PCSK9 AND ITS INHIBITION

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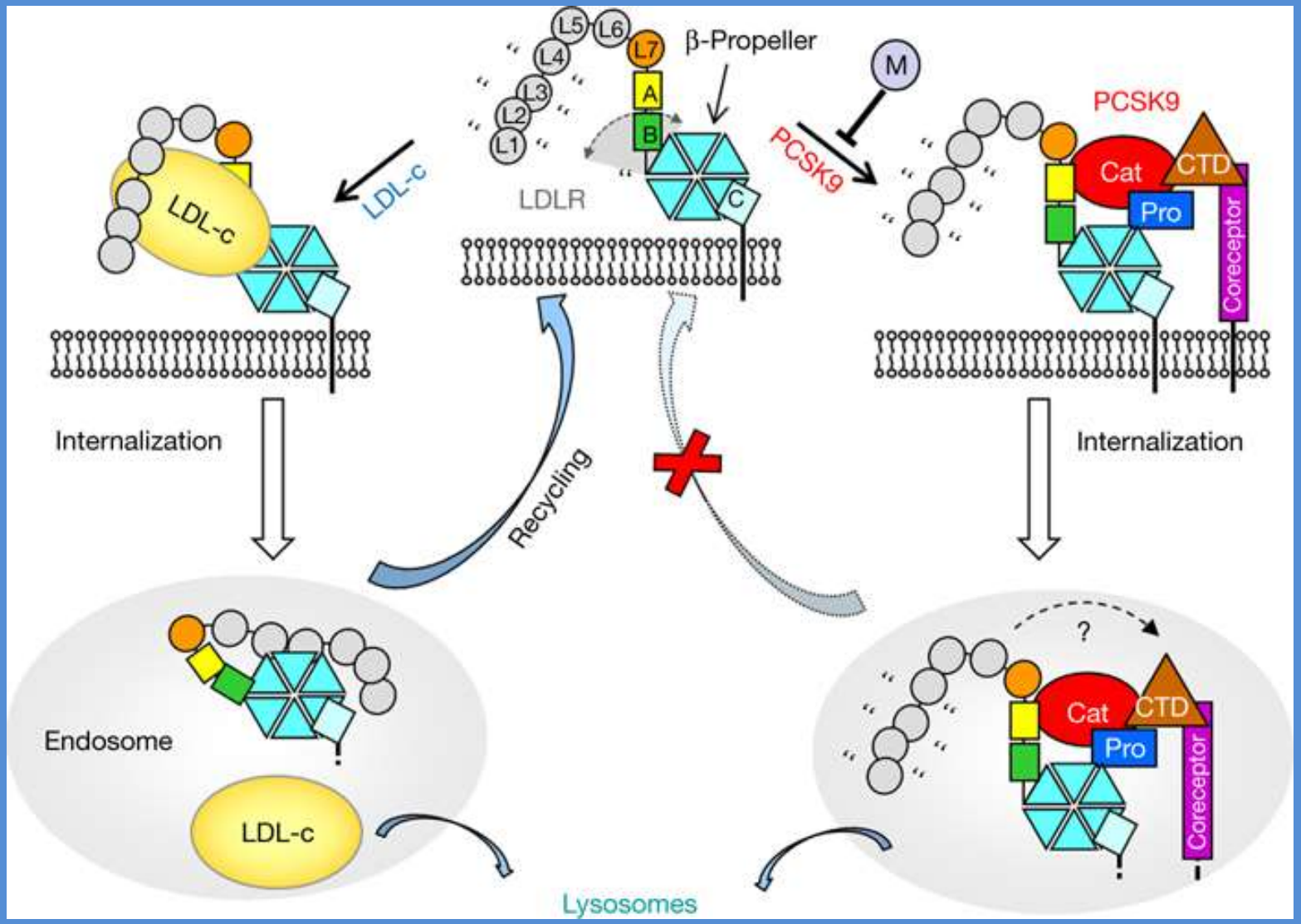
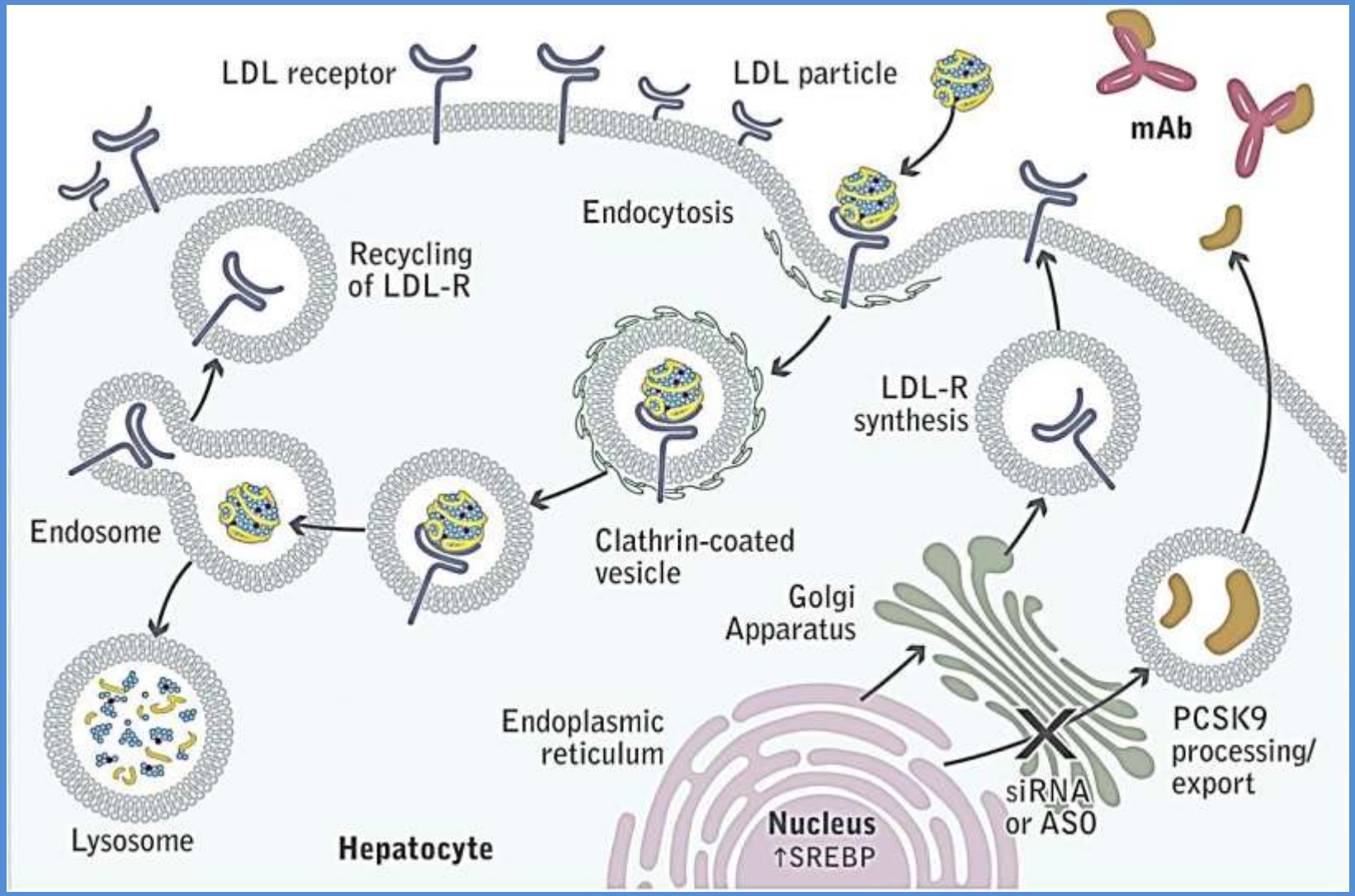
Role of PCSK9



