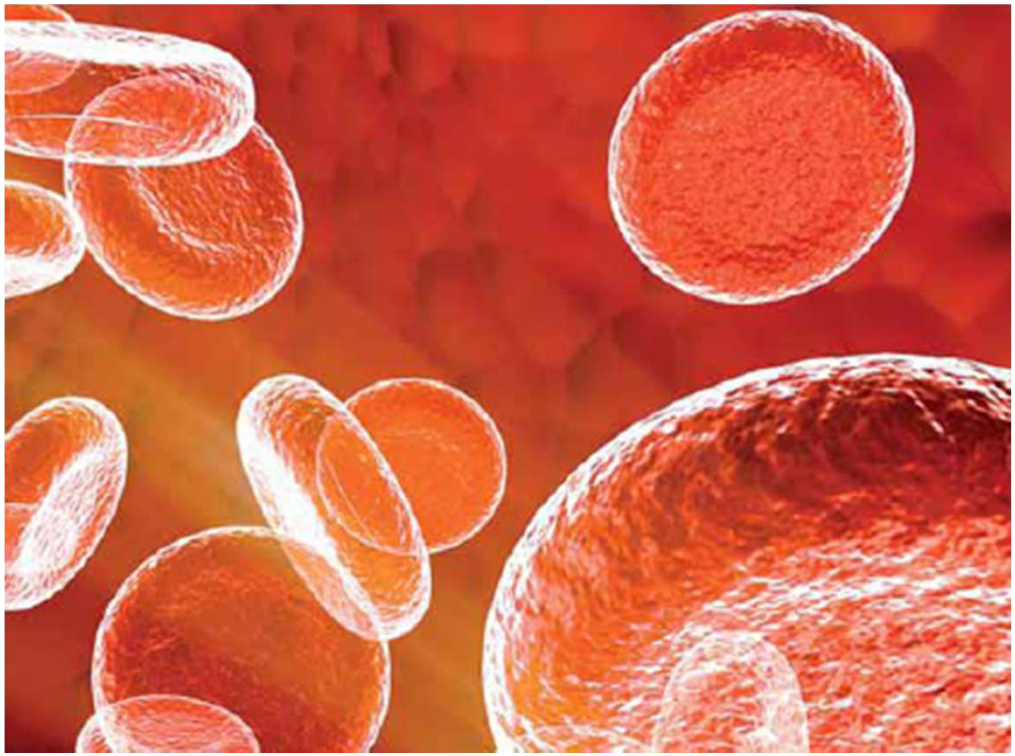
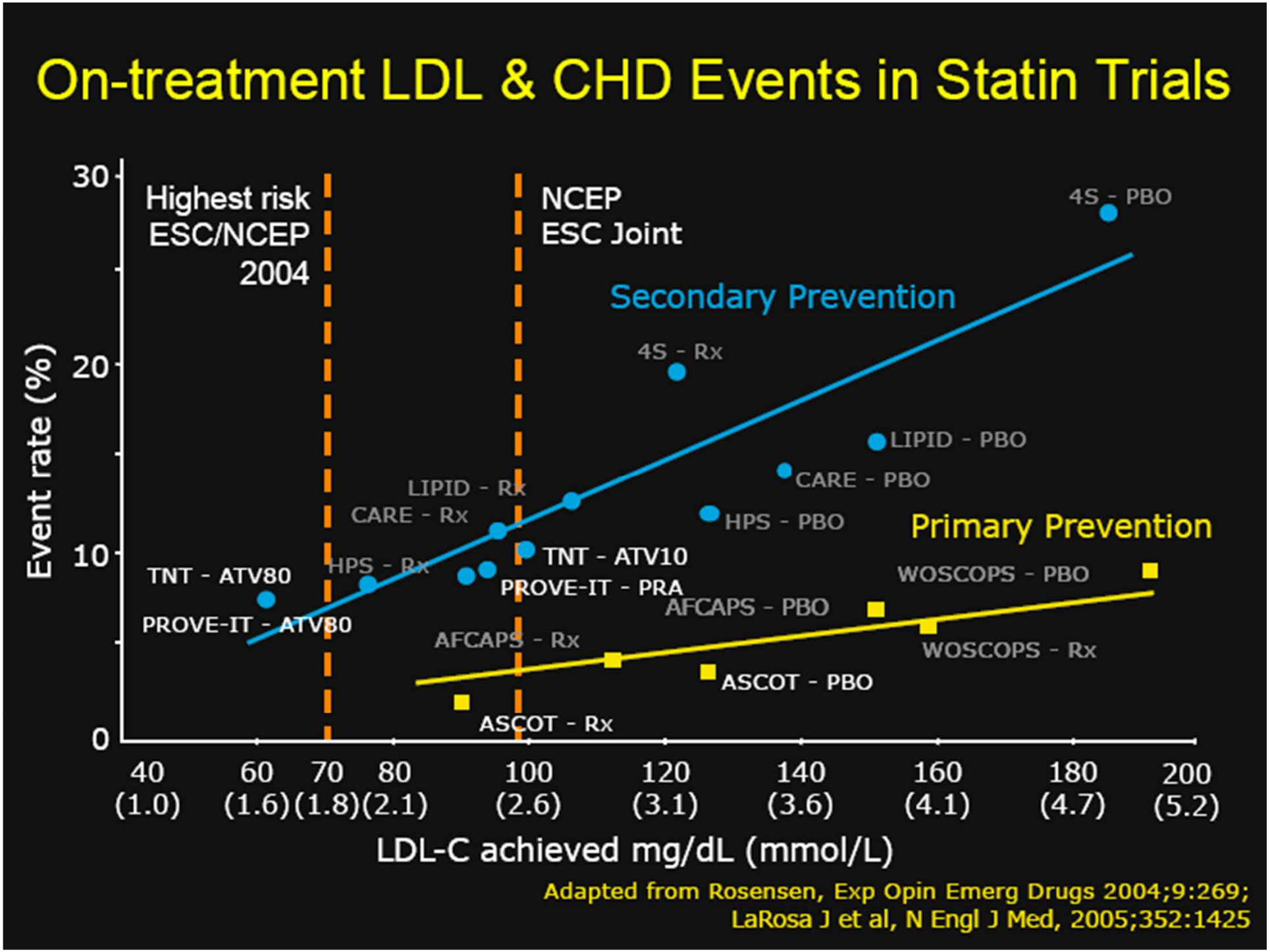


