Update on PCSK9 Inhibitors and New Therapies

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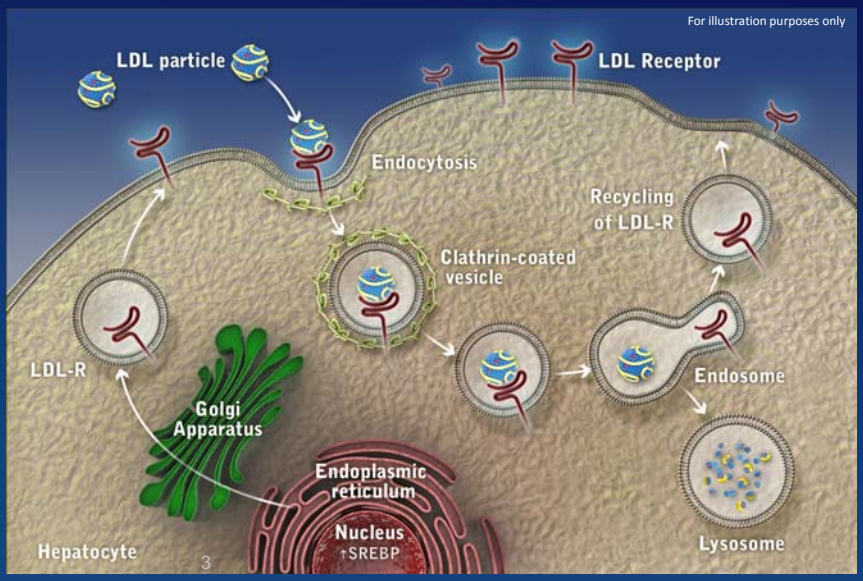
Disclosures
Consultant on development of PCSK9 inhibitors for Amgen, Regeneron/Sanofi, Genentech/Roche and BMS.

PCSK9 Inhibition: insights into a new therapeutic approach for the lowering of LDL cholesterol

- PCSK9 monoclonal antibodies in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
  - Non familial hypercholesterolemia
    - Monotherapy
    - Added to statins
    - Statin adverse patients
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
- Emerging CVD data and Outcomes trials

LDL Receptor Function and Life Cycle



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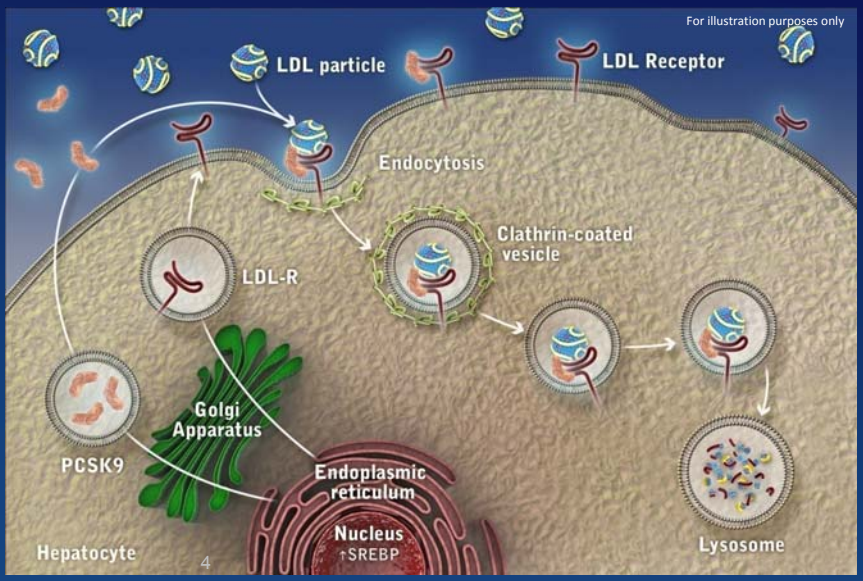
The Role of PCSK9 in the Regulation of LDL Receptor Expression



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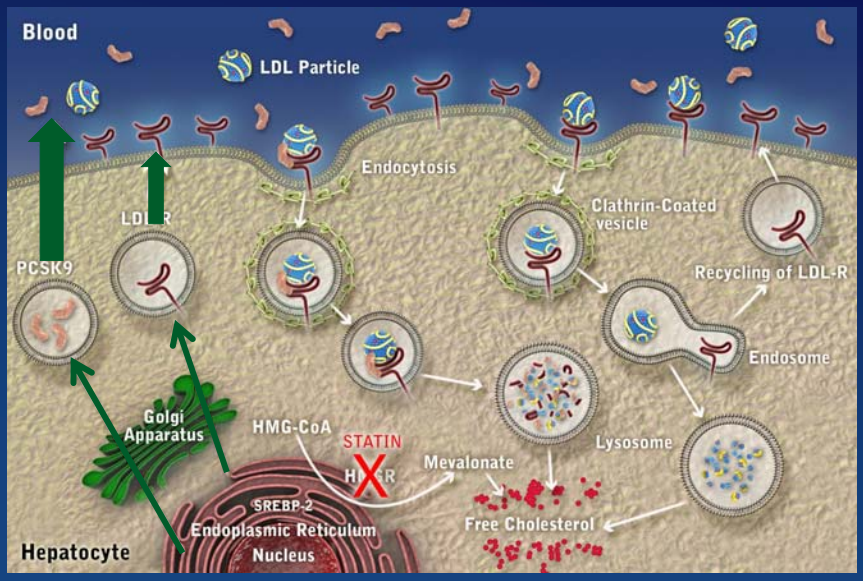
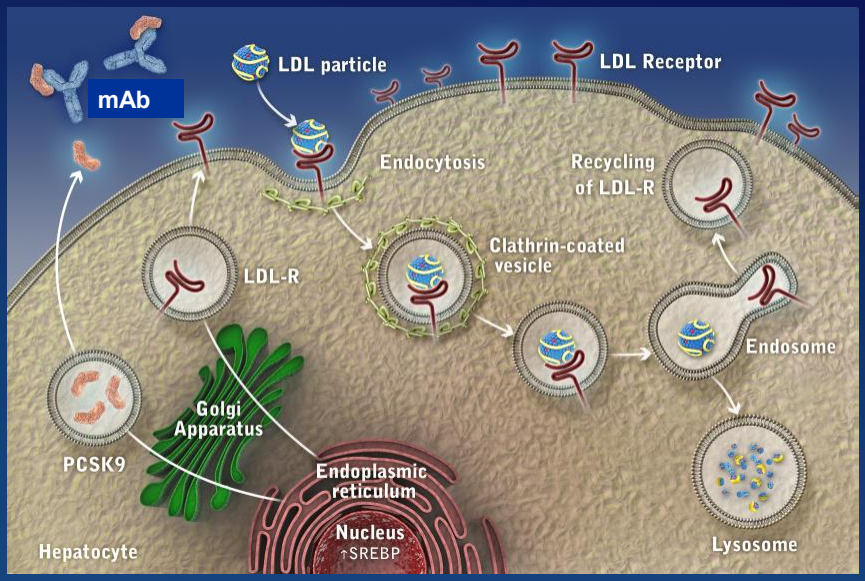
Statin Effect on PCSK9 & LDL receptor



Impact of an PCSK9 mAb on LDL Receptor Expression



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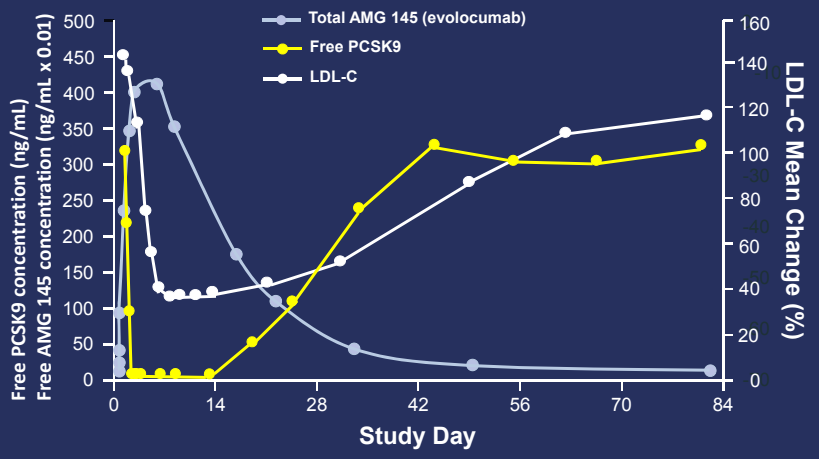
Pharmacokinetics and pharmacodynamics of evolocumab: changes in PCSK9 and LDL-C levels in response to evolocumab (AMG 145)



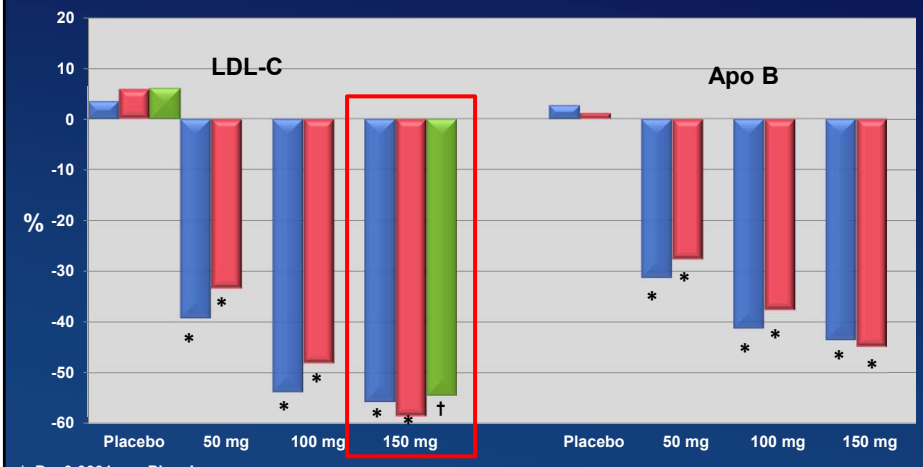
Stein EA & Raal FJ Annu. Rev. Med. 2014. 65:417–31.