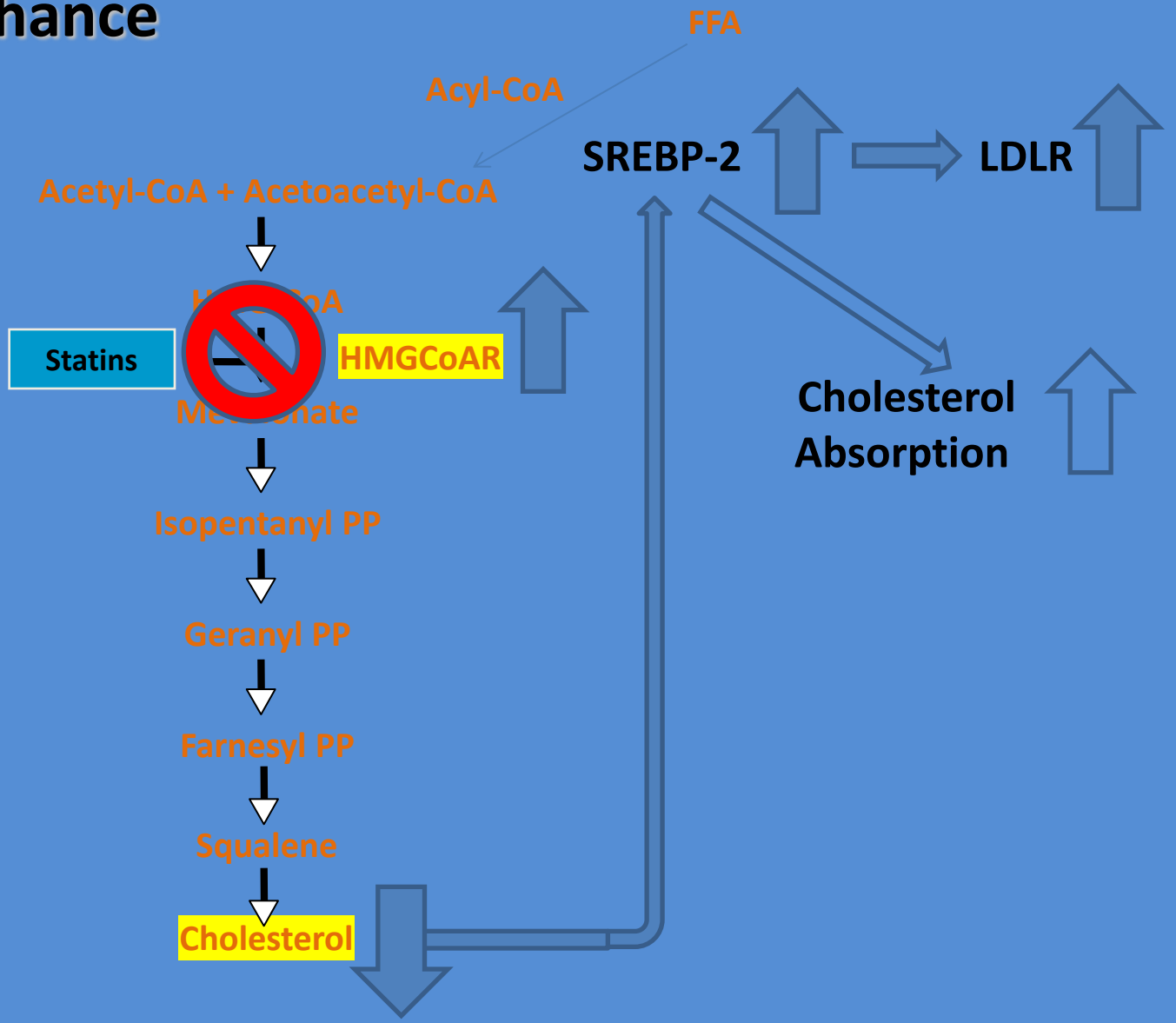
EMBO reports *(2011)* **12**, *1300 - 1305*

Outcome of PCSK9 inhibition



Lambert G et al. J. Lipid Res. 2012;53:2515-2524

Statins may enhance PCSK9

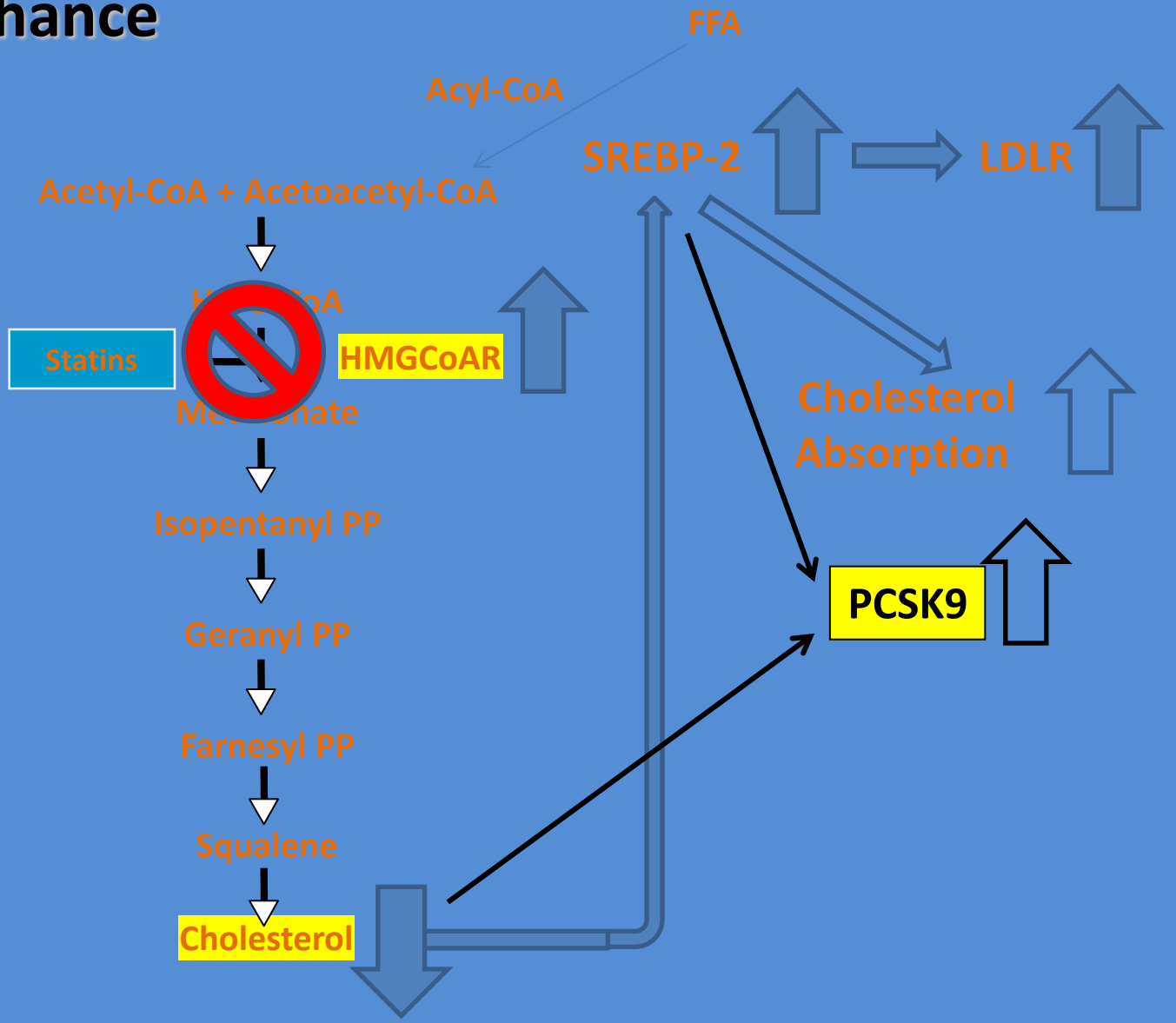


PP = pyrophosphate.

Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

Statins may enhance PCSK9

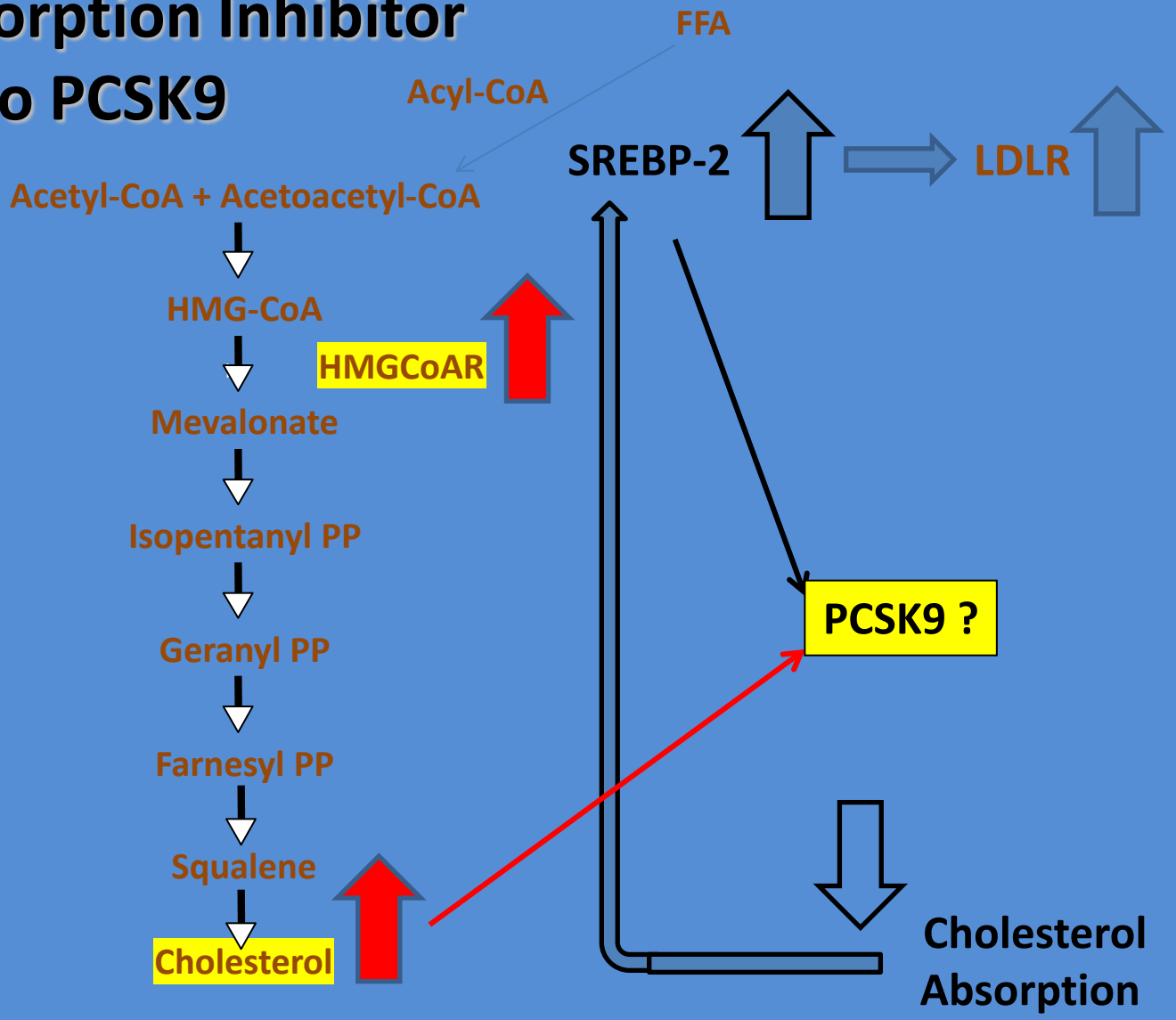


PP = pyrophosphate.

Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

Cholesterol Absorption Inhibitor maybe neutral to PCSK9



PP = pyrophosphate.

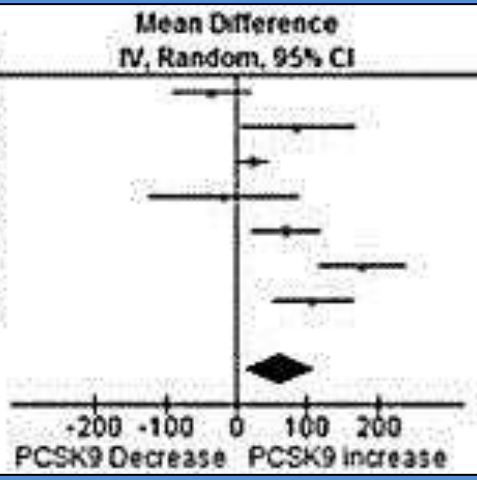
Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

Fibrates increase PCSK9

Study or Subgroup	Post-treatment Mean	SD	Total	Pre-treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Lambert et al., 2008	373	198	115	408	216	115	15.0%	-35.00 [-88.55, 18.55]	2008
Mayne et al., 2008	690	138	19	604	110	19	12.4%	86.00 [6.65, 165.35]	2008
Troutt et al., 2010	120	37.52	22	96	28.14	22	17.8%	24.00 [4.40, 43.60]	2010
Chan et al., 2010	148	147.06	15	166	147.06	15	10.0%	-18.00 [-123.25, 87.25]	2010
Costet et al., 2010	334	82	19	264	65	19	15.7%	70.00 [22.95, 117.05]	2010
Noguchi et al., 2011a	444.8	101.3	14	266.7	56.6	14	14.3%	178.10 [117.32, 238.88]	2011
Noguchi et al., 2011b	380	84.8	14	272	62	14	14.9%	108.00 [52.97, 163.03]	2011
Total (95% CI)			218			218	100.0%	60.37 [11.04, 109.71]	

Heterogeneity: Tau² = 3468.80; Chi² = 39.76, df = 6 (P < 0.00001); I² = 85%
Test for overall effect: Z = 2.40 (P = 0.02)



Circulating Levels of Proprotein Convertase Subtilisin Kexin Type 9 are Elevated by Fibrate Therapy: A Systematic Review and Meta-Analysis of Clinical Trials.
Sahebkar, Amirhossein; PharmD, PhD

Cardiology in Review. 22(6):306-312, November/December 2014.
DOI: 10.1097/CRD.0000000000000025

FIGURE 1 . Forest plot detailing weighted mean difference and 95% confidence intervals for the impact of fibrate therapy on circulating PCSK9 concentrations.

Regulatory factors for PCSK9

- sterol regulatory element (**SRE**) for SREBP binding
- hepatocyte nuclear factor-1α (**HNF1α**) potentiates SRE activity
- **PPAR-alpha** upregulates PCSK9

- **mTOR1** downregulates HNF1α
- **Sirtuin 6**, an NAD^+-dependent histone deacetylase is a transcriptional repressor of the *PCSK9*
- **FoxO3** recruits Sirtuin 6 to the *PCSK9* promoter
- **Farnesoid X** receptor downregulates PSCK9

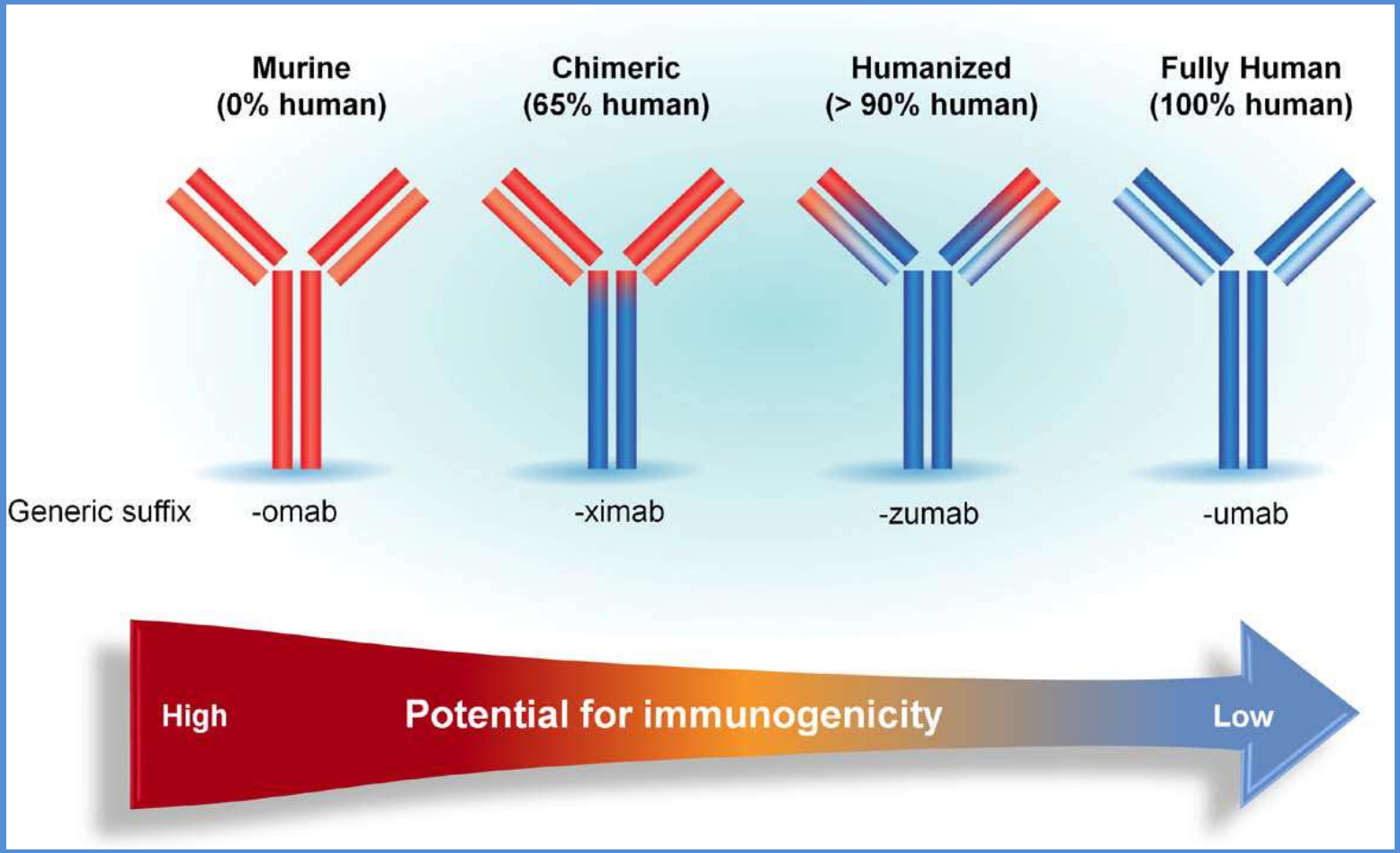
Summary (1)

- PCSK9 competes with LDL particles on the binding with LDLR.
- PCSK9-LDLR destructs LDLR in endosome.
- PCSK9 activity/expression is generally increased under statin/fibrate medication.
- PCSK9 inhibition may increase LDL uptake and enhance cycling of LDLR.