X
Reunión Riesgo Vascular
Alicante

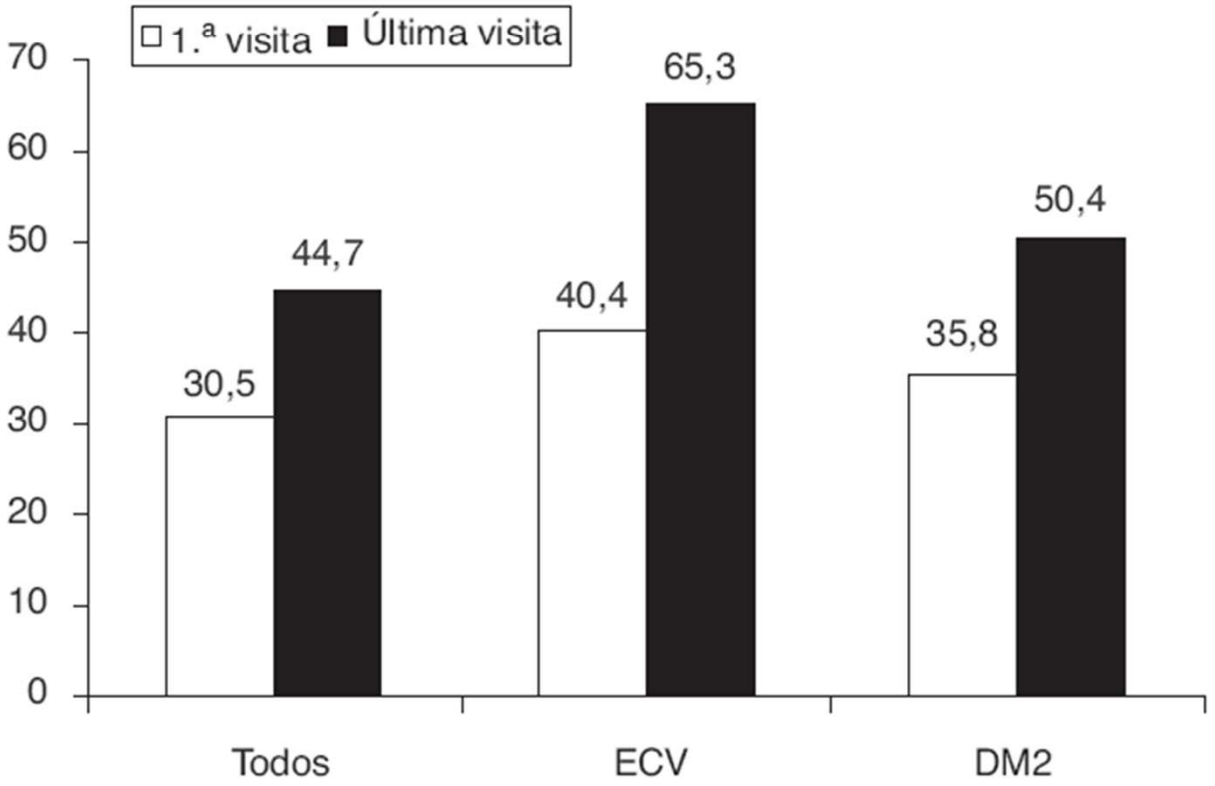
EFICACIA Y SEGURIDAD DE LOS ANTI-PCSK9

Núria Plana Gil
Unitat de Medicina Vascular i Metabolisme
Hospital Universitari de Sant Joan de Reus

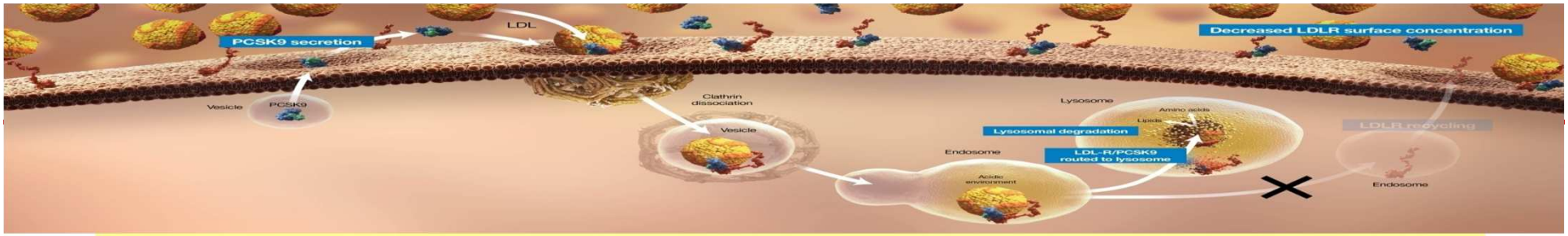

On-treatment LDL & CHD Events in Statin Trials
Highest risk
ESC/NCEP
2004
NCEP
ESC Joint
Secondary Prevention
Primary Prevention
4S - PBO
4S - Rx
LIPID - PBO
CARE - PBO
LIPID - Rx
CARE - Rx
HPS - PBO
TNT - ATV10
HPS - Rx
TNT - ATV80
PROVE-IT - PRA
WOSCOPS - PBO
AFCAPS - PBO
PROVE-IT - ATV80
AFCAPS - Rx
WOSCOPS - Rx
ASCOT - PBO
ASCOT - Rx
Event rate (%)
0
10
20
30
40 (1.0)
60 (1.6)
70 (1.8)
80 (2.1)
100 (2.6)
120 (3.1)
140 (3.6)
160 (4.1)
180 (4.7)
200 (5.2)
LDL-C achieved mg/dL (mmol/L)
Adapted from Rosensen, Exp Opin Emerg Drugs 2004;9:269;
LaRosa J et al, N Engl J Med, 2005;352:1425

Consecución del objetivo terapéutico del colesterol de las lipoproteínas de baja densidad en las unidades de lípidos y riesgo vascular de la Sociedad Española de Arteriosclerosis

Juan Pedro-Botet[a,*], José M. Mostaza[b], Xavier Pintó[c] y José R. Banegas[d], en nombre del grupo de investigadores EDICONDIS-ULISEA[◊]



Clin Invest Arterioscl. 2013;25(4):155-163



Monoclonal antibodies		
Alirocumab (SAR236553, REGN727)	Sanofi (Regeneron)	Phase III
Evolocumab (AMG 145)	Amgen	Phase III
Bococizumab (PF-0490615 /RN316)	Pfizer (Rinat)	Phase III
MPSK 3169A (RG7652)	Genentech (Roche)	Phase II
LY3015014	Lilly	Phase II
PCSK9 protein binding fragment		
Bristol Myers Squibb/Adnexus	BMS-962476 (Adnectin)	Phase I
PCSK9 synthesis inhibitor/siRNA		
Alnylam/The Medicines Co	ALN-PCS02	Phase I
Small molecule		
Serometrix	SX-PCK9	Preclinical

Summary of Designs and Dosing: **Alirocumab** Program (Phase 2)

Randomized Phase 2 population (n=352)
Hypercholesterolemia (HeFH or non-HeFH) and LDL-C ≥100 mg/dL (≥2.59 mmol/L) on background therapy of statin or statin plus ezetimibe 10 mg

Study number	**1003[1]**	**11565[2]**	**11566[3]**
Duration	**12 weeks**	**12 weeks**	**8 weeks**
Patients	**HeFH (n=77)[†]**	**HC (n=183)[†]**	**HC (n=92)[†]**
Alirocumab doses	**150, 200, 300 mg Q4W** **150 mg Q2W (n=16)**	**200–300 mg Q4W** **50–100 mg Q2W** **150 mg Q2W (n=31)**	**150 mg Q2W+ATV 10→80 mg** **150 mg Q2W+ATV 10→10 mg** **(total n=61)**
Placebo	**n=15**	**n=31**	**Placebo+ATV 10→80 mg (n=31)**

Alirocumab 150 mg Q2W
delivered via single 1 mL injection

Pooled analysis population	**Alirocumab 150 mg Q2W n=108[‡]**	**Placebo n=77[‡]**

1.Stein EA et al. *Lancet.* 2012;380:29-36.
2. McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344-2353.
3. Roth EM et al. *N Engl J Med.* 2012;367:1891-1900.

[‡]Respectively, 104 and 75 patients in the alirocumab 150 mg Q2W and placebo groups had LDL-C assessed during treatment and were included in the efficacy analyses.
ATV = atorvastatin; HC = hypercholesterolemic; Q2W = every 2 weeks; Q4W = every 4 weeks.