REGN727/SAR236553* Dose Groups

REGN727/SAR236553 Dose	Patient Group	Total # Pts (R727:Pbo)	HeFH Status	Screening LDL-C (mg/dL)	Atorvastatin Dose
50mg	1	7 (5:2)	HeFH	>100	10-40 mg QD
	2	10 (8:2)	Non-FH	>100	10-40 mg QD
100mg	3	7 (5:2)	HeFH	>100	10-40 mg QD
	4	10 (8:2)	Non-FH	>100	10-40 mg QD
150mg	5	7 (5:2)	HeFH	>100	10-40 mg QD
	6	10 (8:2)	Non-FH	>100	10-40 mg QD
	7	10 (8:2)	Non-FH	>130	None (Diet alone)

*REGN727/SAR236553 is same as alirocumab.
Stein EA, et al. N Engl J Med. 2012;366(12):1108-18.

LDL-C and Apolipoprotein B Response
Mean % Change from Baseline with alirocumab



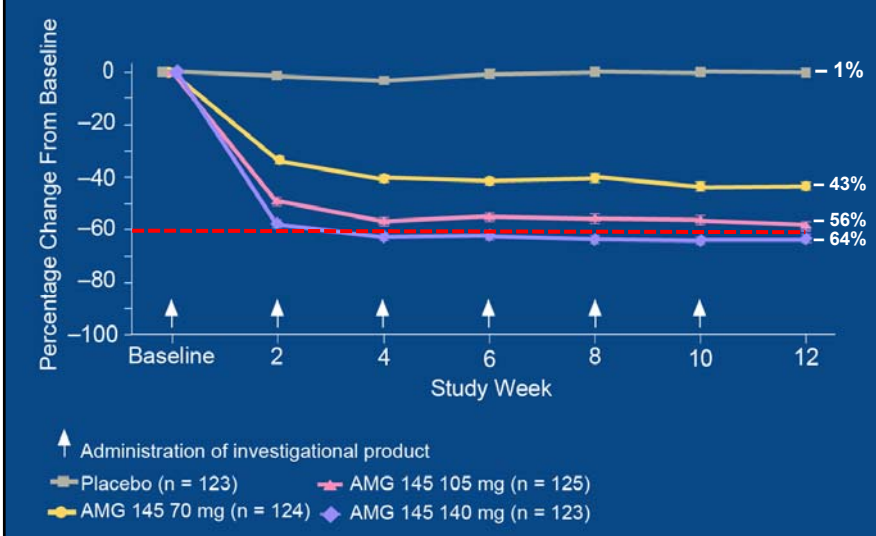
Stein EA, et al. N Engl J Med. 2012;366(12):1108-18.

Inhibition of PCSK9 with mAb

- Is there a limit to LDL-C reduction with a mAb?
- How long will effect last?

mAb = monoclonal antibody.

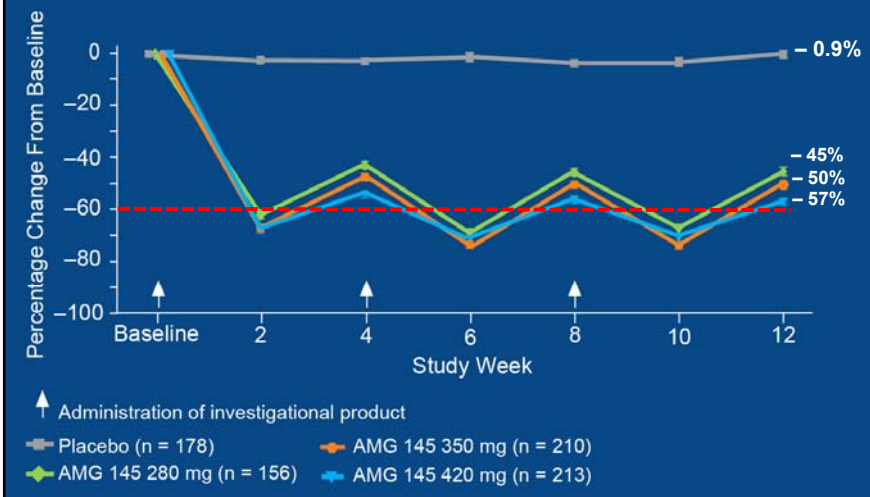
Evolocumab (AMG 145) Every 2 Weeks: LDL-C Percentage Change From Baseline



Mean percentage change from baseline in calculated LDL-C.

Stein EA, et al Euro Heart J 2014 doi:10.1093/eurheartj/ehu085

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 doi:10.1093/eurheartj/ehu085

Inhibition of PCSK9 with mAb

- **Is there a limit to LDL-C reduction with a mAb?**
  - **Yes – once all free PCSK9 is bound no additional LDL-C reductions occurs**
- **How long will effect last?**
  - **The larger the dose the longer the duration of the effect**
  - **'Rule of thumb' is it requires 3 times higher dose to achieve same reduction in LDL-C when dosed every 4 weeks than is required for every 2 week dosing (e.g. 140 Q2W = 420 mg Q4W)**
  - **The physical limitation on the amount of mAb in 1 mL is ~150 mg, thus larger doses require larger injection volumes**

PCSK9 Inhibition: Insights into a new therapeutic approach for the lowering of LDL cholesterol

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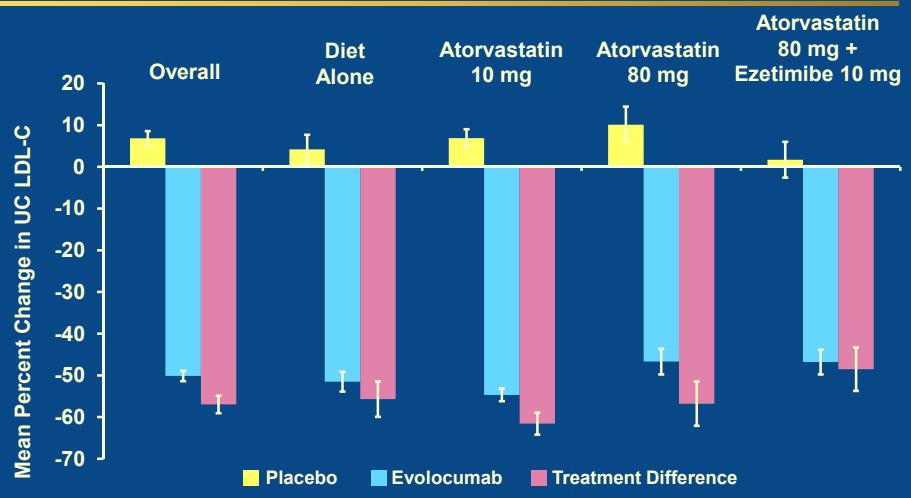
DESCARTES: % Change in LDL-C from baseline in patients on various background treatments



Error bars represent standard error for treatment difference
Treatment difference are least squares mean derived from a repeated measures model
UC LDL-C at week 52

Blom et al NEJM 2014:370:1809-19

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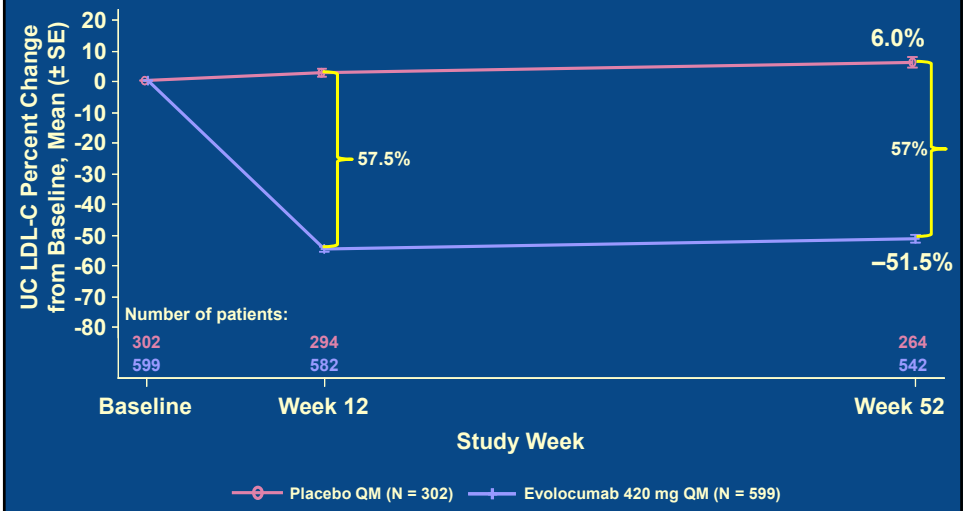
DESCARTES: Long term stability of LDL-C reduction