Selected PCSK9 inhibitors

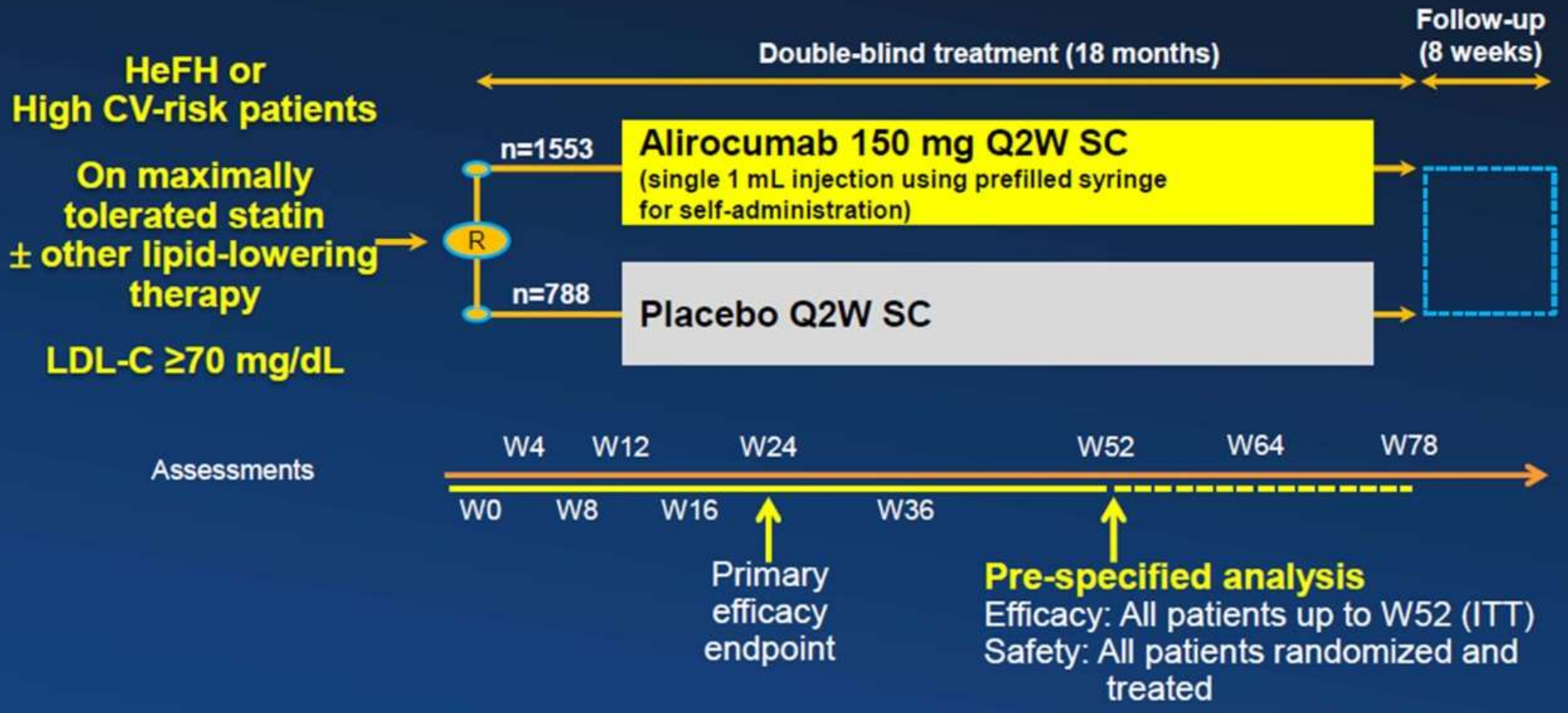
Company	molecule	Description	Clinical stage
Regeneron/sanofi	**Alirocumab**	**mAb**	**Phage 3**
Amgen	**Evolocumab**	**mAb**	**Phase 3**
Pfizer	**Bococizumab**	**mAb**	**Phase 3**
Roche	RG-7652	mAb	Phase 2
Eli Lilly	LY3015014	mAb	Phase 2
Alnylam	ALN-PCS02	RNAi	Phase 1

Antibody Development



Circulation. 2013;127:2222-2230

ODYSSEY LONG TERM Study Design



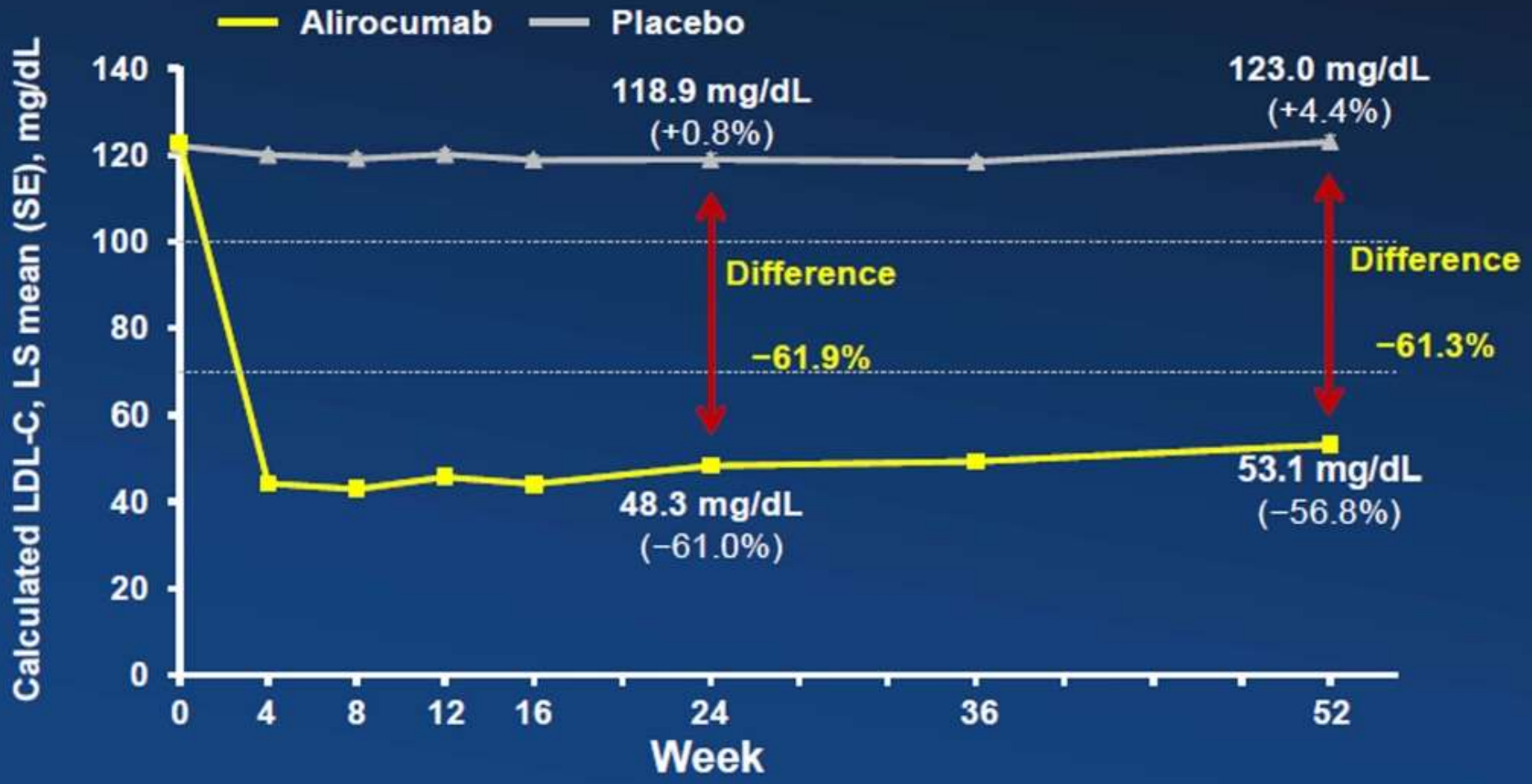
85.8% (2009/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)

ClinicalTrials.gov identifier: NCT01507831.

Alirocumab Maintained Consistent LDL-C Reductions Over 52 Weeks

Achieved LDL-C Over Time

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



Intent-to-treat (ITT) analysis

Overview of ODYSSEY Phase 3 Clinical Trial Program

14 global phase 3 trials including >23,500 patients across >2,000 study centers

HeFH population

Add-on to max-tolerated statin ± other LMT

ODYSSEY FH I (NCT01623115; EFC12492)
LDL-C ≥ 70 mg/dL OR LDL-C ≥100 mg/dL
N=471; 18 months

ODYSSEY FH II (NCT01709500; CL1112)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=250; 18 months

ODYSSEY HIGH FH (NCT01617655; EFC12732)
LDL-C ≥ 160 mg/dL
N=105; 18 months

ODYSSEY OLE (NCT01954394; LTS13463)
Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717
N>1000; 30 months

ODYSSEY LONG TERM (NCT01507831; LTS11717)
LDL-C ≥70 mg/dL
N=2,100; 18 months

HC in high CV risk population

Add-on to max-tolerated statin ± other LMT

ODYSSEY COMBO I (NCT01644175; EFC11568)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=306; 12 months

ODYSSEY COMBO II (NCT01644188; EFC11569)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=660; 24 months

ODYSSEY OUTCOMES (NCT01663402; EFC11570)
LDL-C ≥70 mg/dL
N=18,000; 64 months

Additional populations

ODYSSEY MONO (NCT01644474; EFC11716)
Patients on no background LMTs
LDL-C ≥100 mg/dL
N=100; 6 months

ODYSSEY ALTERNATIVE (NCT01709513; CL1119)
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=250; 6 months

ODYSSEY CHOICE I (NCT01926782; CL1308)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=700; 12 months

ODYSSEY CHOICE II (NCT02023879; EFC13786)
Patients not treated with a statin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=200; 6 months

ODYSSEY OPTIONS I (NCT01730040; CL1110)
Patients not at goal on moderate dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=350; 6 months

ODYSSEY OPTIONS II (NCT01730053; CL1118)
Patients not at goal on moderate dose rosuvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
N=300; 6 months

ODYSSEY

FH=familial hypercholesterolemia; HC=hypercholesterolemia; LMT=lipid-modifying therapy; OLE=open-label extension.
*For the ODYSSEY COMBO II other LMT not allowed at entry.