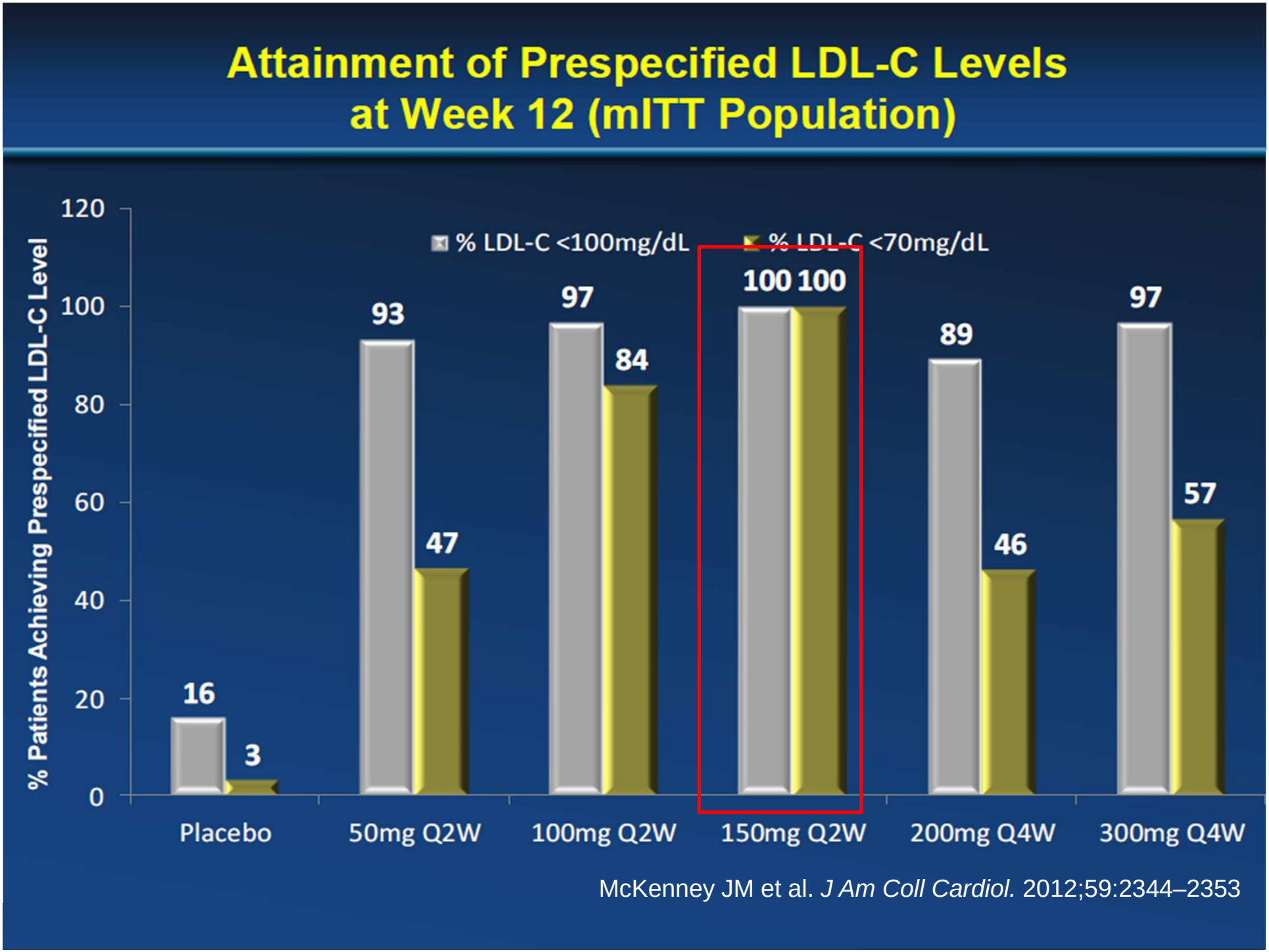
Efficacy of Alirocumab 150 mg Q2W

Patient population (%)	N	LDL-C*	ApoB	Lp(a)	TG
On stable atorvastatin therapy[1]	183	-67.3	-58.3	-28.6	-28.6
On atorvastatin 10 mg[2]	92	-66.2	-54.4	-34.7	-4.0
HeFH[3]	77	-57.3	-43.8	-19.5	-5.7

*Primary efficacy endpoint. Data expressed as % change *vs* placebo (except ref. 2: % change *vs* baseline)

1.Roth EM et al. *N Engl J Med.* 2012;367:1891-1900.
2.McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344-2353.
3.Stein EA et al. *Lancet.* 2012;380:29-36.

Attainment of Prespecified LDL-C Levels at Week 12 (mITT Population)



McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344–2353

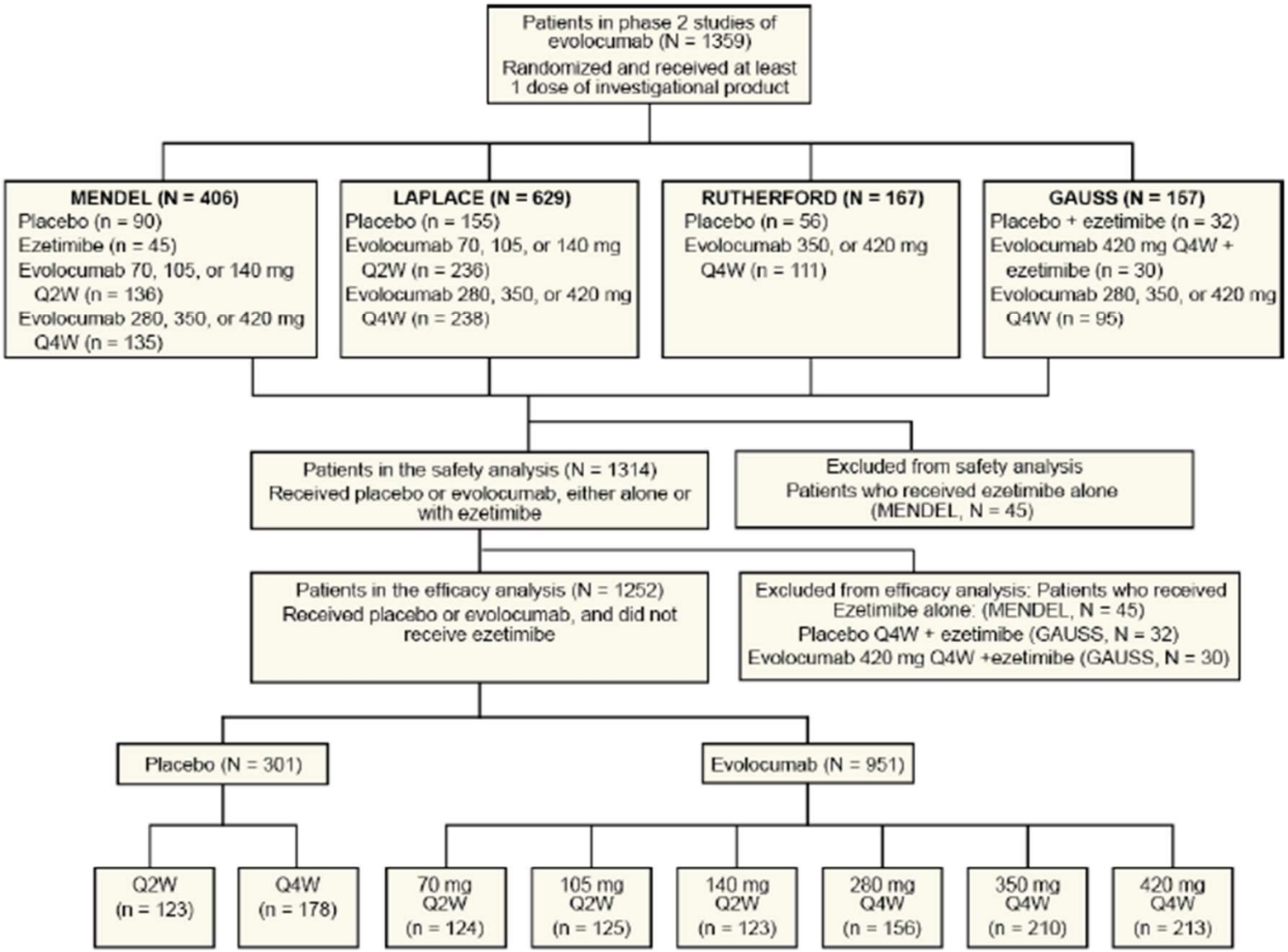
Alirocumab Program (Phase 2)
Safety Summary