FAS = Full analysis set, UC = Ultracentrifugation

Blom et al NEJM 2014:370:1809-19

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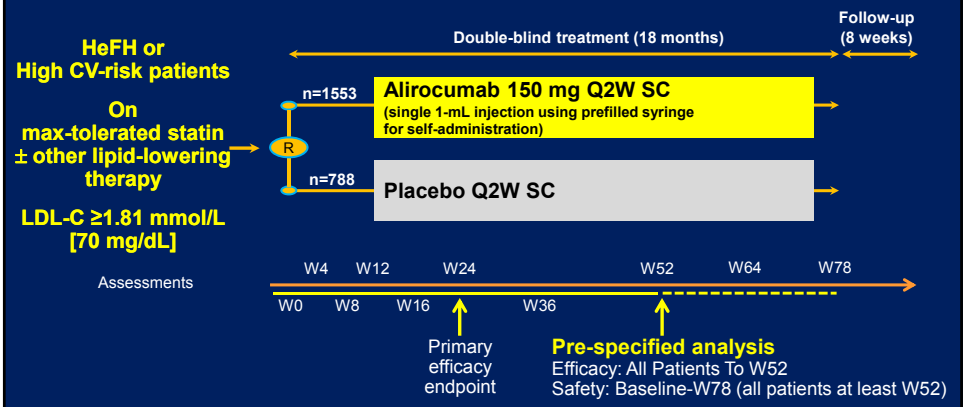
ODYSSEY LONG TERM Study Design



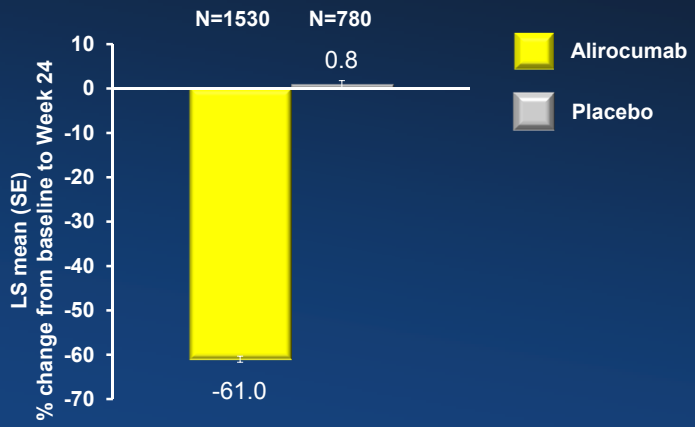
86% (2011/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)

ClinicalTrials.gov identifier: NCT01507831.

Robinson J et al ESC hotline session Barcelona Aug 31, 2014

ODYSSEY LONG TERM Study: LDL-C Reduction

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C
All patients on background of maximally-tolerated statin ± other lipid-lowering therapy



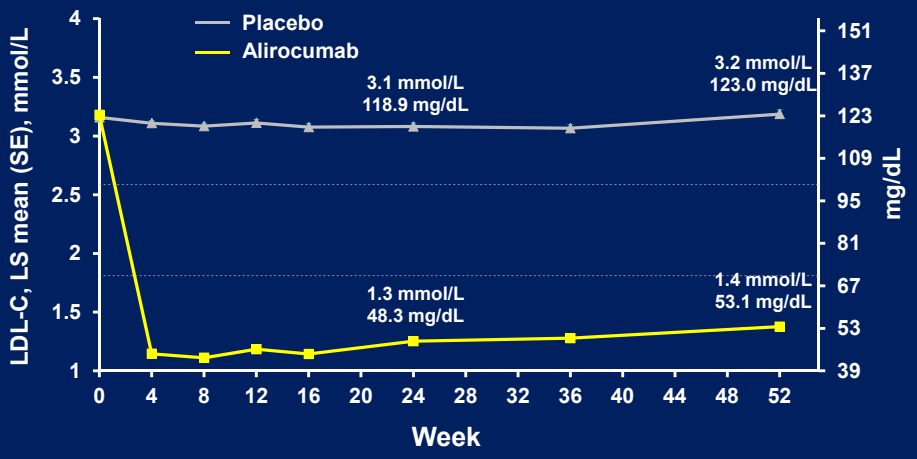
LS mean difference (SE) versus placebo:
−61.9% (1.3); *P*<0.0001

Presented by Robinson J. at the European Society of Cardiology Congress, Barcelona, Spain, August 31, 2014.

ODDYSSY Outcomes: Long term LDL-C reduction with alirocumab 150 mg Q2W

Achieved LDL-C Over Time

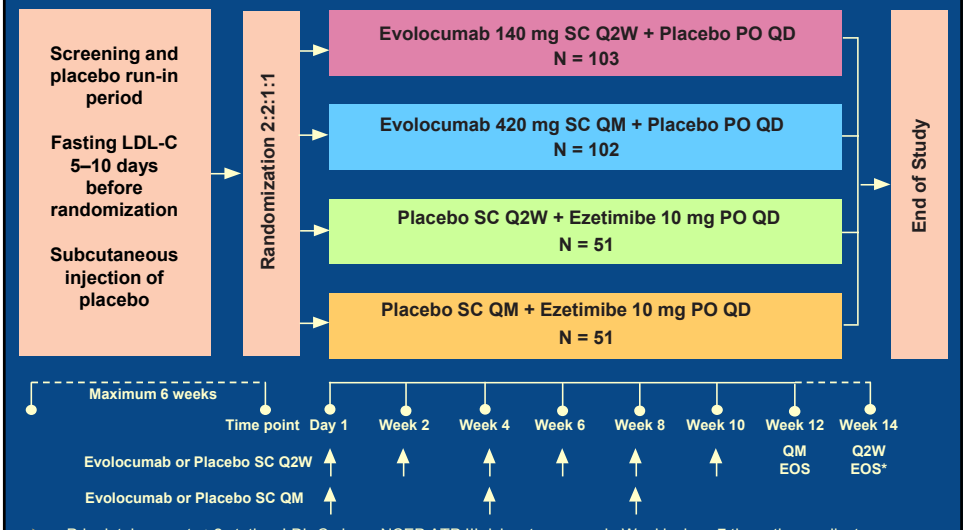
All patients on background of maximally-tolerated statin ±other lipid-lowering therapy



Intent-to-treat (ITT) analysis

Robinson J et al ESC hotline session Barcelona Aug 31, 2014

GAUSS-2 Study Design



- Prior intolerance to ≥2 statins: LDL-C above NCEP ATP III risk category goal : Weekly dose 7 times the smallest available tablet strength or less

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548

GAUSS-2: Statin Intolerance History

	Biweekly		Monthly	
	PBO Q2W + EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
Number of intolerable statins, %				
2	**100**	**100**	**100**	**100**
3	74	81	76	80
≥4	26	19	24	20
Worst muscle-related side effect*, %				
Myalgia	78	78	88	79
Myositis	22	19	8	19
Rhabdomyolysis	0	2	4	2
Any lipid-lowering therapy at baseline, %	29	33	31	36
Any statin at baseline	18	18	20	17

*Data missing for one patient in the evolocumab Q2W arm. EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily.

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548

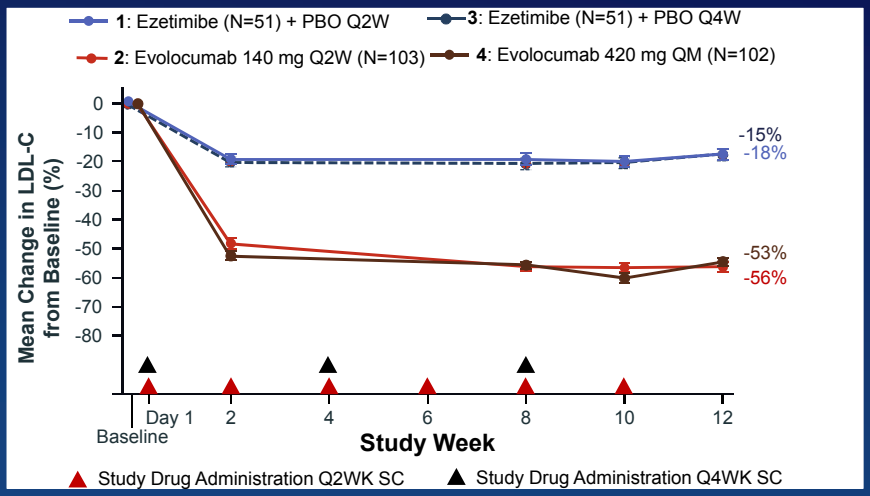
GAUSS-2: Key Baseline Lipids

	Biweekly		Monthly	
	PBO Q2W EZE QD (N = 51)	Evolocumab 140 mg Q2W + PBO QD (N = 103)	PBO QM + EZE QD (N = 51)	Evolocumab 420 mg QM + PBO QD (N = 102)
LDL-C*, mg/dL, mean (SD)	**195 (64)**	**192 (57)**	**195 (52)**	**192 (61)**
ApoB, md/dL, mean (SD)	140 (37)	140 (32)	140 (31)	133 (32)
Lp(a), nmol/L, median (Q1,Q3)	57 (22, 205)	39 (10, 101)	26 (7, 181)	31 (9, 80)
TG, mg/dL, median (Q1,Q3)	170 (120, 243)	165 (123, 224)	168 (124, 240)	139 (103, 190)
PCSK9, ng/mL, mean (SD)	317 (125)	285 (80)	295 (98)	266 (95)

*Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was <40 mg/dL (1.0 mmol/L) or triglyceride levels were >400 mg/dL (3.9 mmol/L).
EZE, ezetimibe; PBO, placebo; Q2W, biweekly; QM, monthly; QD, daily; TG, triglycerides.

