b Apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM, or non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W.

c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM



## Summary of Adverse Events in Phase 3 Trials

	20110114 (Monotherapy)			20110115 (Statin Combination)			20110116 (Statin-Intolerant)		20110117 (HeFH)		20110109	
	12 week (N = 614)			12 week (N = 1896)			12 week (N=307)		12 week (N=329)		52 week (N=601)	
	Pbo	Eze.	EvoMab	Pbo	Eze	EvoMab	Eze	EvoMab	Pbo	EvoMab	Pbo	EvoMab
	N=154	N=154	N=306	N=558	N=221	N=1117	N=102	N=205	N=109	N=220	N=302	N=599
<b>AEs, %</b>	44	46	44	39	40	36	73	66	49	56	74	75
<b>SAEs, %</b>	<1	<1	1	2	<1	2	4	3	5	3	4	6
<b>AEs led to D/C of IP, %</b>	4	3	2	2	2	2	13	8	0	0	1	2
<b>Fatal AEs, %</b>	0	0	0	<1	0	0	0	0	0	0	0	<1

## Primary Hyperlipidemia: AE Overview: Deaths

- Deaths: Total of 15 deaths (any cause)
  - Initial trials: 1 (0.05%) control vs 3 (0.08%) EvoMab
  - Year 1 SoC-controlled OLE: 4 (0.3%) SoC vs 3 (0.1%) EvoMab
  - Year 2+ OLE: 2 (0.3%) EvoMab
  - End of Initial trial: 1 on placebo and 1 on EvoMab
- CV deaths: Total of 11 of 15 deaths deemed CV
  - Initial trials: 2 (0.1%) control vs 4 (0.1%) EvoMab
  - Year 1 SoC-controlled OLE: 1 (0.1%) SoC vs 3 (0.1%) EvoMab
  - Year 2+ OLE: 1 (0.1%) EvoMab

## Serious Adverse Events (SAEs) Overview

- Initial trials:
  - 2.4% placebo vs 2.1% any control vs 3.0% EvoMab Q2W/QM group
  - Small increase seen in EvoMab group for
    - Cardiac Disorders SOC: Pbo 0.3% vs EvoMab 0.7%
    - Preferred Terms Pancreatitis, Appendicitis, Pneumonia and Back pain: all Pbo 0% vs EvoMab 0.1%
- Year 1 SoC-controlled OLE: 5.8% SoC vs 5.4% EvoMab
  - Most common osteoarthritis, angina pectoris and MI
- HoFH trial -271: 7 (7.3%) primarily cardiac in nature

## Primary Hyperlipidemia: AE Overview: AEs that Led to Study Drug Discontinuation

- Initial Trials
  - 1.6% placebo group vs 2.3% any control vs 2.2% EvoMab Q2W/QM group
  - Small increase seen in EvoMab group for nausea
- Year 1 SoC-controlled OLE: EvoMab 2.0%
  - SoC control group did not receive control study drug
    - EvoMab—myalgia most common AE (0.2%)
- Year 2+ uncontrolled OLE: 1.0% reported
  - Notable AE preferred terms include angioedema, drug eruption and pruritus.

## Primary Hyperlipidemia: AE Overview: Common Adverse Events

- Integrated Initial trials: # of subjects reporting AEs balanced between dosing regimens

	Any Placebo (N = 1526) n (%)	Any Control (N = 2080) n (%)	EvoMab (N = 3201) n (%)
Subjects with AEs	753 (49.3)	1031 (49.6)	1599 (50.0)
Upper resp tract infection, %	2.8	2.7	3.2
Headache, %	3.0	3.2	3.1
Back Pain, %	2.9	2.7	3.1
Influenza, %	2.1	2.0	2.3
Myalgia, %	1.8	2.6	2.2
Nausea, %	1.6	1.8	2.1