Safety population	11565[1]		11566[2]		1003[3]	
	Placebo (n=31)	All treatment groups (n=151)	Placebo (n=31)	All treatment groups (n=61)	Placebo (n=15)	All treatment groups (n=62)
Overview of all TEAEs, n (%)						
Patients with any TEAE	14 (45.2)	91 (60.3)	19 (61.3)	32 (52.5)	9 (60.0)	50 (80.6)
Patients with any treatment-emergent SAE	1 (3.2)	3 (2.0)	0 (0)	1 (1.6)	1 (6.7)	0 (0)
Patients with any TEAE leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Patients with any TEAE or treatment-emergent SAE leading to permanent treatment discontinuation	0 (0)	6 (4.0)	4 (12.9)	1 (1.6)	0 (0)	1 (1.6)

- The most common TEAE was mild injection-site reactions
- No persistent or prevalent liver or skeletal muscle safety signals were noted
- 5 Serious AEs were reported in 4 patients in active treatment arms (1.5%) , with 1 patient experiencing 2 SAEs (leukocytoclastic vasculitis and subsequent humerus fracture).
- 2 Serious AEs occurred in two patients (2.6%) who received placebo (sciatica, small bowel obstruction).

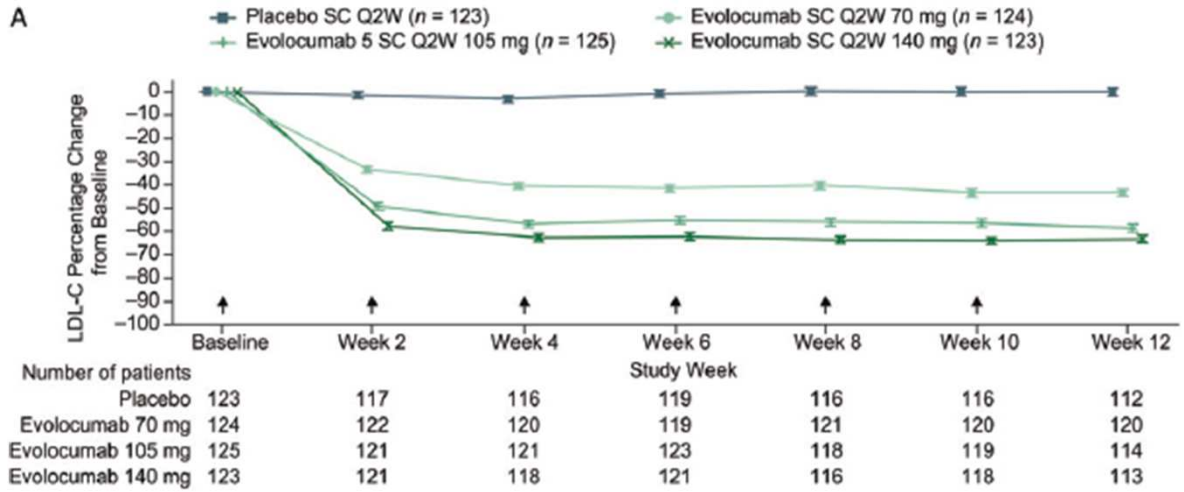
1.McKenney JM et al. *J Am Coll Cardiol.* 2012;59:2344-2353.
2.Roth EM et al. *N Engl J Med.* 2012;367:1891-1900
3.Stein EA et al. *Lancet.* 2012;380:29-36.

Efficacy and Safety of Evolocumab: pooled analysis of 1359 patients in four Phase 2 Trials. PROFICIO Program

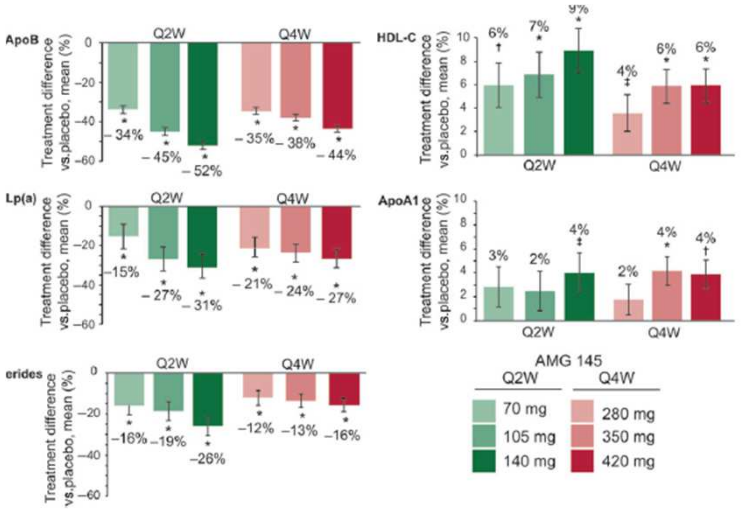


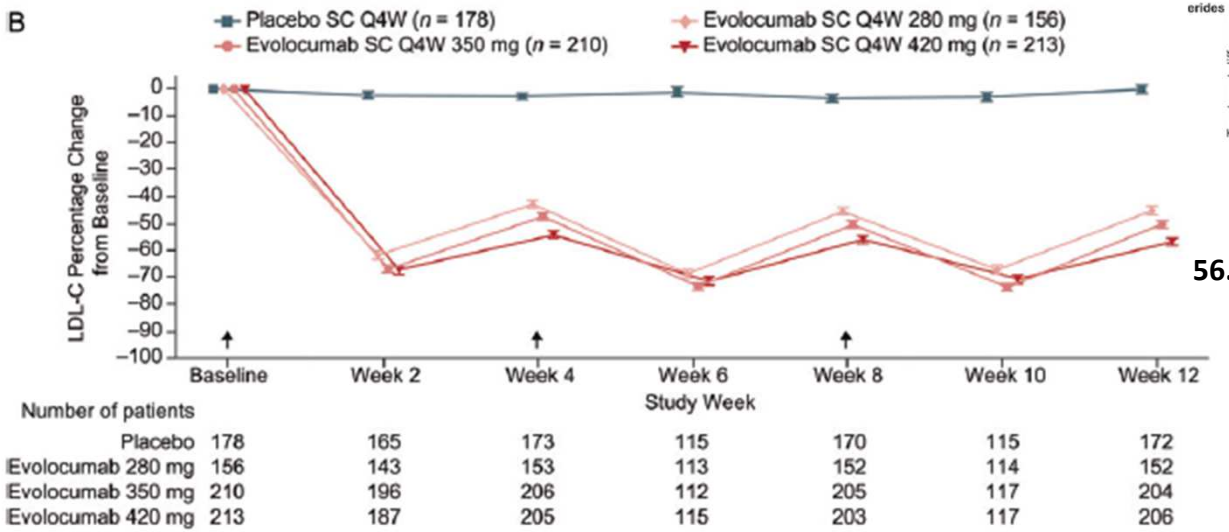
Stein EA et al. Eur Heart J. 2014 Mar 4 (in print)