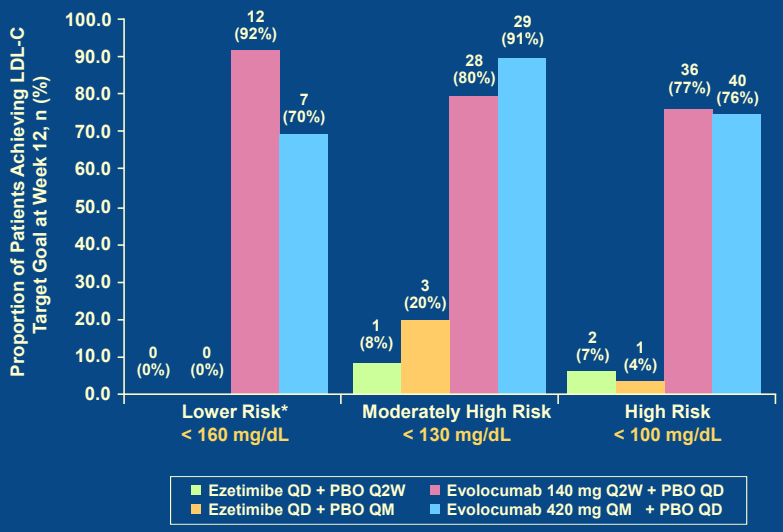
Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548

GAUSS-2: LDL-C Response to evolocumab Q2WK and Q4WK



Stroes, et al. *J Am Coll Cardiol*. 2014;63(23):2541-2548.

GAUSS-2: LDL-C Goal Achievement at Week 12



*Combination of NCEP ATP IIII moderate and low risk categories.
Rate based on subjects with observed values at Week 12 and LDL-C above target goal at baseline

Stroes et al J Am Coll Cardiol. 2014;63(23):2541-2548

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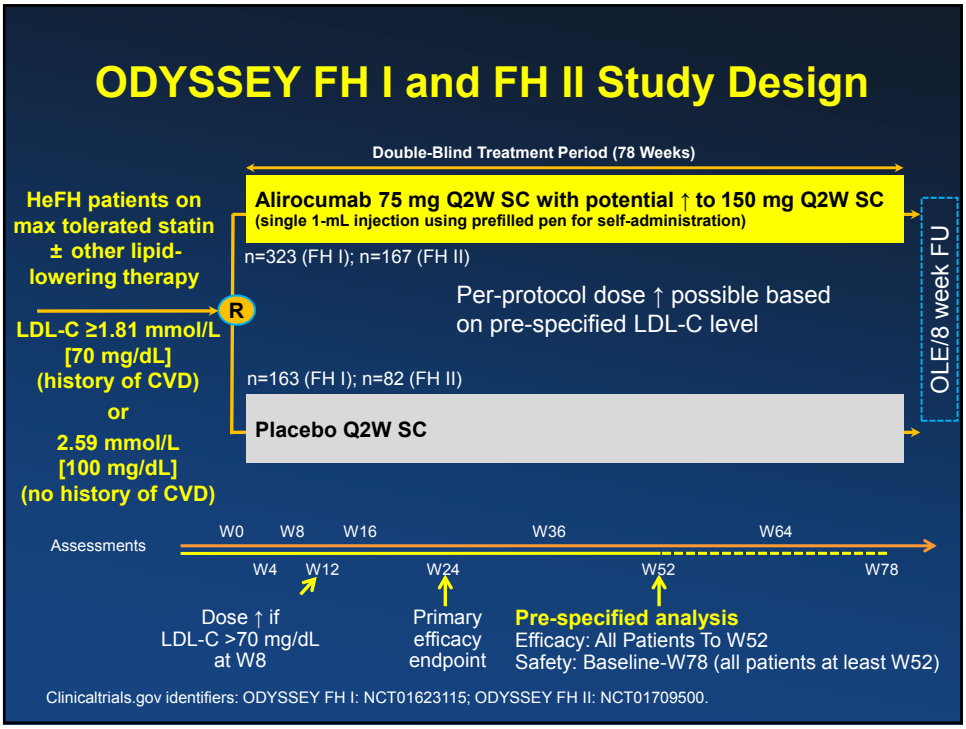
What do PCSK9 monoclonal antibodies offer for FH?

- Will initial phase 1 results seen in small a group of HeFH patients from one center be maintained in a larger and more diverse HeFH population with additional LDL-R defects?
- Is response related to the underlying genetic defect?
- Will PCSK9 mAb be effective in homozygous FH?
- Is response related to underlying genetic defect(s)?

ODYSSEY FH I and FH II Study Design

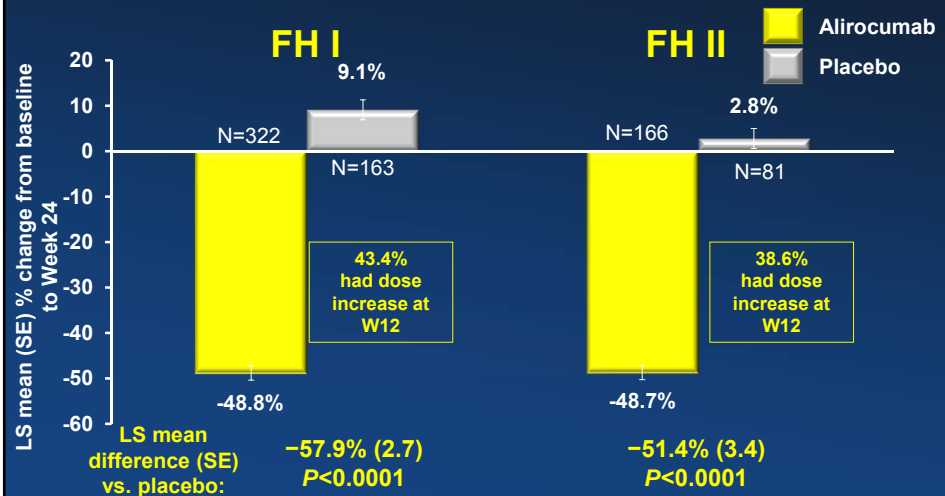


Clinicaltrials.gov identifiers: ODYSSEY FH I: NCT01623115; ODYSSEY FH II: NCT01709500.

ODYSSEY FH I and FH II Study: Primary Efficacy Results

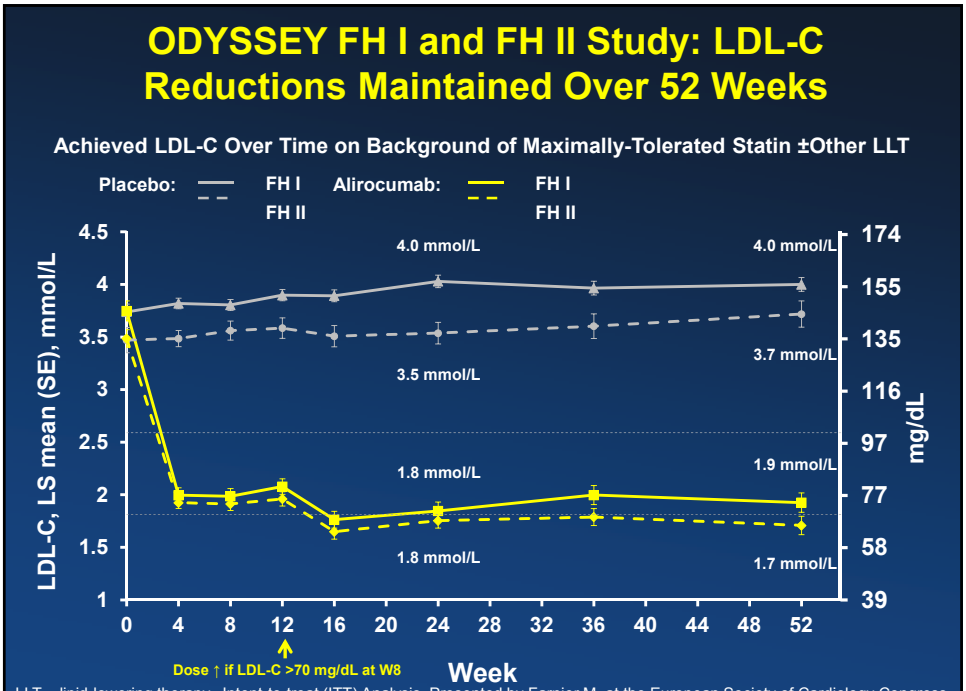
Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

All patients on background max-tolerated statin ±other lipid-lowering therapy



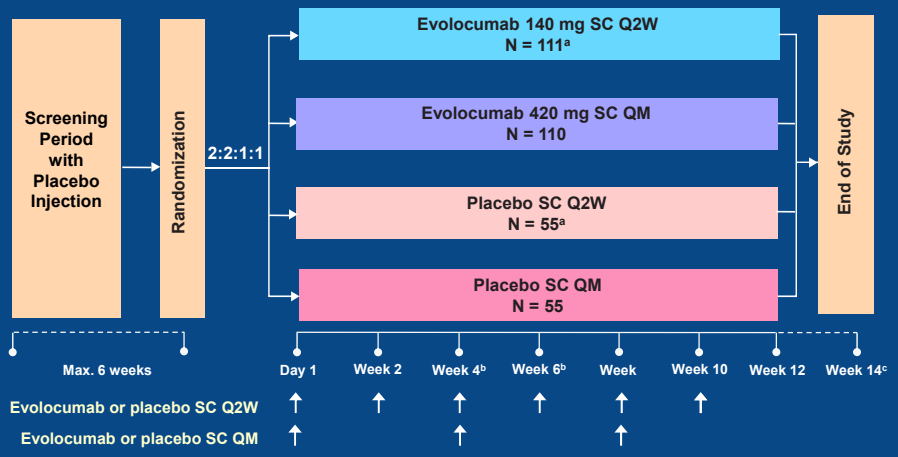
Intent-to-treat (ITT) Analysis. Presented by Farnier M. at the European Society of Cardiology Congress, Barcelona, Spain, August 31, 2014.