## Primary Hyperlipidemia: AE Overview: Common Adverse Events

- Year 1 SoC-controlled OLE:
  - SoC 55% vs EvoMab + SoC 60%
  - Most common AEs where EvoMab > SoC
    - Nasopharyngitis: 7.9% SoC vs 8.5% EvoMab
    - Upper resp. tract inf: 4.0% SoC vs 4.2% EvoMab
    - Arthralgia: 2.5% SoC vs 3.4% EvoMab
    - Back pain: 2.5% SoC vs 3.1% EvoMab
    - Hypertension: 2.7% SoC vs 3.1% EvoMab
    - Influenza: 2.6% SoC vs 3.0% EvoMab

## Adverse Events of Special Interest

- **Diabetes Mellitus**
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

## Glucose Homeostasis and Diabetes Analysis

- Does the LDL receptor play a role in risk of developing T2DM? <sup>1,2</sup>
- PCSK9 and LDLR are expressed in insulin-producing pancreatic islet  $\beta$  cells
  - some animal data suggests this may affect function of these cells<sup>3, 4</sup>
- Diabetes Analysis: Adverse Events consistent with DM
  - Hyperglycaemia-new onset DM standard MedDRA query (SMQ)
    - Initial trials: 0.8% for both placebo and EvoMab
    - Year 1 SoC-controlled period: SoC: 1.6% vs EvoMab: 2.1%

1 Besseling et al. JAMA 2015

2 Preiss et al. 2015

3 Mbikay M et al. FEBS Letters 2010

4 Ishikawa et al. J. Lipid Res 2008

## Diabetes Mellitus Analysis (2)

- New Onset DM Analysis: fasting blood glucose (FBG) subgroups without diabetes mellitus
  - normoglycemic at initial study baseline (ie, FBG < 100 mg/dL at study day 1)
  - baseline impaired fasting glucose (IFG)<sup>1</sup> at initial study baseline
  - Combination of the above groups
- Excluded from analysis due to pre-existing DM
  - Subjects with a medical history of DM, diabetes medication use or FBG  $\geq$  126 mg/dL at baseline
  - Subjects who developed new onset DM in one of the initial trials were excluded from the Year 1 SoC-controlled analysis

<sup>1</sup> FBG of 100 to < 126 mg/dL at the latest time point prior to or on initial study day 1

## Diabetes Mellitus Analysis (3)

- New onset DM definition
  - Laboratory data
  - Adverse event data
  - Concomitant medication data
  
- Baseline characteristics of treatment groups
  - slightly higher incidence of baseline HbA1c  $\geq 6.5\%$  in subjects randomized to evolocumab.

## Incidence of New Onset DM in Initial Trials

Subjects from the Initial Trials with	Any Placebo (N=1343) n (%)	EvoMab 140 mg Q2W or 420 mg QM (N=2753) n (%)
Baseline FBG < 126 mg/dL (normoglycemia or IFG)	1329	2721
<b>Post baseline new onset diabetes</b>	<b>11 (0.8)</b>	<b>31 (1.1)</b>
Baseline normoglycemia (FBG < 100 mg/dL)	901	1778
<b>Post baseline new onset diabetes</b>	<b>0</b>	<b>2 (0.1)</b>
<b>Baseline IFG (<math>100 \leq \text{FBG} &lt; 126</math> mg/dL)</b>	428	943
<b>Post baseline new onset diabetes</b>	<b>11 (2.6)</b>	<b>29 (3.1)</b>

## Incidence of New Onset DM: Year 1 SoC-controlled Studies (datacut 1 July 2014)

Subjects from the Year 1 SoC-controlled studies with	SoC (N=1257) n (%)	EvoMab + SoC (N=2550) n (%)
<b>Baseline FBG &lt; 126 mg/dL (normoglycemia or IFG)</b>	1246	2523
<b>Post baseline new onset diabetes</b>	<b>13 (1.0)</b>	<b>38 (1.5)</b>
<b>Baseline normoglycemia (FBG &lt; 100 mg/dL)</b>	834	1647
<b>Post baseline new onset diabetes</b>	<b>3 (0.4)</b>	<b>9 (0.5)</b>
<b>Baseline IFG (100 ≤ FBG &lt; 126 mg/dL)</b>	412	876
<b>Post baseline new onset diabetes</b>	<b>10 (2.4)</b>	<b>29 (3.3)</b>