Efficacy and Safety of Evolocumab: pooled analysis of 1359 patients in four Phase 2 Trials. PROFICIO Program



62.6%





56.2 %

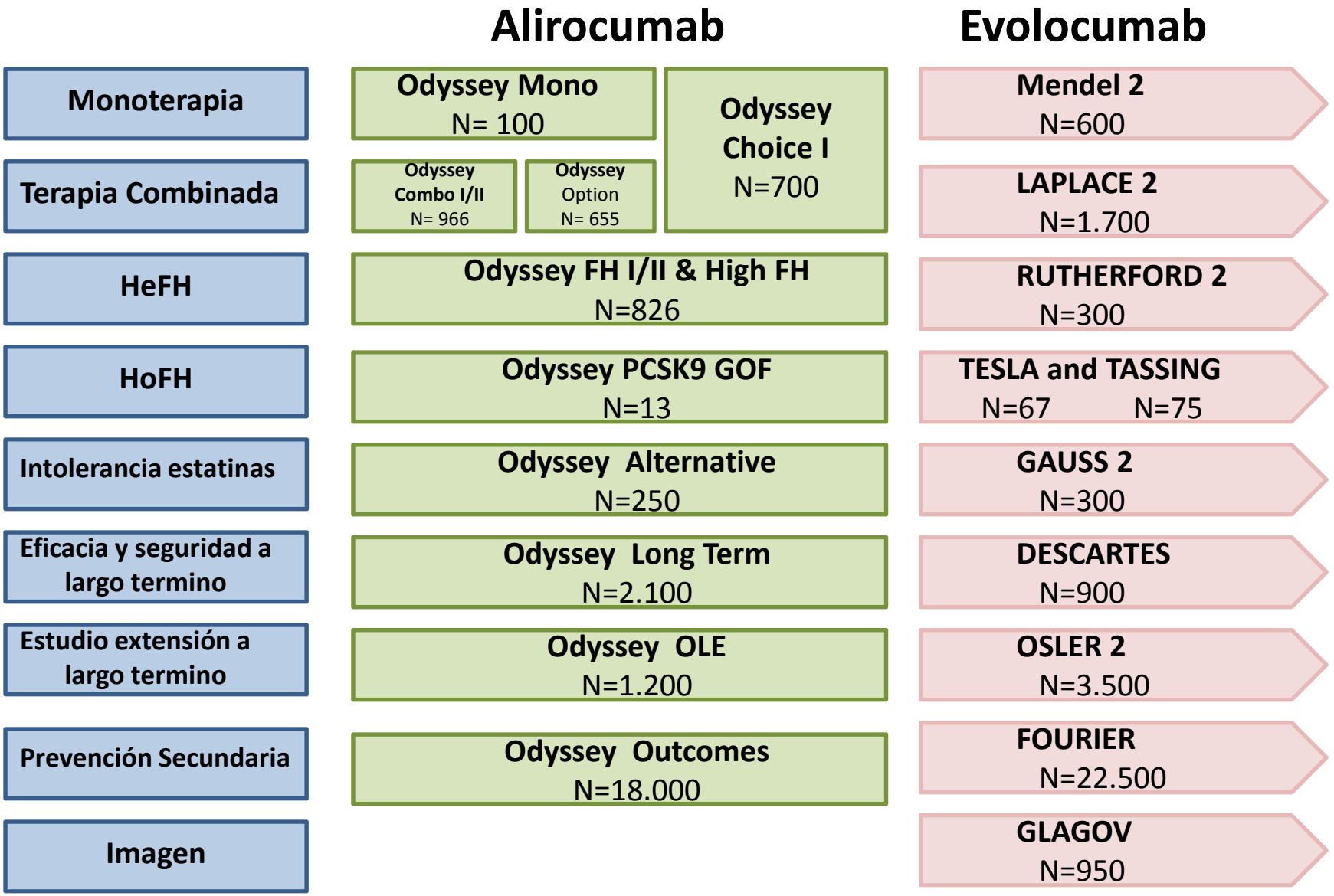
Stein EA et al. Eur Heart J. 2014 Mar 4 (in press)

Efficacy and Safety of Evolocumab: pooled analysis of 1359 patients in four Phase 2 Trials. PROFICIO Program

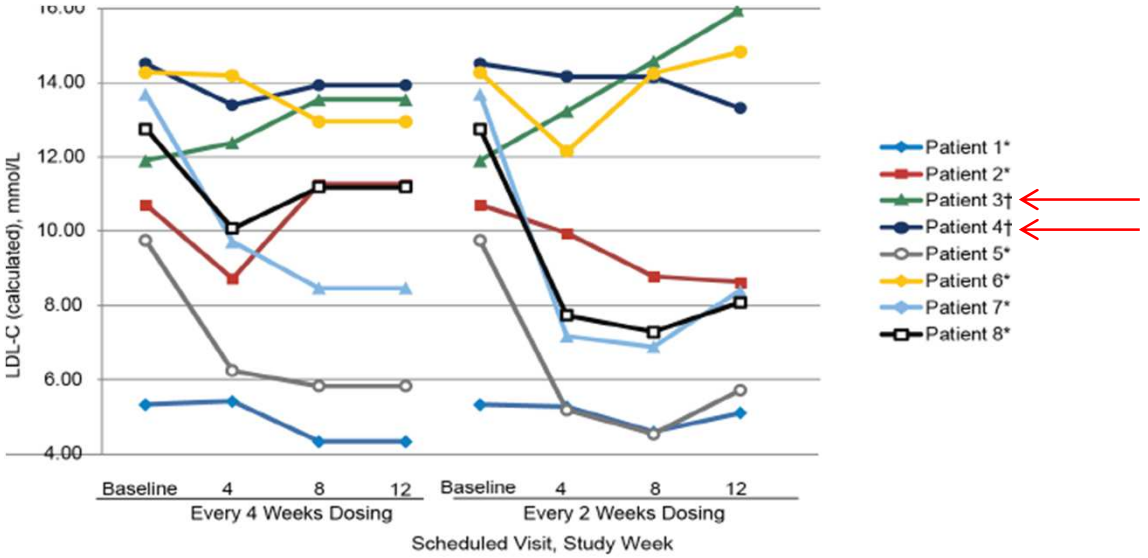
	Placebo(nº333)	Evolocumab(nº981)
Alguno	164(49.2%)	557(56.8%)
Grave	4(1.2%)	20(2.0%)
Transas x3	2(0.6%)	4(0.4%)
CPK x 5	3(0.9%)	**14(1.4%)**
Los más frecuentes		
Rinofaringitis	25(7.5%)	**81(8.3%)**
Infección respiratoria alta	11(3.3%)	32(3.3%)
Mialgia	4(1.2%)	**32(3.3%)**
Cefalea	11(3.3%)	32(3.3%)
Dolor de espalda	7(2.3%)	**28(2.9%)**
Ac Anti PCSK9	1(0.3%)	1(0.1%)