ODYSSEY FH I and FH II Study: LDL-C Reductions Maintained Over 52 Weeks



LLT = lipid-lowering therapy. Intent-to-treat (ITT) Analysis. Presented by Farnier M. at the European Society of Cardiology Congress, Barcelona, Spain, August 31, 2014.

RUTHERFORD-2 Study: Evolocumab in HeFH

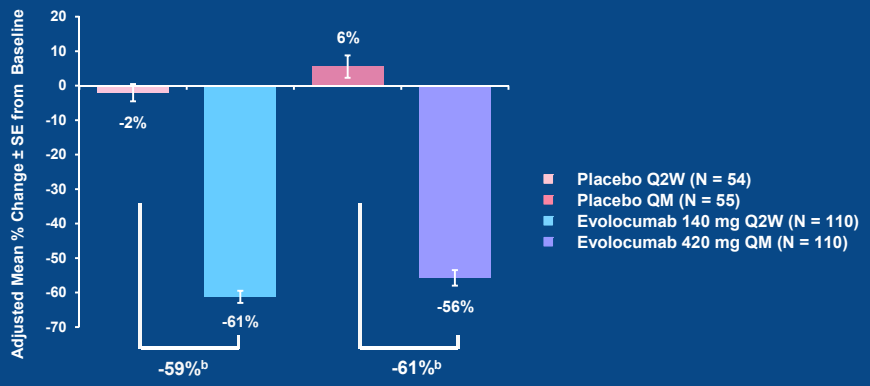


[a] N's are number of patients randomized. One patient in each of the placebo Q2W and evolocumab Q2W groups did not receive any doses of the study drug and were not included in the analyses
[b] Injections at weeks 4 and 6 were done at home
[c] Week 14 was a follow-up call for Q2W patients to capture adverse events and concomitant medications

Q2W, biweekly; QM, monthly; SC, subcutaneous

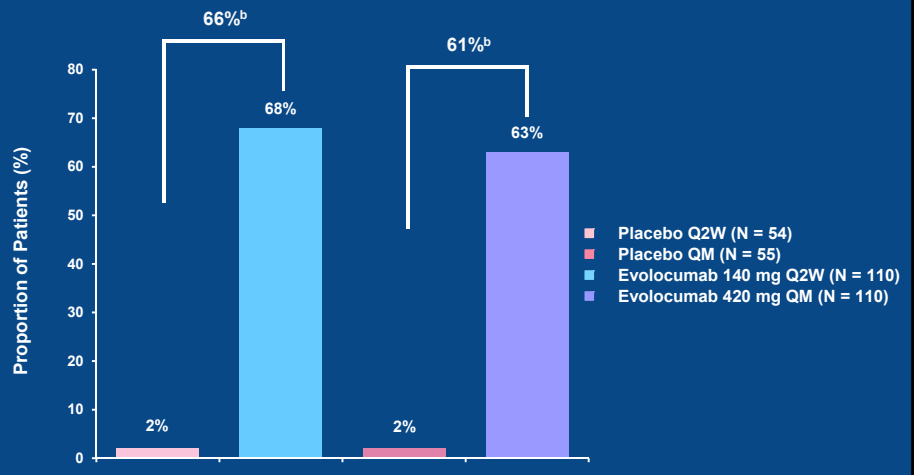
Raal, et al. Lancet 2014;385:331-40

RUTHERFORD-2: Mean % Change in LDL-C[a] from Baseline to Week 12



[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL
[b] P < 0.001; placebo-adjusted treatment difference analyzed using repeated measures model which included treatment group, stratification factors (from IVRS), scheduled visit and the interaction of treatment with scheduled visit as covariates
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly; SE, standard error

RUTHERFORD-2: LDL-C[a] Goal Achievement < 70 mg/dL at week 12



[a] Determined by the Friedewald formula with reflexive testing via preparative ultracentrifugation when calculated LDL-C was < 40 mg/dL or triglyceride levels were > 400 mg/dL
[b] P < 0.001; analyzed using CMH test, stratified by the stratification factors
LDL-C, low-density lipoprotein cholesterol; Q2W, biweekly; QM, monthly

Raal, et al. Lancet 2014;385:331-40

RUTHERFORD-2: demographics and lipid parameters in patients in the genetic sub-analysis

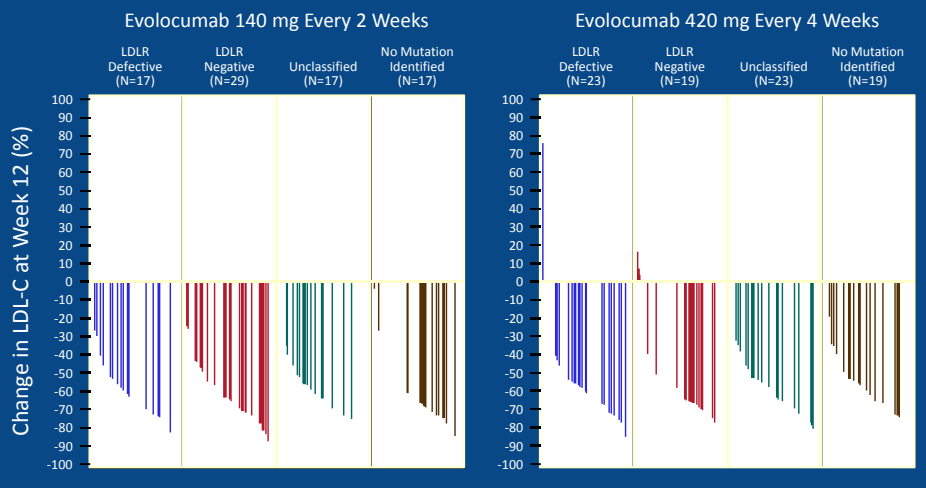
Mutations causative of familial hypercholesterolaemia were found in 80% (211/264) of patients who consented to the genetic analysis

	LDLR Mutation (n=195)				
	Negative (n=66)	Defective (n=75)	Unclassified (n=54)	Apo B Mutation (n=9)	HoFH/Compound HeFH (n=7)
Age (years), mean (SD)	48·1 (13·0)	49·5 (12·3)	51·0 (12·8)	57·1 (11·2)	53 (10·3)
Coronary artery disease, n (%)	23 (34·8)	15 (20·0)	23 (42·6)	2 (22·2)	4 (57·1)
LDL-C (mg/dL), mean (SD)	170 (50)	153 (39)	154 (46)	143 (39)	205 (108)
Apo B (mg/dL), mean (SD)	120 (30)	110 (20)	120 (30)	100 (20)	150 (60)
LDL-C reduction* at wk 12 (mean %)	61%	62%	64%	51%	68%

*evolocumab 140 mg every 2 weeks

Raal, et al. Lancet 2014;385:331-40

Percent Change (Baseline to Wk 12) in LDL-C for Each Patient with HeFH by Genetic Subgroup



Raal, et al. Lancet 2014;385:331-40

PCSK9 Monoclonal Antibodies in FH

- Phase 1 results seen in small a group of HeFH patients from one center are maintained in a larger and more diverse HeFH population with additional LDL-R defects? **YES**
- Response **IS NOT related** to the underlying genetic defect
- Will PCSK9 mAb be effective in homozygous FH?
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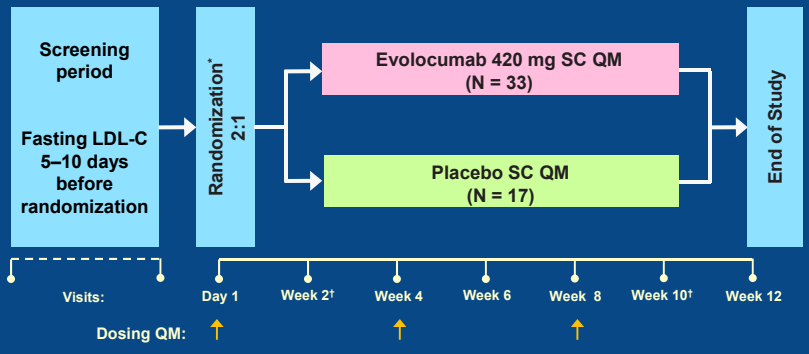
Trial Evaluating Evolocumab, a PCSK9 Antibody, in Patients with Homozygous FH (TESLA part B): a Global, Phase 3, Randomized, Double-blind, Placebo-controlled Trial: Study Design



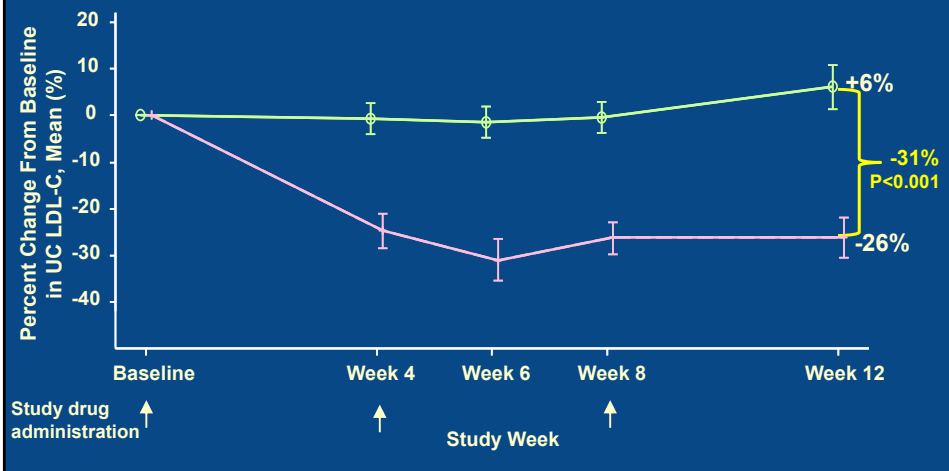
↑ Study drug administration

*Randomization stratified by screening LDL-C (<10.9 mmol/L or ≥10.9 mmol/L).
†Week 2 and week 10 study visits were optional.
SC = subcutaneous; QM = every 4 weeks; LDL-C = low-density lipoprotein cholesterol

Primary endpoint: % change from baseline in ultracentrifugation LDL-C at week 12

Raal, et al. Lancet 2014;385:341-50

TESLA part B: Percent Change in UC LDL-C From Baseline to Week 12



Vertical lines represent the standard error around the mean. Plot is based on observed data with no imputation for missing values.