## Diabetes Summary

- In the longer duration trials in those with IFG at baseline, slightly greater proportion of EvoMab-treated patients with new onset DM by AE, lab data or initiation of DM medications.
- Majority of patients glycemic status remained stable
- Changes in glucose homeostasis are monitorable and treatable
- With statins, we believe that the modest diabetogenic effect is outweighed by the CV event reduction, which has been shown in CV outcomes trials in patients with diabetes.

## Adverse Events of Special Interest

- Diabetes Mellitus
- **Pancreatitis**
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

## Pancreatitis Events

- Non-clinical:
  - No drug-related pancreas lesions observed with evolocumab in any species.
  - No convincing evidence of gallbladder adverse effects observed with evolocumab
- As 01 July 2014: 7 participants with 8 events of pancreatitis.
  - All participants had been exposed to EvoMab in either initial trial and/or OLE trial

## Pancreatitis Events (2)

- 3 cases in initial trials (0.08% EvoMab vs 0% control)
- 5 events of pancreatitis occurred in OLE period
  - 3 occurred in evolocumab+SoC arm
  - 2 occurred in SoC control arm
    - Remote history (hx) of evolocumab exposure, not likely to be drug-related
- Conclusion:
  - Overall incidence low but all had current or remote EvoMab exposure.
  - Cases confounded by hx of gallstones, cholecystitis or diabetes; concomitant meds associated w/ pancreatitis such as valproate; scheduled endoscopic procedure w/ puncture of pancreatic cyst and alcohol use.

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- **Neurocognitive Findings**
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

# Neurocognitive Events

- Theoretical concern for neurocognitive issues in the setting of chronic low LDL levels
- Central nervous system
  - Evolocumab unlikely to cross blood brain barrier (BBB) due to size
  - Peripheral cholesterol transfer blocked by BBB
  - Brain cholesterol derived by de novo synthesis<sup>1</sup>
  - Brain largely independent from circulating cholesterol levels

<sup>1</sup> Björkhem et al. Arterioscler Thromb Vasc Biol. 2004

# Neurocognitive Analysis

- Analysis using neurocognitive-related adverse event terms
  - deliria (including confusion)
  - cognitive and attention disorders and disturbances
  - dementia and amnesic conditions
  - disturbances in thinking and perception
  - mental impairment disorders
- Initial Trial Period
  - Neurocognitive AEs: 6 (0.3%) any control vs 5 (0.1%) EvoMab

## Neurocognitive Analysis: Year 1 SoC-controlled OLE

- Year 1 SoC-controlled OLE Period
  - Neurocognitive AEs: 3 (0.2%) control vs 16 (0.6%) EvoMab
- 16 subjects reporting AEs on EvoMab
  - 13 of 16 participants had  $\geq 1$  risk factor for neurocognitive events (previous memory loss, hx of depression, concurrent statins, concomitant meds such as benzodiazepine, gabapentin and topiramate)
  - For the majority of the cases, treatment with evolocumab was continued without interruption.

## Nervous System and Psychiatric Disorders

### Exploratory Analysis: EvoMab-Achieved Low LDL Subgroups

- Achieved LDL-C < 40 mg/dL subgroup vs  $\geq$  LDL-C 40 mg/dL subgroup
  - Not randomized comparisons
- Baseline characteristics of LDL < 40 mg/dL subgroup:
  - Lower baseline lipid levels
  - More baseline statin use and more use of moderate- and high-intensity statins
  - Slightly greater % with coronary artery disease, diabetes or hypertension

# Nervous System/Psychiatric Disorders

## Exploratory Analysis (2)

- Initial trials and Year 1 SoC-controlled OLE studies
  - Few nervous system/psychiatric disorder events and no notable imbalance among LDL subgroups
- Narratives for neurocognitive events and LDL-C < 40 mg/dl
  - Cases were confounded by other conditions or medications that could also affect cognitive function.
  - Many of these participants had an LDL-C > 40 mg/dL prior to the event.