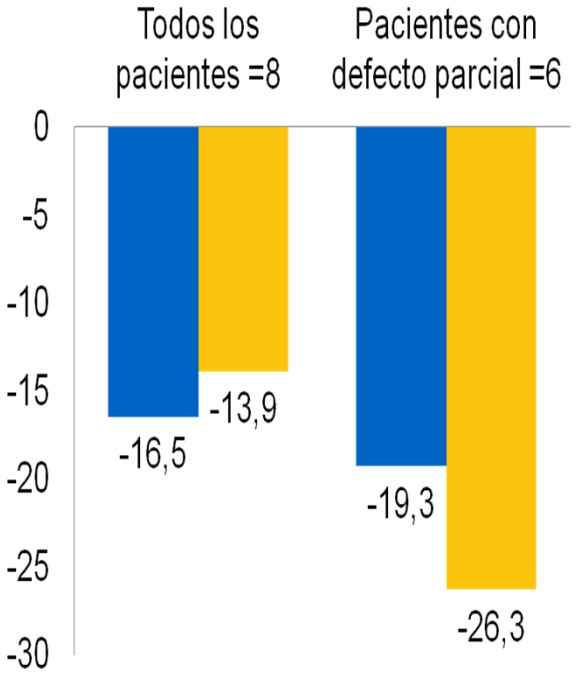
Stein EA et al. Eur Heart J. 2014 Mar 4 (in press)

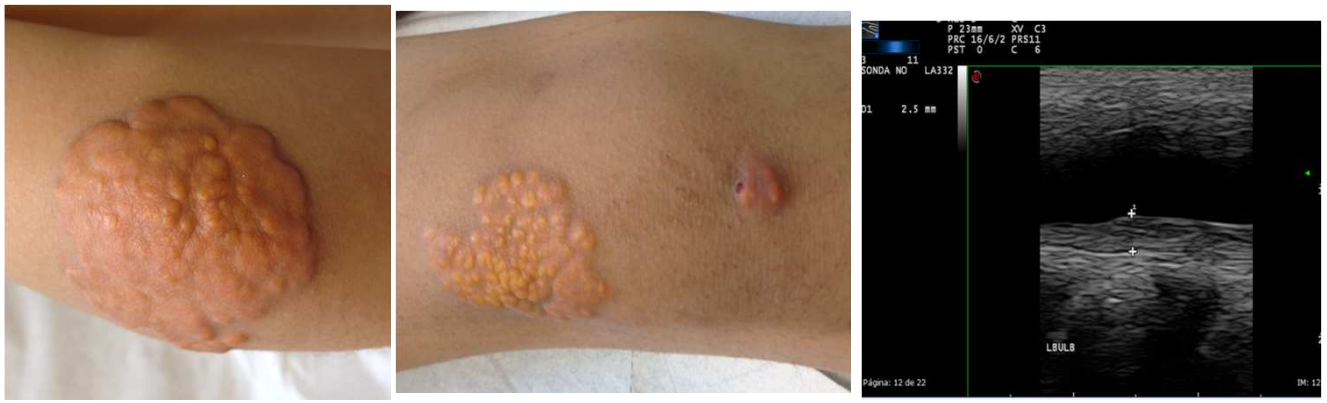
PROGRAMA EN FASE III: ODYSSEY (ALIROCUMAB) Y PROFICIO (EVOLOCUMAB)



Eficacia del Evolocumab en pacientes con HF Homocigota. Descenso del C-LDL tras 12 semanas. TESLA





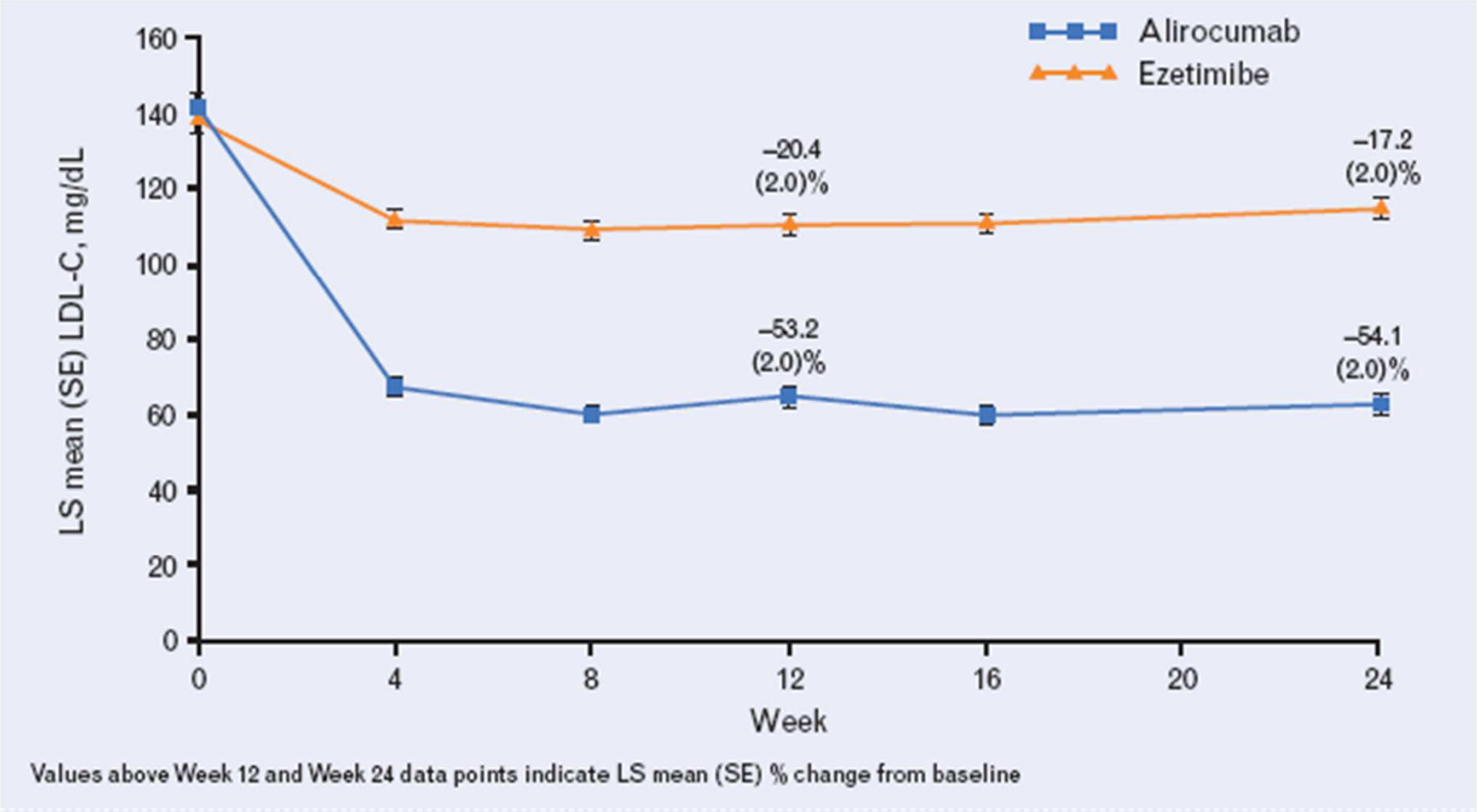


Stein et al Circulation 2013;128: 2113-2120

A 24-Week Study of Alirocumab as Monotherapy versus Ezetimibe: The First Phase 3 Data of a Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor.

