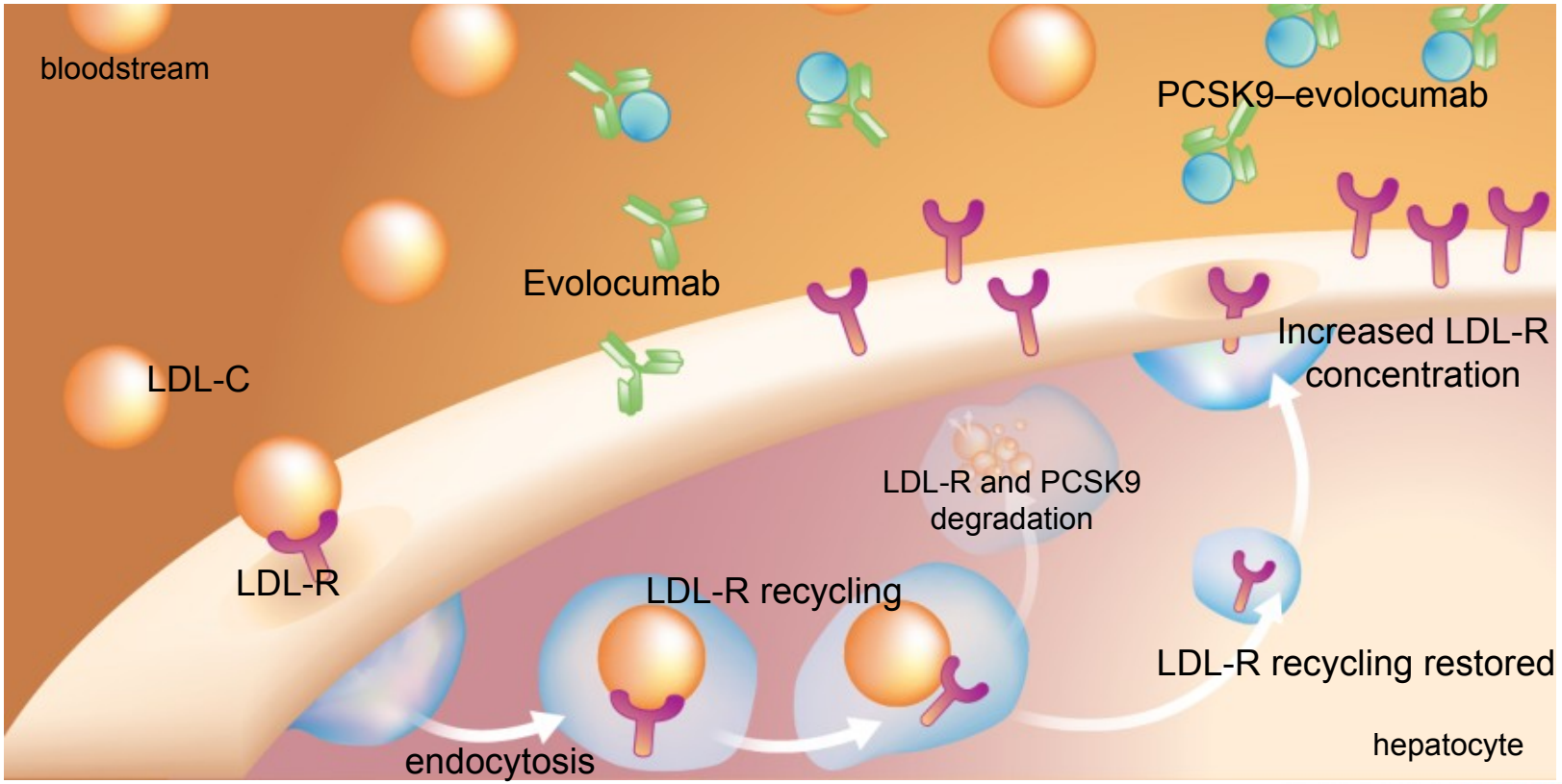
Repatha (Evolocumab) inhibits PCSK9, thereby blocking PCSK9–LDL-R interaction, increasing LDL-R expression and increasing LDL-C clearance

Presence of evolocumab = absence of PCSK9

- More LDL-R
- Lower plasma LDL-C



LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.
Elaborated from Chan JC et al. PNAS 2009;106:9820–5.