ClinicalTrials.gov. ODYSSEY Phase 3 Trials. http://clinicaltrials.gov. Accessed February 12, 2014.

SANOFI

REGENERON

Table 2. Summary of efficacy of alirocumab and evolocumab in high cardiovascular risk patients with or without other lipid-lowering therapy. Data from phase III trials

Reference	Trial	Patient population	N	MAb dose regimen	Comparator regimen	% LDL-C reduction
Evolocumab						
[32]	LAPLACE-2	Primary hypercholesterolaemia and mixed dyslipidaemia. Moderate to high intensity statin	2067	140 mg/2 weeks or 420 mg/month	Ezetimibe 10 mg daily or placebo	Mean at weeks 10 and 12: 66–75% (140 mg/2 weeks) 63–75% (420 mg/month) 17–21% (ezetimibe)
[33]	DESCARTES	Hyperlipidaemia, on diet with or without LLT	901	420 mg/ 4 weeks	Placebo	Mean at week 52: 57%; 56% on diet alone 62% on ATOR 10 mg 57% on ATOR 80 mg 49% on ATOR 80 mg/EZE 10 mg
[34,35]	OSLER	Primary hypercholesterolaemia, mixed dyslipidaemia or HeFH with or without LLT (70% on statin)	4465	140 mg/2 weeks or 420 mg/month	Placebo	Mean week 12: 61%
Alirocumab						
[36]	ODYSSEY COMBO I	Hypercholesterolaemia, on maximally tolerated statin ± other LLT	316	75/150 mg every 2 weeks[a]	Placebo	LS mean week 24: 46%
[37]	ODYSSEY COMBO II	Hypercholesterolaemia, on maximally tolerated statin	720	75/150 mg every 2 weeks[a]	Ezetimibe 10 mg/day	LS mean week 24: 51% [alirocumab] 21% [ezetimibe]
[38]	ODYSSEY OPTIONS I	Hypercholesterolaemia, on ATOR 20 or 40 mg	355	75/150 mg every 2 weeks[a]	Ezetimibe 10 mg/day Doubling ATOR dose Switching to ROS 40 (ATOR 40 only)	LS mean week 24: 44–54% [alirocumab], 21–23% [ezetimibe], 4.8–5.0% [Doubling ATOR dose], 21% [Switching to ROS]
[39]	ODYSSEY OPTIONS II	Hypercholesterolaemia, on ROS 10–20 mg	305	75/150 mg every 2 weeks[a]	Ezetimibe 10 mg/day doubling ROS dose	LS mean week 24: 38–51% [alirocumab], 11–14% [ezetimibe], 16% [Doubling ROS dose]
[40]	ODYSSEY CHOICE I	Hypercholesterolaemia, on maximally tolerated statin therapy or statin-naïve or intolerant	803	75/150 mg every 2 weeks[a] or 300 mg/4 weeks	Placebo	LS mean week 24: statin-naïve 52%, on statin 59% (300 mg/4 week)
[41]	ODYSSEY CHOICE II	Hypercholesterolaemia, on EZE, FEN or diet alone	233	75/150 mg every 2 weeks[a] or 150 mg/4 weeks	Placebo	LS mean week 24: 56% (150 mg/4 week)
[42]	ODYSSEY LONG TERM	Hypercholesterolaemia, on maximally tolerated statin ± other LLT	2341	150 mg/2 weeks	Placebo	Mean week 24: 62%

ATOR, atorvastatin; EZE, ezetimibe; FEN, fenofibrate; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; LS, least squares; MAb, monoclonal antibody; N, number of patients; ROS, rosuvastatin.
Trial acronyms: LAPLACE-2: LDL-C Assessment With Proprotein Convertase Subtilisin Kexin Type 9 Monoclonal Antibody Inhibition Combined With Statin Therapy 2; DESCARTES: Durable Effect of PCSK9 Antibody Compared with Placebo Study; OSLER: Open Label Study of Long Term Evaluation Against LDL-C Trial.
[a]Alirocumab dose was increased to 150 mg every 2 weeks at week 12 if LDL-C >1.8 mmol/l or 70 mg/dl at week 8, or not achieving LDL-C goal at week 8 (OPTIONS I and II).

Chapman MJ, Stock JK, Ginsberg HN; PCSK9 Forum (http:www.pcsk9forum.org). PCSK9 inhibitors and cardiovascular disease: heralding a new therapeutic era. Curr Opin Lipidol. 2015 Dec;26(6):511-20.

Agent (Trial)	Study description	LDL-C (% change from baseline to study end-point, except as indicated)						
SAR	12-week double-blind, placebo-controlled trial in 183 patients with LDL-C ≥100 mg/dl on stable atorvastatin therapy [36▪▪]	Placebo	SAR 50 mg Q2W	SAR 100 mg Q2W	SAR 150 mg Q2W	SAR 200 mg Q4W	SAR 300 mg Q4W	
		−5.1	−39.6*	−64.2*	−72.4*	−43.2*	−47.7*	
	8-week double-blind, placebo-controlled trial in 92 patients with LDL-C ≥100 mg/dl on atorvastatin 10 mg therapy [37]	Atorvastatin 80 mg and Placebo		Atorvastatin 10 mg and SAR 150 mg Q2W		Atorvastatin 80 mg and SAR 150 mg Q2W		
		−17.3		−66.2†		−73.2†		
	12-week double-blind, placebo-controlled trial in 77 patients with heterozygous FH and LDL-C ≥100 mg/dl on stable statin dose (with or without ezetimibe) therapy [38▪▪]	Placebo	SAR 150 mg Q4W	SAR 200 mg Q4W	SAR 300 mg Q4W	SAR 150 mg Q2W		
		−10.6	−28.9	−31.5	−42.5*	−67.9*		
AMG (LAPLACE-TIMI57)	12-week double-blind, placebo-controlled trial in 631 patients with LDL-C ≥85 mg/dl on stable statin dose (with or without ezetimibe) therapy [39]	AMG 70 mg Q2W	AMG 105 mg Q2W	AMG 140 mg Q2W	AMG 280 mg Q4W	AMG 350 mg Q4W	AMG 420 mg Q4W	
		−41.8*,α	−60.2*,α	−66.1*,α	−41.8*,α	−50.0*,α	−50.3*,α	
(RUTHERFORD)	12-week double-blind, placebo-controlled trial in 167patients with heterozygous FH and LDL-C ≥100 mg/dl on stable statin dose (with or without ezetimibe) therapy [40▪▪]	Placebo		AMG 350 mg Q4W		AMG 420 mg Q4W		
		1.1		−42.7††		−55.2††		
(MENDEL)	12-week randomized, placebo-controlled trial for AMG (ezetimibe not masked) in 406 patients not already on a statin [41▪]	AMG 70 mg Q2W	AMG 105 mg Q2W	AMG 140 mg Q2W	AMG 280 mg Q4W	AMG 350 mg Q4W	AMG 420 mg Q4W	Ezetimibe 10 mg
		−37.3*,α	−40.2*,α	−47.2*,α	−43.6*,α	−47.7*,α	−52.5*,α	−14.7
(GAUSS)	12-week double-blind, placebo and ezetimibe-controlled trial in 160 statin-intolerant patients [42▪▪]	AMG 280 mg Q4W	AMG 350 mg Q4W	AMG 420 mg Q4W	AMG 420 mg Q4W and Ezetimibe 10 mg		Placebo Q4W and Ezetimibe 10 mg	
		−40.8#	−42.6#	−50.7#	−63.0#		−14.8	

AMG, AMG145; FH, familial hypercholesterolemia; Q2W, every 2 weeks; Q4W, every 4 weeks; SAR, SAR236553/REGN727.
*$P < 0.0001$ versus placebo.
†$P < 0.001$ versus atorvastatin 80 mg and placebo.
††$P < 0.001$ versus placebo.
#$P < 0.001$ versus ezetimibe and placebo.
αmean change in LDL-C versus placebo.