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- **Safety in Low LDL-C Subgroup**
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

# Low LDL-C Subgroups in Initial Trials

	LDL-C < 40 mg/dL	LDL C ≥ 40 mg/dL	
	Any EvoMab N=2565	Any EvoMab N=1339	Control N=2038
<b>Median exp., months</b>	3.2	3.0	3.2
<b>All AEs</b>	1308 (51.0%)	696 (52.0%)	1018 (50.0%)
<b>SAEs</b>	70 (2.7%)	35 (2.6%)	41 (2.0%)
<b>Nervous System Disorders SOC</b>	7.1%	8.4%	8.0%
amnesia	<0.1%	0.1%	0%
memory impairment	0%	0.1%	<0.1%
paraesthesia	0.6%	0.5%	0.4%
<b>Psychiatric Disorders SOC</b>	1.9%	2.5%	2.0%
disorientation	0%	0.1%	0.1%
<b>Other AEs of interest</b>			
DM	0.3%	0.3%	0.3%
Type 2 DM	0.2%	0.1%	0.2%
Hyperglycaemia	0.1%	0.2%	0.1%
<b>Eye Disorder SOC</b>	1.4%	1.7%	1.4%

# Low LDL-C Subgroups in Year 1 SoC-controlled OLE Studies

	LDL-C <40 mg/dL	LDL C ≥ 40 mg/dL	
	EvoMab+SoC: N=1369	EvoMab+SoC N=1427	SoC alone: N=1380
<b>Median exposure, months</b>	8.2	7.2	7.4
<b>All AEs</b>	814 (59.5%)	882 (61.8%)	774 (56.1%)
<b>SAEs</b>	68 (5.0%)	85 (6.0%)	80 (5.8%)
<b>Nervous System Disorders SOC</b>	<b>8.5%</b>	<b>8.5%</b>	<b>7.2%</b>
memory impairment	0.3%	0.2%	0.1%
amnesia	0.1%	0%	0.1%
mental impairment	0.1%	0.1%	0%
hypoesthesia	0.4%	0.6%	0.4%
paraesthesia	0.4%	0.8%	0.5%
neuropathy peripheral	0.4%	0%	0.1%
<b>Other AEs of interest</b>			
Diabetes	1.5%	0.6%	0.4%
Type 2 DM	0.4%	0.6%	0.4%
Hyperglycaemia	0.4%	0.1%	0.2%
<b>Eye Disorders SOC</b>	<b>3.1%</b>	<b>2.5%</b>	<b>2.0%</b>
Cataract	0.8%	0.8%	0.8%

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- **Anti-evolocumab Antibody Formation**
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

## Anti-evolocumab Antibody Formation

- 0.1% (7 out of 4846) participants developed binding antibodies after at least one dose of evolocumab.
- Four out of these 7 participants transiently positive (negative at the last time point tested)
- No one has developed neutralizing antibodies.
- From the 2 studies supporting the indication in patients with HoFH, no one developed anti-evolocumab antibodies.
- No temporal correlation between the development of binding antibodies and SAEs or specific adverse events, such as hypersensitivity.

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- **Hypersensitivity**
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

# Hypersensitivity

- Hypersensitivity SMQ (narrow search)
  - Includes MedDRA High Level Terms such as dermatitis, rashes, urticaria and angioedema
- Initial Trials
  - Placebo 2.4% vs Control 2.4% vs EvoMab 3.2%
- Year 1 SoC-controlled OLE Studies
  - Control 3.3% vs EvoMab 4.4%
- Year 2+ OLE Studies
  - EvoMab 5.7%