ODYSSEY MONO

Nº: 103 pacients **Nº: 51 Ali 75 mg/2W+ PL oral** **Nº: 52 PL SC+ EZT 10 mg/día**



Roth EM et al. Poster presentation at ACC 2014. Abstract 1183-125.

A 24-Week Study of Alirocumab as Monotherapy versus Ezetimibe: The First Phase 3 Data of a Proprotein Convertase Subtilisin/Kexin Type 9 Inhibitor.

ODYSSEY MONO

	Alirocumab(nº51)	Ezetimiba(nº:52)
Alguno	36(69.2%)	40(77.8%)
Grave	1(1.9%)	1(2%)
Transas x3	0	0
CPK x 3 x10	0 0	**1(2%)** **1(2%)**
Más frecuentes >5%		
Rinofaringitis	**12(23.1%)**	8(15.7%)
Diarrea	**6(11.5%)**	2(3.9%)
Gripe	**6(11.5%)**	3(5.9%)
Artralgia	**3(5.8%)**	2(3.9%)
Cefalea	**3(5.8%)**	2(3.9%)
Musculares	8(15.4%)	**11(21.6%)**

Roth EM et al. Poster presentation at ACC 2014. Abstract 1183-125.

OneYear Open label Treatment with Alirocumab 150 mg every two weeks in Heterozygous Familial Hypercholesterolemia Patients

ODYSSEY FH

76% dosis elevadas de estatinas

72% combinación con Ezetimiba

Estudio de Extensión abierto con Alirocumab 150 mg 2Q

Si cLDL <25 mg/dL (2) Alirocumab 75 mg 2Q

	Basal (58)	Week 64 (54)
cLDL	152.3(5.1)	-59.5(3.6)*
Apo-B	121.4(3.2)	-45.0(3.3)*
Lp(a) mg/dL	40(5-104)	-28.6(-48 a -112)*
CT	230(5.8)	-38.4(2.7)*
C-NoHDL	178.4(5.5)	-50.5(3.4)*
TG	114.8(95-150)	-8.7(-26 a18)
cHDL	52.2(1.9)	4.1(2.0)#
Apo-A1 g/L	147.7(3.2)	7.1(1.6)‡

*P <0.0001

#P <0.001

‡P <0.05

80% cLDL<100mg/dL

74% cLDL< 70 mg/dL

Stein EA et al. Poster presentation at ACC 2014. Abstract 1183-126

OneYear Open label Treatment with Alirocumab 150 mg every two weeks in Heterozygous Familial Hypercholesterolemia Patients

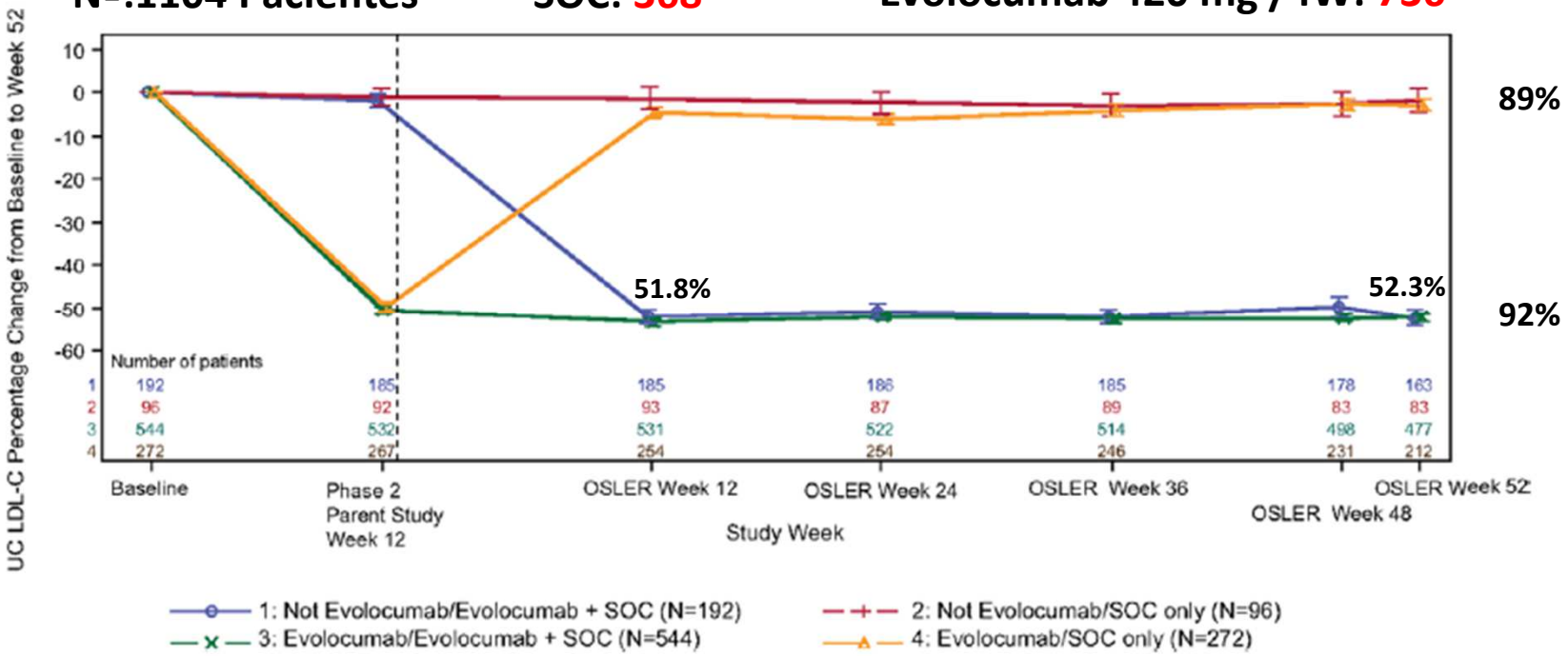
ODYSSEY FH

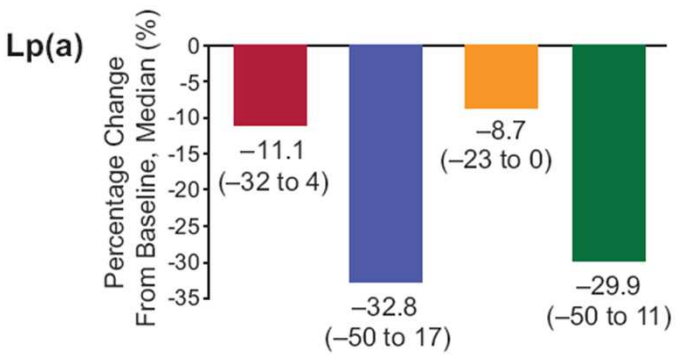
	Alirocumab(nº58)
Alguno	52(89.7%)
Relacionado Tratamiento	26(44.8%)
Grave	7(12.1%)
Transas x3	0
CPK x3	0
Infección	32(55.2%)
Reacción local	20(34.5%)
Alteración Muscular	24(41.4%)
Gastrointestinal	17(29.1%)
Alt. Sistema Nervioso	17(29.1%)

Roth EM et al. Poster presentation at ACC 2014. Abstract 1183-125.