Current Opinion in Lipidology Volume 24(3), June 2013, p 251–258

Outcome studies

	FOURIER	ODYSSEY OUTCOMES	SPIRE I	SPIRE II
PCSK9 inhibitor v. Placebo	Evolocumab	Alirocumab	Bococizumab	Bococizumab
Planned Enrollment	22,500	18,000	12,000	6,300
Primary Endpoint	CV death, MI, hospitalization for unstable angina, stroke, or coronary revascularization	CHD death, MI, ischemic stroke, or unstable angina requiring hospitalization	CV death, MI, stroke, or hospitalization for unstable angina needing urgent revascularization	CV death, MI, stroke, or hospitalization for unstable angina needing urgent revascularization
Study Population	History of CV disease and high risk for recurrent event	Hospitalized for ACS in previous 4-52 weeks	High risk for CV events	High risk for CV events
LDL-C at Entry	≥ 70 mg/dL	≥ 70 mg/dL	70-100 mg/dL	≥ 100 mg/dL
Dose (if available) & Frequency of Study Drug	Q2W and QM	Q2W	150 mg Q2W	150 mg Q2W
Estimated Completion Date	December 2017	January 2018	August 2017	August 2017

Summary (2)

- PCSK9 inhibition induces LDLc reduction by more than 50%.
- PCSK9 inhibition also reduces Lp(a) levels.
- Effects of PCSK9 inhibitor seem to be consistent even under maximal statin doses, or even for hetero-FH patients. Moreover interpersonal variation seems to be small, too.
- CVD prevention through PCSK9 inhibition will be proved soon. (FOURIER study etc.)

Question 1 ;

- PCSK9 is mainly expressed in adult liver, small intestine, kidneys, and pancreas and circulating PCSK9 can inhibit VLDLR, apoER2, LRP1, CD36 in those organs and adipose tissue. ; PCSK9 inhibition may be associated with fatty deposition in fat and liver (NASH) ?
- Annexin A2, a natural extrahepatic PCSK9 inhibitor, is highly distributed in adrenal gland ; PCSK9 inhibitor does little to adrenal gland

Question 2

- PCSK9 is highly expressed in pancreatic beta cells ; why ?
- Could PCSK9 inhibition aggravate insulin resistance (MS) ?
- LDLR and CD81, 2 HCV entry receptors are dose dependently downregulated by PCSK9 ; May PCSK9 inhibition increase the risk of HCV infection ?

Question 3

- PCSK9 may enhance CD36-related activities (in macrophages); may be of atherogenic ?

Stawowy P. Proprotein convertases in atherogenesis. Curr Opin Lipidol. 2015 Aug;26(4):338-44.

PCSK9 is not alone

PCSK		Tissue distribution	Subcellular localization	Secretion
Kexin-like	(R/K)Xn(R/K)↓			
PCSK1		Neuroendocrine	Acidic regulated secretory granules	Secreted
PCSK2		Neuroendocrine	Acidic regulated secretory granules	Secreted
PCSK3 (Furin)		Ubiquitous	TGN, cell surface and endosomes	Shed
PCSK4		Germinal	Cell surface?	Shed
PCSK5		Widespread: adrenal cortex, intestine, kidney and ovary	Cell surface and ECM	PCSK5A: secreted; PCSK5B: shed
PCSK6 (PACE4)		Widespread: muscle, heart, pituitary, intestine, cerebellum and kidney	Cell surface and ECM	Secreted
PCSK7		Ubiquitous	TGN, cell surface and endosomes	Not secreted
Pyrolysin-like	RX(L/V/I)X↓			
PCSK8 (SKI-1)		Ubiquitous	*cis*- and *medial*-Golgi	Not secreted
Proteinase K-like	(V/I/L)FAQ↓			
PCSK9		Liver, intestine and kidney	TGN and extracellular	Secreted

ECM, extracellular matrix; PACE4, paired basic amino acid cleaving enzyme 4; SKI-1, subtilisin/kexin isozyme 1; TGN, *trans*-Golgi network. Adapted and reprinted with permission from [2].

Stawowy P. Proprotein convertases in atherogenesis. Curr Opin Lipidol. 2015 Aug;26(4):338-44.

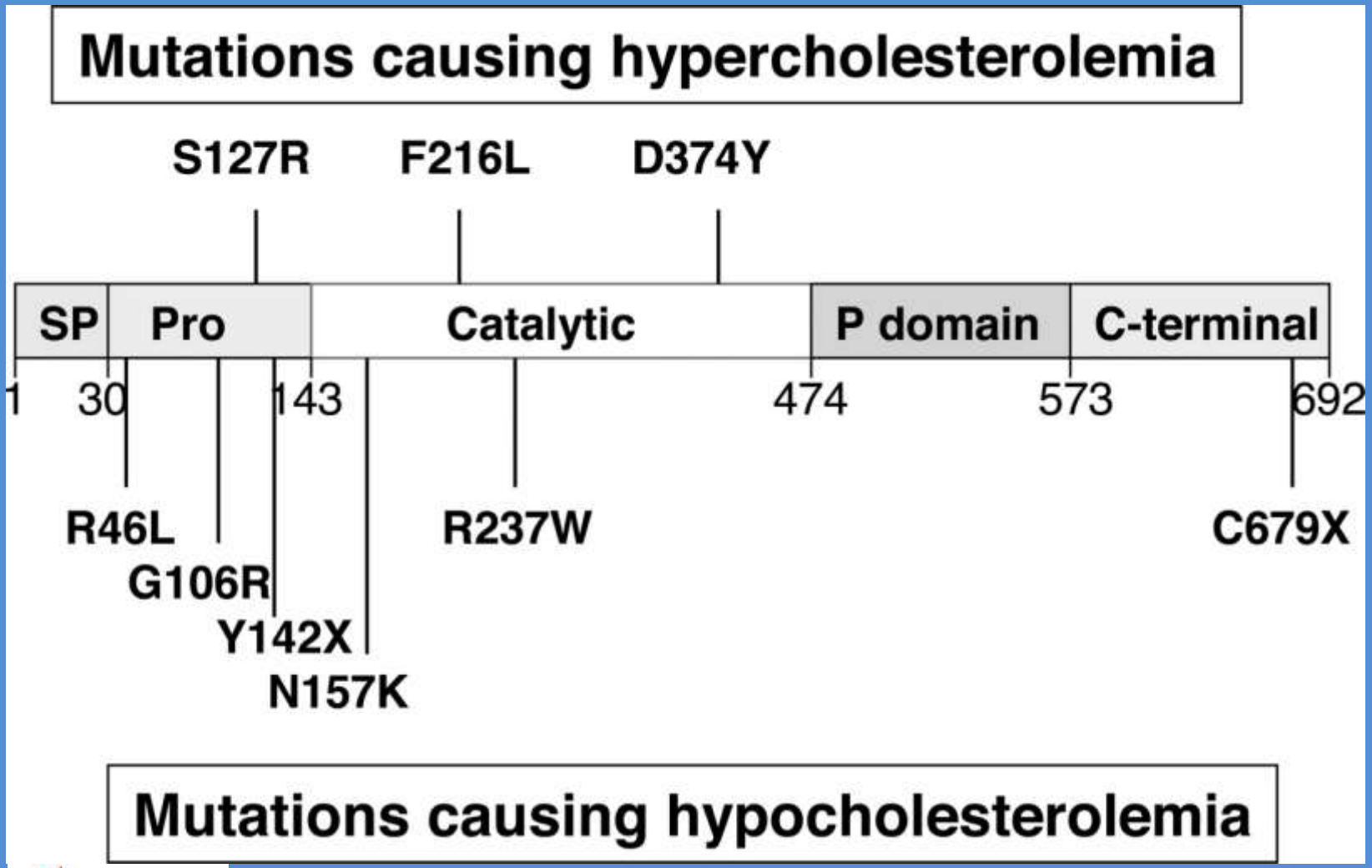
	Carotid ath	VSMC	Ma	Adipose	Cardio-myo
1	●	-	-	● (?)	-
2	●	-	-	-	-
3 (F)	●	●	-	● ●	●
4	●	-	-	-	-
5	●	-	-	●	-
6 (P)	● ●	-	●	-	-
7	● ●	-	-	-	-
8	●	-	-	-	-
9	●	-	●	● (?)	-

Other Future Perspetives

- Other PCSK9 inhibition ;
  - vaccination ; Vaccination with small peptides directed to the PCSK9 N-terminus, which interacts with the LDL-R, resulted in prolonged antibody production (half-life about 4 months), accompanied by a significant reduction in lipoproteins for up to 1 year (> 50% LDL-C reduction in LDL-$R^{+/-}$mice)
  - chemicals ; Adnectin BMS-962476 (molecular weight ~ 11 kDa; Bristol-Myers Squibb) successfully reduced free PCSK9 (>99% reduction) and LDL-C (~ 55% reduction), with succeeding increases in total PCSK9 indicating reduced clearance of the Adnectin/PCSK9 complex.
- Other PCSK modulators ; 3 and 6 ?

Stawowy, Philipp Current Opinion in Lipidology. 26(4):338-344, August 2015.

PCSK9 gene.



American Heart Association.