## Hypersensitivity (2)

- 9 hypersensitivity events in 8 participants (2 control: 6 EvoMab) across the 3 treatment periods
- 6 EvoMab cases of hypersensitivity:
  - 4 reported antibiotic-associated drug hypersensitivity
  - 1 reported urticaria related to oral prednisone administration
  - 1 reported related to EvoMab
- EvoMab 140 mg Q2W: 2 events on same day
  - 68 yr-old male in trial 116 (statin-intolerant):
  - 16 days after 1<sup>st</sup> dose and 1 day after last dose of EvoMab prior to event → swelling of throat and sore throat
  - Received 2 additional doses over next 4 weeks
  - Events resolved day after last dose of EvoMab
  - Led to withdrawal of EvoMab

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- **Musculoskeletal Issues**
- Hepatic Issues
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

## Musculoskeletal Adverse Events

- Initial trials:
  - 12.8% placebo vs 13.7% any control vs 14.6% EvoMab
- Most common AEs where EvoMab > placebo
  - Back pain: 3.1% EvoMab vs 2.9% placebo vs 2.7% control
  - Myalgia: 2.2% EvoMab vs 1.8% placebo vs 2.6% control
- Year 1 SoC-controlled OLE period:
  - 15.2% SoC vs 19.1% EvoMab
- Most common AEs where EvoMab > control
  - Arthralgia (3.4%, vs 2.5%); back pain (3.1% vs 2.5%); myalgia (2.5% vs 2.4%); pain in extremity (2.5% vs 1.5%)

## Creatine Kinase (CK) Elevations

- Initial trials:
  - CK > 5xULN: 0.7% placebo vs 0.7% any control vs 0.6% EvoMab
  - CK > 10xULN: 0.3% placebo vs 0.2% any control vs 0.2% EvoMab
- Year 1 SoC-controlled OLE period:
  - CK > 5xULN: 1.2% SoC vs 0.5% EvoMab
  - CK > 10xULN: 0.6% SoC vs 0.2% EvoMab
- Confounding factors include concurrent severe hypothyroidism, muscle and joint injuries, tendonitis, and concomitant statin therapy

## Phase 1 Studies: CK > 10xULN

- Enrolled healthy individuals not on concomitant statin therapy
- white male after a single dose of EvoMab 210 mg:
  - Day 22: CK 4xULN;
  - Day 24: CK 51xULN;
  - associated activity of walking at car show;
  - Day 26: CK near normal and within normal range at following visits;
  - Creatinine remained normal; investigator considered this a treatment-related AE

## Phase 1 Studies: CK > 10xULN (2)

- 26 year-old black male: received 2 doses of EvoMab separated by ~8 weeks:
  - Screening: CK 2.6xULN; Baseline: CK 2.1xULN; creatinine 1.3 mg/dL
  - Day of 2<sup>nd</sup> and last dose: CK 1.6xULN; creatinine 1.4 mg/dL
  - End of study visit (56 days after 2<sup>nd</sup> dose): CK 15.3xULN; AE of rhabdomyolysis reported
  - 3 days later: CK 62.2 xULN
  - 2 weeks later: CK 2.3xULN, AE reported as resolved
  - Not hospitalized, no associated muscle sx's, no other AEs reported; not related according to investigator

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- **Hepatic Issues**
- Cardiovascular Events
- Safety of 420 mg Q2W Dose

## Hepatobiliary Disorders Adverse Events

- Initial trials:
  - SAEs: 0.1% any control vs 0.1% any EvoMab
  - AEs: 0.4% any control vs 0.3% EvoMab
  
- Year 1 SoC-controlled OLE Period:
  - SAEs: 0.1% control vs 0.1% EvoMab
  - AEs: 0.6% control vs 0.5% EvoMab

# Transaminase Elevations

- Initial trials:
  - ALT or AST > 5xULN: 0.3% control vs 0.2% EvoMab
  - No cases of ALT/AST >3 x ULN and total bilirubin > 2 x ULN
- Year 1 SoC-controlled OLE Period
  - ALT or AST > 5xULN: 0.3% control vs 0.2% EvoMab
  - 2 cases of AST/ALT levels >3 x ULN and total bilirubin > 2 x ULN or INR>1.5
    - 1st case: 3 days after admitted to rehabilitation for alcohol detox;
    - 2nd case (SAE of hepatic function abnormality): Liver biopsy c/w drug-induced hepatitis. LFTs eventually normalized after suspending nitrofurantoin, evolocumab, simvastatin, diclofenac and other medications.