Raal, et al. Lancet 2014;385:341-50

TESLA part B: LDL-C Lowering by Type of Mutation

Percent Change from Baseline in UC LDL-C at Week 12, Mean (SE)

Mutation Status	N	Placebo	Evolocumab 420 mg QM	Treatment Difference
All	49	7.9 (5.3)	-23.1 (3.8)	-30.9 (6.4)*
LDLR				
Defective/any†	28	11.2 (5.1)	-29.6 (3.4)	**-40.8 (6.1)‡**
Defective/defective	13	15.1 (7.3)	-31.8 (5.8)	**-46.9 (9.4)‡**
Negative/defective	9	3.5 (5.8)	-21.0 (4.0)	**-24.5 (7.0)§**
Unclassified‖	22	3.8 (11.7)	-17.9 (8.8)	**-21.7 (13.9)**
Median (Q1, Q3)		7.2 (0.0, 9.9)	-39.2 (-48.8, -14.6)	-
Negative/negative	1	-	10.3	-
LDLR Heterozygous	1	-	-55.7	-
Apolipoprotein B	2	-10.8, 13.1	-	-
ARH	1	-	3.5	-

Data are least squares (LS) mean for groups with sufficient data; otherwise actual value at week 12. LS mean is from the repeated measures model, which includes treatment group, screening LDL, scheduled visit and the interaction of treatment with scheduled visit as covariates. *Adjusted P-value < 0.001; †Receptor defective in at least one of two affected alleles. ‡ Nominal P-value < 0.001; §Nominal P-value = 0.013; ‖Function of one or both LDLR mutations is unknown (includes 6 patients from the defective/any group).

Raal, et al. Lancet 2014;385:341-50

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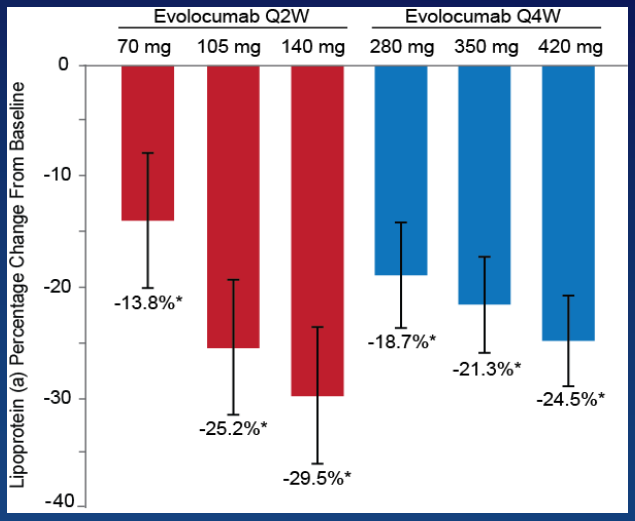
  - Heterozygous familial hypercholesterolemia
  - Homozygous familial hypercholesterolemia
- Effect on Lp(a)
- Safety and tolerability
- Emerging CVD data and Outcomes trials

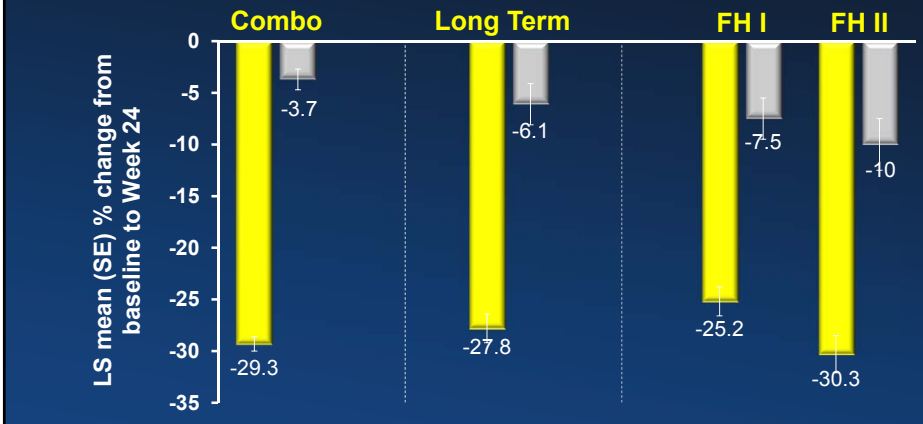
Reduction in Lipoprotein(a) With PCSK9 Monoclonal Antibody Evolocumab (AMG 145):a Pooled Analysis of More Than 1,300 Patients in 4 Phase II Trials



Error bars represent standard error. * P < 0.001

Raal et al JACC 2014;():. doi:10.1016/j.jacc.2014.01.006 Online First

Alirocumab: Lp(a) Reductions in ODYSSEY Combo II, Long Term, FH I and FH II Studies



All comparisons vs. placebo are *P*<0.0001

Alirocumab + max-tolerated statin ±other LLT

Placebo + max-tolerated statin ±other LLT

Adjusted mean (SE) shown for Lp(a). LLT = lipid-lowering therapy.

Presented by Robinson J. at the European Society of Cardiology Congress, Barcelona, Spain, August 31, 2014. Presented by Robinson J. at the European Society of Cardiology Congress, Barcelona, Spain, August 31, 2014. Presented by Farnier M. at the European Society of Cardiology Congress, Barcelona, Spain, August 31, 2014.

PCSK9 Inhibition: Insights into a new therapeutic approach for the lowering of LDL cholesterol

- PCSK9 monoclonal antibodies in LDL cholesterol homeostasis
- PCSK9 inhibition efficacy in various pheno- and geno-types
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AMG 145 Pooled analysis >1300 patients: Clinical Adverse Effects

	AMG 145 – by dose and dose frequency						Placebo	All AMG 145
	70 mg Q2W (n=124)	105 mg Q2W (n=125)	140 mg Q2W (n=123)	280 mg Q4W (n=156)	350 mg Q4W (n=210)	420 mg Q4W (n=213)	(n=333)	(n=981)
AEs[a]	65 (52.4)	74 (59.2)	69 (56.1)	89 (57.1)	118 (56.2)	122 (57.3)	164 (49.2)	557 (56.8)
Nasopharyngitis	11 (8.9)	10 (8.0)	8 (6.5)	11 (7.1)	20 (9.5)	18 (8.5)	25 (7.5)	81 (8.3)
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 Euro Heart J 2014 doi:10.1093/eurheartj/ehu085

AMG 145 Pooled analysis >1300 patients: Lab of Interest

	AMG 145 – by dose and dose frequency						Placebo	All AMG 145
	70 mg Q2W (n=124)	105 mg Q2W (n=125)	140 mg Q2W (n=123)	280 mg Q4W (n=156)	350 mg Q4W (n=210)	420 mg Q4W (n=213)	(n=333)	(n=981)
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[b]	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)

[b]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 Euro Heart J 2014 doi:10.1093/eurheartj/ehu085

ODYSSEY LONG TERM Study: TEAEs

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

% (n) of patients All patients on background of max-tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
TEAEs	**78.6%** (1218)	**80.6%** (635)
Treatment-emergent SAEs	**16.5%** (255)	**17.6%** (139)
TEAE leading to death	**0.5%** (7)	**1.0%** (8)
TEAEs leading to treatment discontinuation	**6.2%** (96)	**5.5%** (43)

- **Mean treatment duration: 65 weeks (both treatment arms)**
- **26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) completed 78 weeks**
- **Statistical analyses have not been performed.**

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ODYSSEY LONG TERM Study: TEAEs ≥5%

% (n) of patients	**Alirocumab (n=1550)**	**Placebo (n=788)**
Infections and infestations	**45.5%** (705)	**46.1%** (363)
Musculoskeletal and connective tissue disorders	**27.2%** (422)	**28.6%** (225)
Gastrointestinal disorders	**18.6%** (288)	**18.8%** (148)
Nervous system disorders	**17.0%** (264)	**17.8%** (140)
General disorders and administration site conditions	**15.4%** (238)	**17.0%** (134)
Injury, poisoning, and procedural complications	**13.4%** (207)	**14.2%** (112)
Respiratory, thoracic, and mediastinal disorders	**11.0%** (171)	**10.9%** (86)
Cardiac disorders	**9.1%** (141)	**11.8%** (93)
Skin and subcutaneous tissue disorders	**9.1%** (141)	**8.5%** (67)
Metabolism and nutrition disorders	**9.1%** (141)	**8.4%** (66)
Vascular disorders	**7.9%** (122)	**8.9%** (70)
Eye disorders	**6.5%** (100)	**6.1%** (48)
Investigations (lab parameters)	**6.1%** (95)	**5.2%** (41)
Psychiatric disorders	**5.9%** (91)	**8.0%** (63)