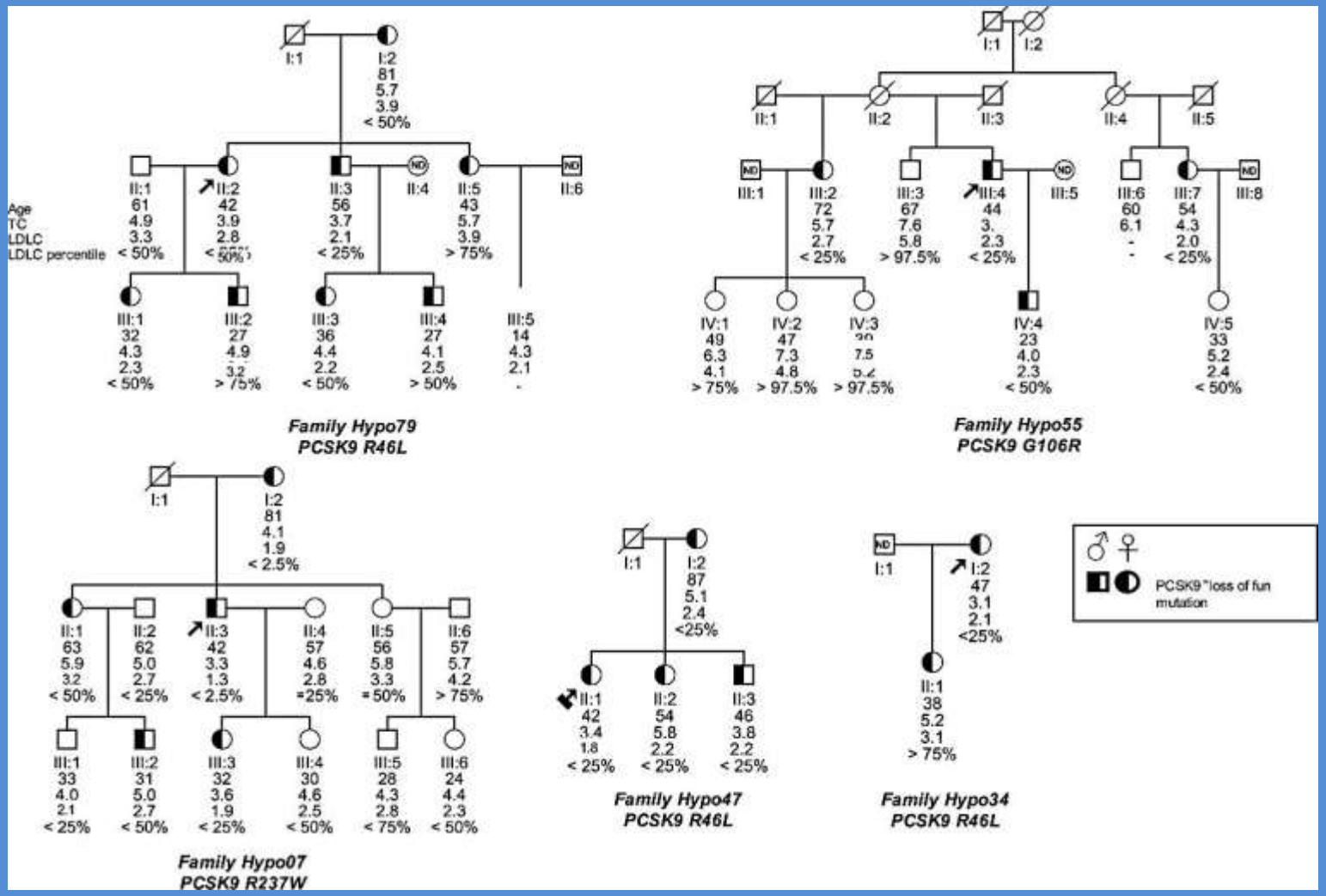
Knut Erik Berge et al. Arterioscler Thromb Vasc Biol. 2006; 26:1094-1100

Table 1
Loss-of-function and gain-of-function PCSK9 mutations in different geographical patients and clinical features associated with the mutations.

Mutations of PCSK9		Geographical origin	Clinical features	Change of LDL-C concentration	*In vitro* testing	References
Loss-of-function	C679X	French, American	Reduce 88% risk of CAD	Decreased by 27%	Cell culture	Cohen JC et al. [16,20]
	R46L	Danish, American	Reduce 47% risk of CAD	Decreased by 8–9%; 9–15%; 11–16%	Cell culture	Cohen JC et al. [20]
	Y142X	French	Hypocholesterolemia	Decreased by 28%		Cohen JC et al. [20]
	G236S	Norway	Hypocholesterolemia	Not available	Determined in HepG2 or HEK293 cells transiently transfected	Cameron J et al. [30]
	N354I			Not available		
	Q152H	French-Canadian family	Hypocholesterolemia	Decrease 48%	Cells transiently transfected with PCSK9-Q152H cDNA	Mayne J et al. [15]
Gain-of-function	R215H	Norway	Hypercholesterolemia	Not available	Determined in HepG2 or HEK293 cells transiently transfected	Cameron J et al. [30]
	S127R	French	Hypercholesterolemia	Not available		Abifadel et al. [10]
	E32K	Japanese	Hypercholesterolemia	2.1-Fold, 1.4-fold higher than control, separately	Transiently transfected HepG2 cells	Noguchi T et al. [31]
	E670G	Chinese	Increasing HDL-C and ApoA1/ ApoB in male;	Not available	Not available	Aung LH et al. [32]
		Taiwan	Reducing LDL-C	Not available	Not available	Hsu LA et al. [34]

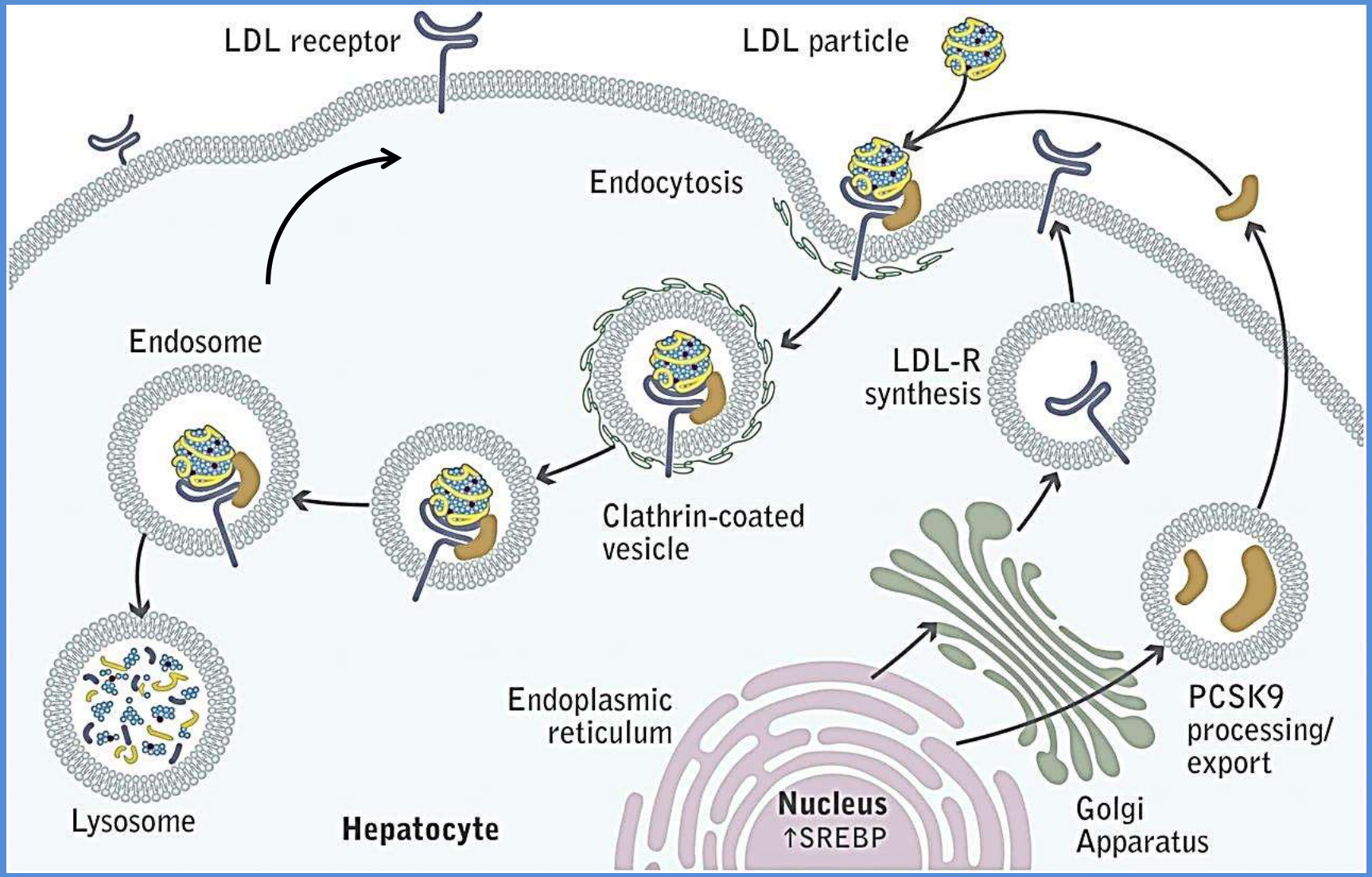
N.-Q.Wu, J.-J. Li / Clinica Chimica Acta 431 (2014) 148–153

Pedigrees of families with mutations R46L, G106R, N157K, or R237W in the PCSK9 gene.