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- **Cardiovascular Events**
- Safety of 420 mg Q2W Dose

# Adjudicated Cardiovascular Events: Trial -109

	<b>Trial 20110109</b>	
	52-week ; blinded, placebo-controlled	
	Placebo (N = 302) n (%)	EvoMab: 420 mg QM (N = 599) n (%)
<b># of participants with any positively adjudicated CV event</b>	<b>2 (0.7)</b>	<b>6 (1.0)</b>
Median exposure, months	12	12
Death (all cardiovascular)	0	3 (0.5)*
Non-fatal myocardial infarction	0	1 (0.2)
Revascularization (PCI or CABG)	2 (0.7)	1 (0.2)
Cerebrovascular event (TIA)	0	1 (0.2)

\*One adjudicated event of Death occurred during the 30day follow up.  
This subject completed study 3 weeks prior to Death.

## Adverse Events of Special Interest

- Diabetes Mellitus
- Pancreatitis
- Neurocognitive Findings
- Safety in Low LDL-C Subgroup
- Anti-evolocumab Antibody Formation
- Hypersensitivity
- Musculoskeletal Issues
- Hepatic Issues
- Cardiovascular Events
- **Safety of 420 mg Q2W Dose**

# Safety of the 420 mg Q2W Dose

## Data Cutoff 01 July 2014

	20110271: HoFH		
	Q2W Only <sup>a</sup>	QM and Q2W <sup>b</sup>	QM Only <sup>c</sup>
# of Participants N (%)	28	47	25
Adverse events	23 (82.1)	29 (61.7)	16 (64.0)
SAEs	4 (14.3)	6 (12.8)	0
AEs leading to d/c of evolocumab	0	1 (2.1)	0

a Apheresis subjects who did not switch from their initial dose of 420 mg Q2W.  
b Non-apheresis subjects who switched from their initial dose of 420 mg QM to 420 mg Q2W, and apheresis subjects who switched from their initial dose of 420 mg Q2W to 420 mg QM.  
c Non-apheresis subjects who did not switch from their initial dose of 420 mg QM.

## Evolocumab Benefit:Risk Profile

### Potential Benefits

- Evolocumab (420 mg QM): reduces LDL-C by ~ 60% after 12 and 52 weeks of treatment.
- Evolocumab, at doses of 140 mg Q2W and 420 mg QM, yield similar LDL-C reductions.
- In patients with HoFH, evolocumab (420 mg QM), compared to placebo, reduced LDL-C from baseline to Week 12 by 31%.
  - The mean LDL reduction from baseline to Week 12 within the evolocumab arm alone was 23%.
  - Increasing to 420 mg Q2W associated with a small LDL reduction.
- Efficacy limitation: The effect of evolocumab on cardiovascular morbidity and mortality in any population has not been determined

# Evolocumab Benefit:Risk Profile

## Potential Risks

- No marked disparities in deaths, SAEs or AEs leading to discontinuation between evolocumab and control groups
- Safety database for 140 mg Q2W/420 mg QM doses: limited in long-term, placebo-controlled data in patients with substantial CVD burden.
- Limited amount of safety and efficacy data for the 420 mg Q2W dose.
- Given the potential for widespread use, even small observed differences in events, if true, would have significant public health implications.
- Potential safety issues identified in evolocumab-treated subjects:
  - a small increased incidence in pancreatitis and hypersensitivity /skin-related adverse reactions
  - possible increase in new onset DM in those with baseline IFG
  - musculoskeletal AEs and CK elevations, which may have been confounded by statin use
  - transaminase elevations and hepatobiliary AEs, which may have been confounded by concomitant use of statins and other medications
  - adverse reactions that may be related to chronic, low levels of LDL-C induced by a drug that have yet to be identified

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