Efficacy and Safety of Longer-Term Administration of Evolocumab (AMG 145) in patients With Hypercholesterolemia:52 Week result the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) Randomized Trial

Nº:1104 Pacientes **SOC: 368** **Evolocumab 420 mg /4W: 736**





cLDL < 100 mg/dL
SOC:3%
EVO:72%

cLDL < 50 mg/dL
EVO:55%

cLDL < 25mg/dL
EVO:13%

Koren MJ et al Circulation 2014 Jan 14;129(2):234-43

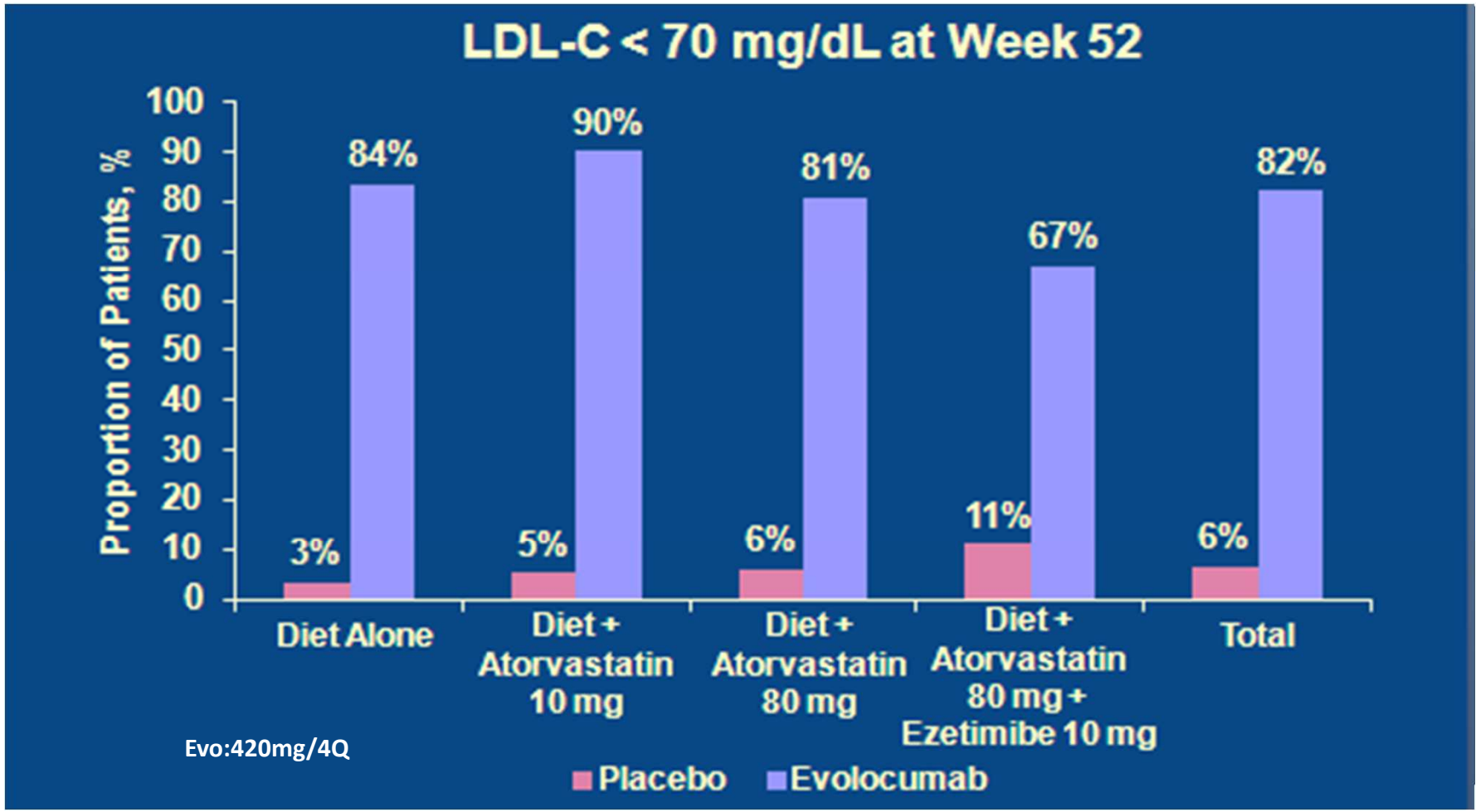
Efficacy and Safety of Longer-Term Administration of Evolocumab (AMG 145) in patients With Hypercholesterolemia:52 Week result the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) Randomized Trial

	SOC(nº368)	Evolocumab(nº736)
Alguno	269(73.1%)	599(81.4%)
Grave	23(6.3%)	52(7.1%)
Transas x3	6(1.6%)	13(1.8%)
CPK x 5	7(1.9%)	7(1%)
Los más frecuentes		
Rinofaringitis	30(9.8%)	**90(12.2%)**
Infección respiratoria	28(7.6%)	57(7.7%)
Gripe	19(5.2%)	**57(7.1%)**
Artralgia	16(4.3%)	**51(6.9%)**
Dolor de espalda	20(5.4%)	**48(6.5%)**

Koren MJ et al Circulation 2014 Jan 14;129(2):234-43

A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlidemia. DESCARTES

Nº:905 Pacientes **Nº: 112 Dieta sólo, 74 Evo y 37 PL.** **Nº: 219 ATV 80 mg/día, 146 Evo y 73 PL.**
Nº: 385 ATV 10 mg/día, 256 Evo y 129 PL. **Nº: 189 ATV 80 mg/día+ EZT 10mg/día, 126 Evo y 63 PL.**



Blom DJ et al. *N Engl J Med* 2014; 370:1809-1819 May 8

A 52-Week Placebo-Controlled Trial of Evolocumab in Hyperlidemia. DESCARTES

	Placebo (nº302)	Evolocumab (nº599)
Alguno	224(74.2%)	448(74.8%)
Grave	13(4.3%)	33(5.5%)
Transas x 3 x 5	3(1%) 1(0.3%)	5(0.8%) 3(0.5%)
CPK x 5 x 10	1(0.3%) 1(0.2%)	3(0.5%) **7(1.2%)**
Los más frecuentes		
Rinofaringitis	29(9.6%)	**63(10.5%)**
Infección respiratoria	19(6.3%)	**56(7.5%)**
Gripe	19(6.3%)	**45(7.1%)**
Dolor de espalada	17(5.6%)	**37(6.2%)**

Blom DJ et al. *N Engl J Med* 2014; 370:1809-1819 May 8

Conclusiones

✓ **Con los datos que disponemos en la actualidad, Alirocumab y Evolocumab reducen de forma eficaz los niveles de cLDL en las poblaciones estudiadas:**

- **HC no HFH, HFH y en HoFH con LDLr defectuoso.**
- **En combinación con dieta, estatinas y ezetimiba.**
- **Intolerancia a estatinas o tolerancia a dosis bajas de estatinas.**

✓ **Los niveles de cLDL se mantienen reducidos de forma estable hasta la semana 64 de tratamiento.**

✓ **Los datos de los ensayos clínicos en fase 2 y 3 de Alirocumab y Evolocumab, han mostrado ser seguros.**

✓ **Deberemos esperar la finalización de los ensayos en fase 3 en pacientes con ECV establecida para constatar, si el descenso en los niveles de cLDL inducidos por Alirocumab y Evolocumab, se acompaña de una disminución de la morbi-mortalidad.**