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PCSK9 Inhibition: Insights into a new therapeutic approach for the lowering of LDL cholesterol

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- PCSK9 inhibition efficacy in various pheno- and geno-types
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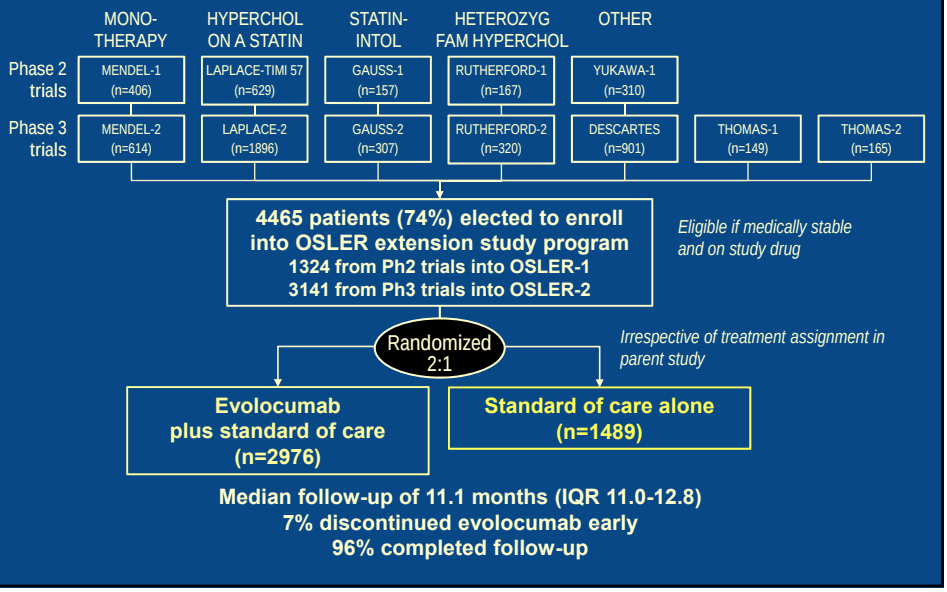
OSLER Program

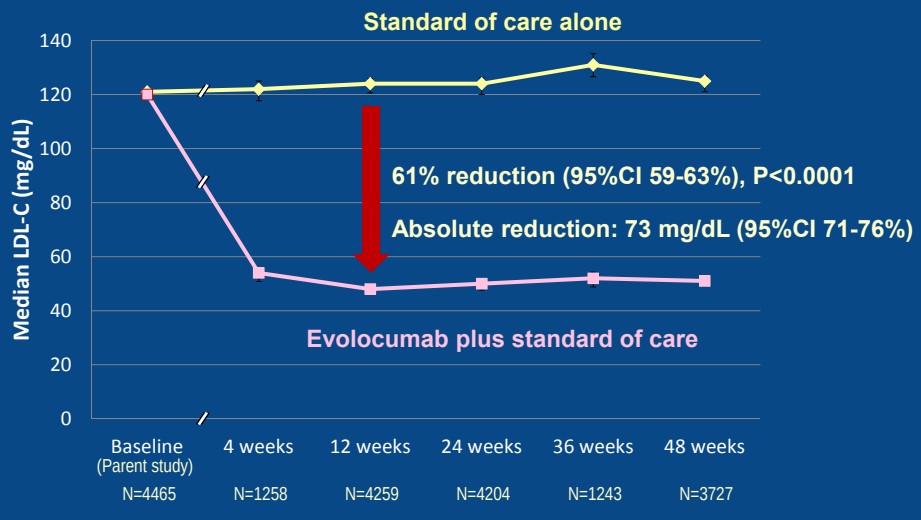


Osler: Methods

- Evolocumab
  - Open-label
  - Dosed either 140 mg every 2 weeks or 420 mg monthly SC
- Endpoints
  - Adverse events (primary) & tolerability
  - LDL-cholesterol (secondary) & other lipid parameters
  - Cardiovascular (CV) clinical outcomes (prespecified, exploratory): adjudicated by TIMI Study Group CEC, blinded to treatment
    - Death
    - Coronary: myocardial infarction (MI), unstable angina (UA) requiring hospitalization, revascularization
    - Cerebrovascular: stroke or transient ischemic attack (TIA)
    - Heart failure (HF) requiring hospitalization
  - CV outcomes data through 1/21/2015; safety & lipids 10/31/2014

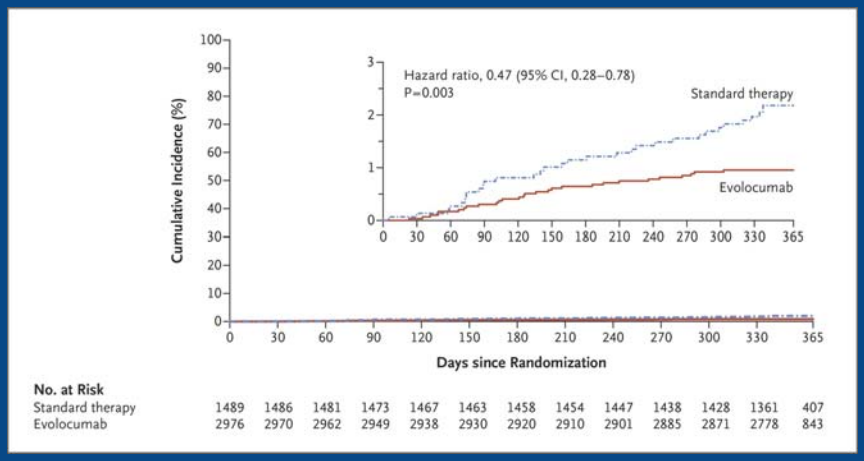
Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Osler: LDL Cholesterol



Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Evolocumab: Cumulative Incidence of Cardiovascular Events.

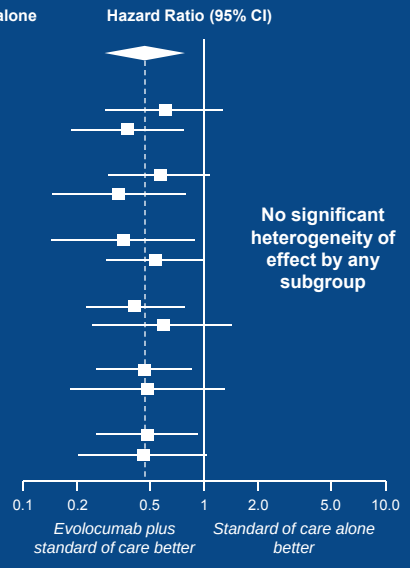


Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Osler: CV Events in Subgroups

Baseline Subgroup	Number	Evolocumab	Stnd of care alone
Overall	4465	0.95%	2.18%
Age			
<65 yr	3103	0.73%	1.29%
≥65 yr	1362	1.47%	4.10%
Sex			
Male	2255	1.28%	2.37%
Female	2210	0.61%	1.96%
LDL cholesterol			
<120 mg/dL	2202	0.55%	1.53%
≥120 mg/dL	2263	1.35%	2.75%
Statin use			
Yes	3128	0.83%	2.21%
No	1337	1.24%	2.11%
NCEP class			
High or mod. high	2025	1.51%	3.51%
Mod. or lower	2440	0.49%	1.04%
Known vascular disease			
Yes	1125	2.31%	5.01%
No	3340	0.50%	1.19%

% are KM event rates at 1 year



No significant heterogeneity of effect by any subgroup

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

Osler: Adverse Events by Achieved LDL-C

	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	SOC Alone (n=1489)
	<25 mg/dL (n=773)	25 to <40 mg/dL (n=759)	<40 mg/dL (n=1532)	≥40 mg/dL (n=1426)		
Adverse Events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Lab results (%)						
ALT/AST >3×ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5×ULN	0.4	0.9	0.7	0.5	0.6	1.2

Sabatine MS et al. N Engl J Med 2015;372:1500-1509

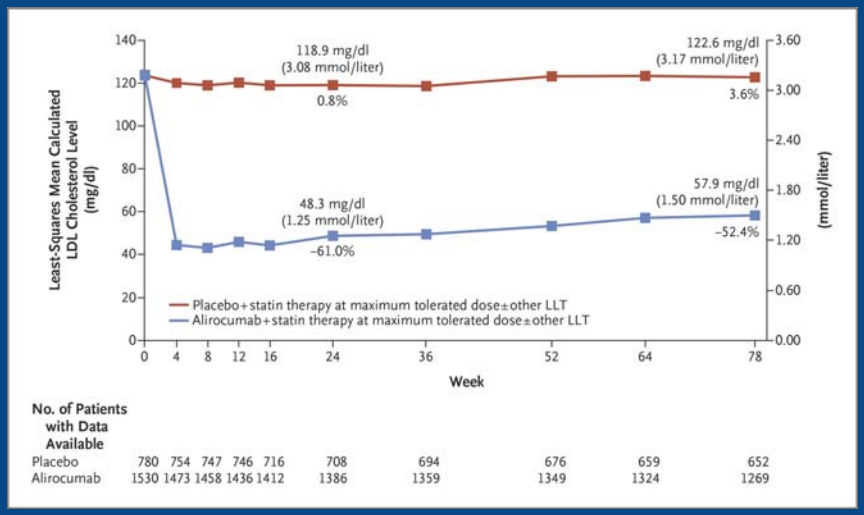
ODYSSEY LONG TERM: Baseline Characteristics