Knut Erik Berge et al. Arterioscler Thromb Vasc Biol. 2006; 26:1094-1100

The role of PCSK9



Lambert G et al. J. Lipid Res. 2012;53:2515-2524

Comparison of Small-Molecule and Monoclonal Antibody Therapeutics

	Small Molecule	Monoclonal Antibody
Size, kDa	≈0.5	≈150
Structure	Chemical entity	Immunoglobulin
Method of production	Controlled chemical synthesis; easily controlled	Purification from cell culture media; more complex
Target	Intracellular or extracellular	Extracellular
Target specificity	Low(er)	High
Metabolism disposition	Hepatic/renal	RES, target-mediated
Administration	Oral	Parenteral
Dosing	Approximately daily	Approximately Q2W–Q4W
Can cross BBB	Potentially	No

Q2W indicates every 2 weeks; Q4W, every 4 weeks; and RES, reticuloendothelial system.

Circulation. 2013;127:2222-2230

Table Marketed Therapeutic Monoclonal Antibodies With Food and Drug Administration–Approved Indications* (as of December 2012)

Agent	Binding	Target	Mechanism of Action†	Type of Antibody	Indication(s)
Oncology					
Alemtuzumab	(Campath)	CD52	ADCC, CDC	Humanized	CLL
Bevacizumab	(Avastin)	VEGF	Ag	Humanized	CRC, non–small-cell lung and renal cell carcinomas, glioblastoma
Brentuximab vedotin	(Adcetris)	CD30	ADC	Chimeric, with MMAE (microtubule-disrupting agent)	HL, systemic anaplastic large-cell lymphoma
Cetuximab	(Erbitux)	EGFR	Ag, ADCC	Chimeric CRC,	squamous cell carcinoma of the head and neck
Ibritumomab	(Zevalin)	CD20	Ag	Murine, with yttrium-90 or indium-111 (delivery of radionuclide)	NHL
Ipilimumab	(Yervoy)	CTLA-4	Ag	Human	Melanoma
Ofatumumab	(Arzerra)	CD20	Ag,ADCC,CDC	Human	CLL
Panitumumab	(Vectibix)	EGFR	Ag	Human	CRC
Pertuzumab	(Perjeta)	HER2	Ag, ADCC	Humanized	Breast cancer
Rituximab	(Rituxan)	CD20	Ag,ADCC,CDC	Chimeric	NHL, CLL
Tositumomab	(Bexxar)	CD20	Ag (delivery of radionuclide), possibly ADCC and CDC	Murine, with iodine-131	NHL
Trastuzumab	(Herceptin)	HER2	Ag, ADCC	Humanized	Breast cancer, gastric or gastroesophageal junction adenocarcinoma
Immunomodulatory settings					
Adalimumab	(Humira)	TNFα	Ag,ADCC,CDC38	Human	RA, PsA, AS, CD, PsO, JIA
Basiliximab	(Simulect)	CD25	Ag	Chimeric	Organ (kidney) transplantation rejection
Belimumab	(Benlysta)	Soluble human BlyS	Ag	Human	Systemic lupus erythematosus
Canakinumab	(Ilaris)	IL-1β	Ag	Human	Cryopyrin-associated periodic syndrome
Certolizumab pegol	(Cimzia)	TNFα	Ag	Humanized pegylated Fab	RA, CD
Golimumab	(Simponi)	TNFα	Ag,ADCC,CDC38	Human	RA, PsA, AS
Infliximab	(Remicade)	TNFα	Ag,ADCC,CDC38	Chimeric	RA, PsA, AS, CD, ulcerative colitis, PsO
Natalizumab	(Tysabri)	α4-Integrin	Ag	Humanized	Multiple sclerosis, CD
Omalizumab	(Xolair)	IgE	Ag	Humanized	Allergic asthma
Rituximab	(Rituxan)	CD20	Ag,ADCC,CDC	Chimeric	RA, Wegener granulomatosis, microscopic polyangiitis
Tocilizumab	(Actemra)	IL-6 receptor	Ag	Humanized	RA, systemic JIA
Ustekinumab	(Stelara)	p40 Subunit of IL-12 and IL-23	Ag	Human	PsO
Cardiology					
Abciximab	(ReoPro)	Glycoprotein IIb/IIIa	Ag	Chimeric Fab	Percutaneous coronary intervention
Other					
Denosumab	(Prolia, Xgeva)	RANKL	Ag	Human	High fracture risk from PMO, CRPC, or aromatase inhibitor–treated breast cancer
Eculizumab	(Soliris)	Complement protein C5	Ag	Humanized	Paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome
Palivizumab	(Synagis)	RSV F protein	Ag	Humanized R	SV infection
Ranibizumab	(Lucentis)	VEGF-A	Ag	Humanized	Wet age-related macular degeneration, macular edema postretinal vein occlusion
Raxibacumab	(ABthrax)	Bacillus anthracis toxin	Ag	Human	Inhalation anthrax

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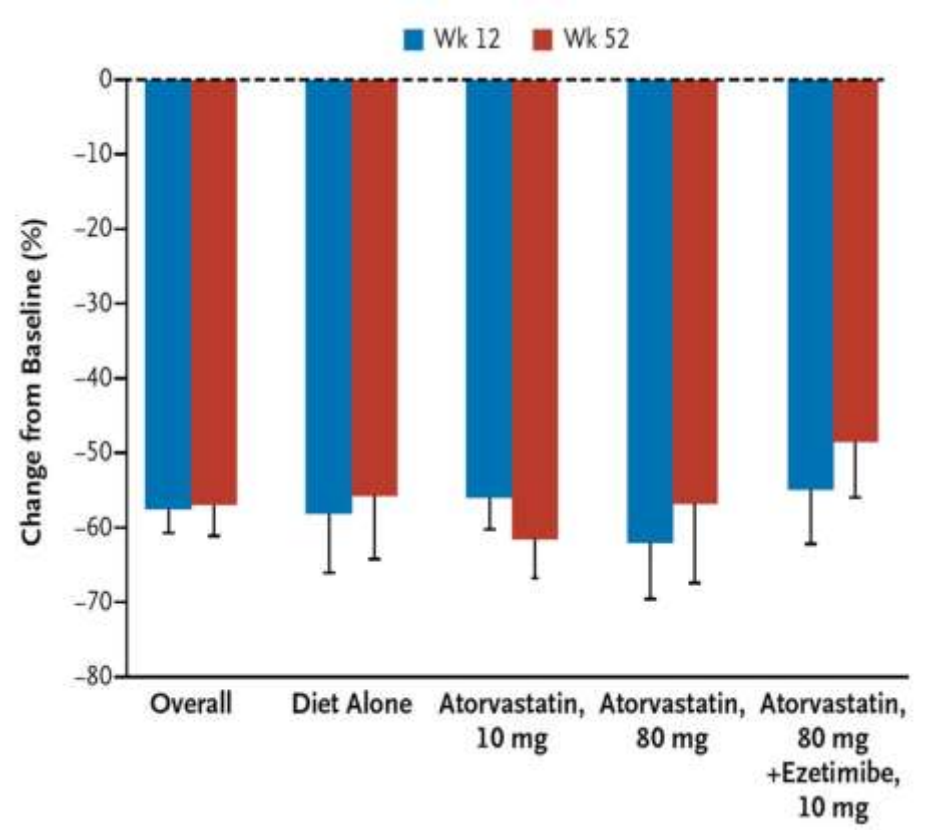
DESCARTES: 52-week efficacy and safety of evolocumab 420mg q4w



%	Placebo N=302	Evolocumab N=599
Any AE	74.2	74.8
SAE	4.3	5.5
Discontinue	1.0	2.2

Blom et al. NEJM 2014

ODYSSEY LONG TERM: safety

% (n) of patients All pts on background of maximal statin therapy ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with 2 consecutive LDL cholesterol <25 mg/dL (n = 562)	Placebo (n=788)
TEAEs	78.6% (1218)	71.9% (404)	80.6% (635)
Treatment-emergent SAEs	16.5% (255)	14.6% (82)	17.6% (139)
TEAE leading to death	0.5% (7)	0.5% (3)	1.0% (8)
TEAEs leading to treatment discontinuation	6.2% (96)	3.6% (20)	5.5% (43)

% (n) of patients All pts on background of maximally tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with 2 consecutive LDL-C <25 mg/dL (n=562)	Placebo (n=788)
General allergic reaction events*	9.0% (140)	6.0% (34)	9.0% (71)
Treatment-emergent local injection site reactions	5.8% (90)	3.7% (21)	4.3% (34)
Neurological events‡	4.2% (65)	1.8% (10)	3.9% (31)
All cardiovascular events†	4.0% (62)	3.2% (18)	4.4% (35)
Ophthalmological events‡	2.5% (38)	1.8% (10)	1.9% (15)
Neurocognitive disorders‡	1.2% (18)	0.5% (3)	0.5% (4)
Haemolytic anaemia	0	0	0