All patients on background of max-tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1553)	Placebo (n=788)
Age, years, mean	**60.4**	**60.6**
HeFH, %	**17.8%**	**17.6%**
CHD history, %	**67.9%**	**70.1%**
Type 2 diabetes, %	**34.9%**	**33.9%**
Any statin, %	**99.9%**	**99.9%**
High-intensity statin, %	**44.4%**	**43.4%**
Any LLT other than statins, %	**28.1%**	**27.9%**
Ezetimibe, %	**13.9%**	**15.0%**
LDL-C, calculated mean, mg/dL	**122.7**	**121.9**
Non-HDL-C, mean, mg/dL	**152.6**	**152.0**
Apo B, mean, mg/dL	**101.9**	**101.4**
Lp(a), mg/dL, median	**22.2**	**20.9**

Robinson JG et al. N Engl J Med 2015;372:1489-1499

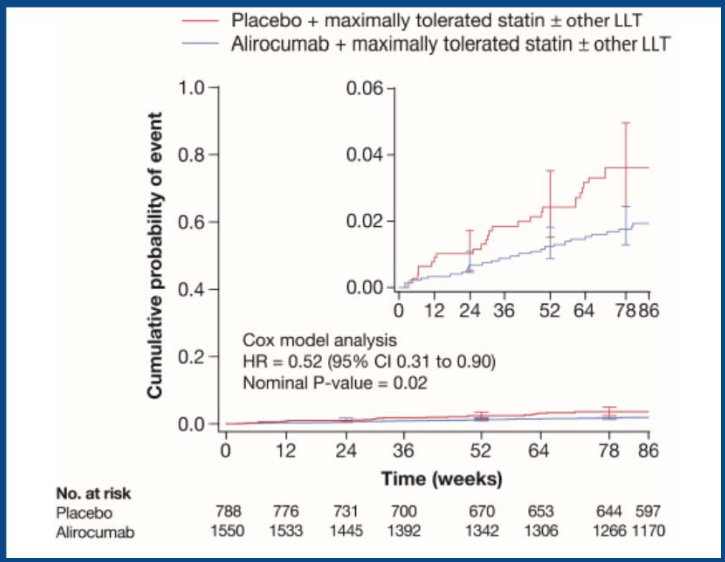
ODYSSEY LONG TERM: Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).



Robinson JG et al. N Engl J Med 2015;372:1489-1499

Alirocumab: Cumulative Incidence of Cardiovascular Events.



Robinson JG et al. N Engl J Med 2015;372:1489-1499

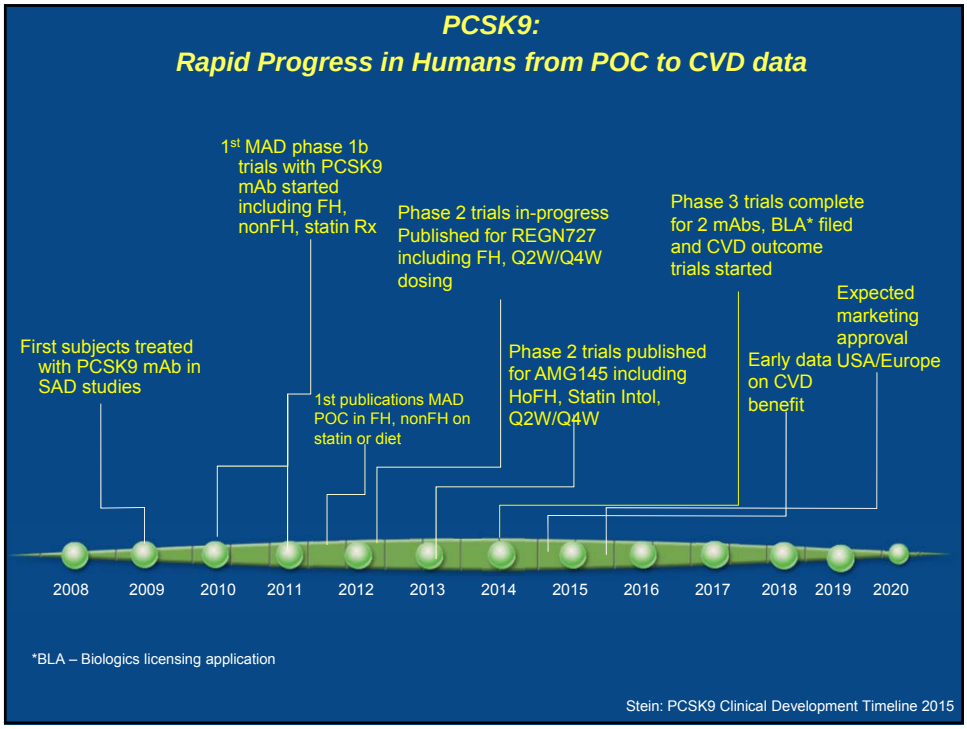
PCSK9 Inhibitor Cardiovascular Outcomes Trials

	Evolocumab (AMG 145)	Alirocumab (SAR236553 /REGN727)	Bococizumab (RN 316)	
Sponsor	Amgen	Sanofi / Regeneron	Pfizer	
Trial	**FOURIER**	**ODYSSEY Outcomes**	**SPIRE I**	**SPIRE II**
Sample size	27,500	18,000	17,000	9,000
Patients	MI, stroke or PAD	4-52 wks post-ACS	High risk of CV event	
Statin	Atorva ≥20 mg or equiv	Evid-based med Rx	Lipid-lowering Rx	
LDL-C mg/dL(mmol/L)	≥70 (≥1.8)	≥70 (≥1.8)	70-99 (1.8-2.6)	≥100 (≥2.6)
PCSK9i Dosing	Q2W or Q4W	Q2W	Q2W	
Endpoint	1°: CV death, MI, stroke, revasc or hosp for UA, Key 2°: CV death, MI, or stroke	CHD death, MI, ischemic stroke, or hosp for UA	CV death, MI, stroke, or urgent revasc	
Completion	12/2017	1/2018	8/2017	

www.clinicaltrials.gov [accessed May 6, 2015]

PCSK9 Inhibition: Conclusions

- Inhibition of PCSK9 with monoclonal antibodies is the most effective approach to reducing LDL-C including in patients:
  - With nonFH, HeFH and LDLr defective HoFH
  - On statins or diet alone
  - When added to all existing therapy
  - Unable to tolerate statins, or effective doses of statins.
  - SC delivery every 2 or 4 weeks
- PCSK 9 inhibitors have also been shown to significantly reduce Lp(a)
- In large phase 2 and 3 program of 2 agents of over 6,000 patients no significant adverse effects have emerged so far
- Early data on CVD is encouraging and in the right direction
- Four large CVD outcome trials are already underway with the Amgen (evolocumab), Sanofi (alirocumab) and Pfizer (bocomizumab) monoclonal antibodies.



Case 1

- A male aged 53 years with HeFH treated at a lipid clinic since his late 20s. He is part of large family with 2 brothers and 3 sisters and has 2 children, a son aged 24 and daughter 27 years old (who has a 6 year old son).
- At the initial diagnosis his total cholesterol was 472 mg/dL, triglycerides 175 mg/dL, HDL-C 38 mg/dL, LDL-C 399 mg/dL on a low fat low cholesterol diet.
- For the last 6 years he has been treated with atorvastatin 80 mg plus ezetimibe 10 mg daily with good adherence. He has previously been tried on bile acid sequestrants but had constipation and bloating. His latest lipids were: TC 276 mg/dL, TG 125 mg/dL, HDL-C 45 mg/dL, LDL-C 201 mg/dL. His Lp(a) is moderately elevated at 56 mg/dL.
- Five years ago he had an episode of acute chest pain and was found to have a 90% occlusion of his LAD which was treated with PCI but 2 years ago after complaining of tiredness and discomfort on effort was found to have developed further occlusion of in both the right and left coronary arteries and underwent 3 vessel CAGB.
- He works as a building contractor and often performs manual labor.
- He smoked a pack of cigarettes until his early 30s but has not smoked for the last 20 years, drinks about 6 beers over the weekends, and has no history of diabetes, hypertension, thyroid or liver disease. His weight of 185 lbs is acceptable for his height of 6'1".

Case 1

Question 1: Would you perform DNA analysis to assess the underlying LDL receptor defect to determine the response to your selection of other therapies?

1. Yes
2. No

Case 1

Question 2: What LDL-C goal would you recommend and aim for in this patient

1. None – it is sufficient to treat with atorvastatin 80 mg and the patient can consider stopping ezetimibe
2. LDL-C <130 mg/dL
3. LDL-C <100 mg/dL
4. LDL-C <70 mg/dL

Case 1

Question 3: What would you do next for this patient?

1. Niacin; Immediate release (3 to 5 gm/day), or extended release (2 gm/day)
2. LDL apheresis
3. Lomitapide
4. Mipomersen
5. PCSK9 monoclonal antibody

Case 1

Question 4: In regard to his family what would you recommend?

1. Screening of his children by measuring their fasting lipids and doing a physical exam
2. Screening of his children by doing DNA analysis for defects in LDL receptors, Apo B and PCSK9
3. Tell him that there is no point in checking his children until they are at least 30 years old
4. Screening only his male child as the FH gene is sex-linked and does not effect females