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Human Population Genetics Strongly Supports Pursuing PCSK9 Inhibition

PCSK9 Variant	LDL-C	CHD Risk
Gain-of-Function Mutations	> 300 mg/dL[2]	Premature CAD[1,2]
R46L	↓ 15%[3]	↓ 47%[3]
Y142X or C679X	↓ 28%–40%[3,4]	↓ 88%[3]

LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; CAD = coronary artery disease

1. Haddad L, Day INM, et al. J Lipid Res. 1999, 40:1113-1122; 2. Abifadel M, Varret M, Rabes JP, et al. *Nat Genet*. 2003;34:154-156; 3. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. N Engl J Med. 2006;354:1264-1272; 4. Cohen J, Pertsemlidis A, Kotowski IK, et al. *Nat Genet*. 2005, 37:161-165.

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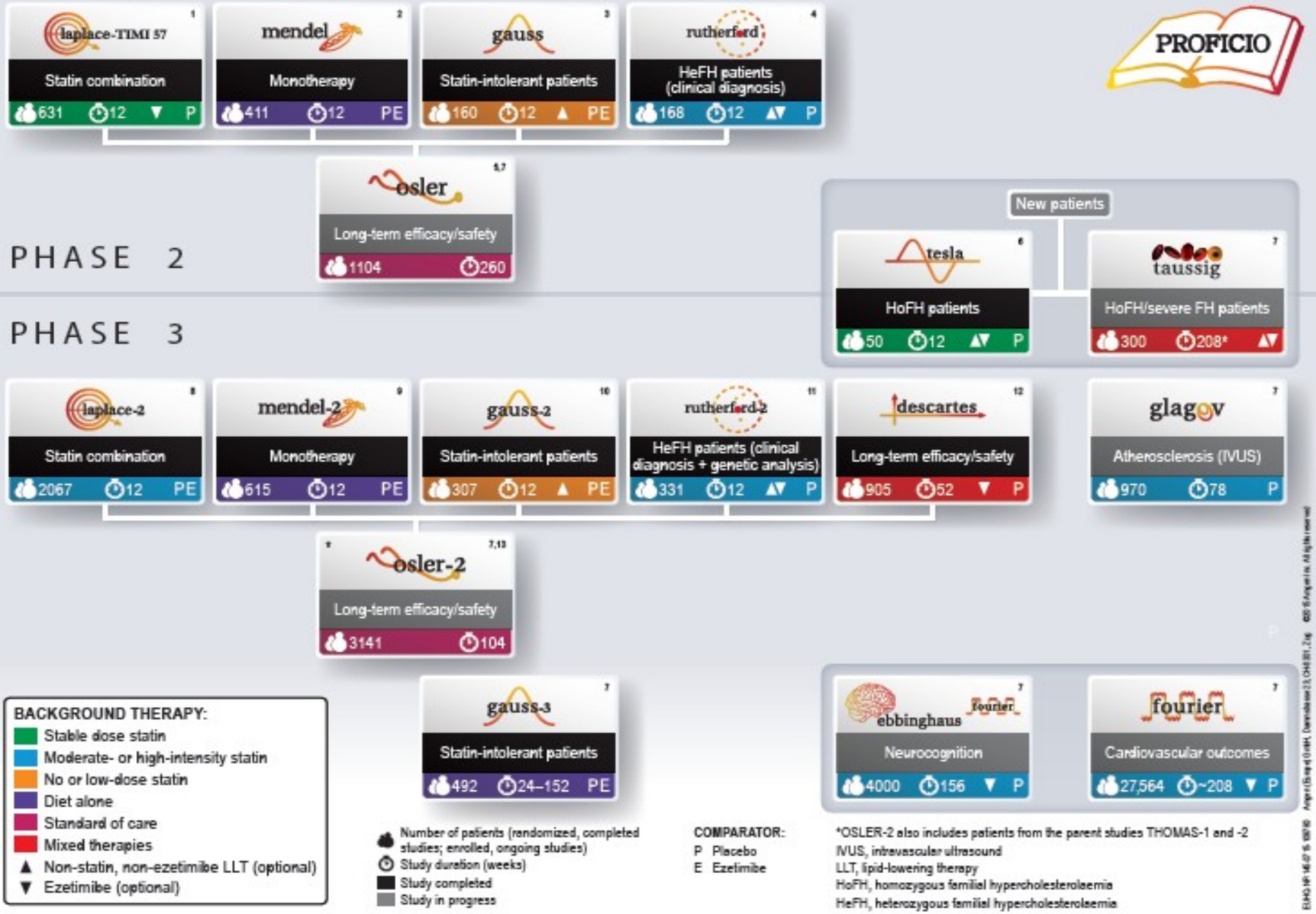

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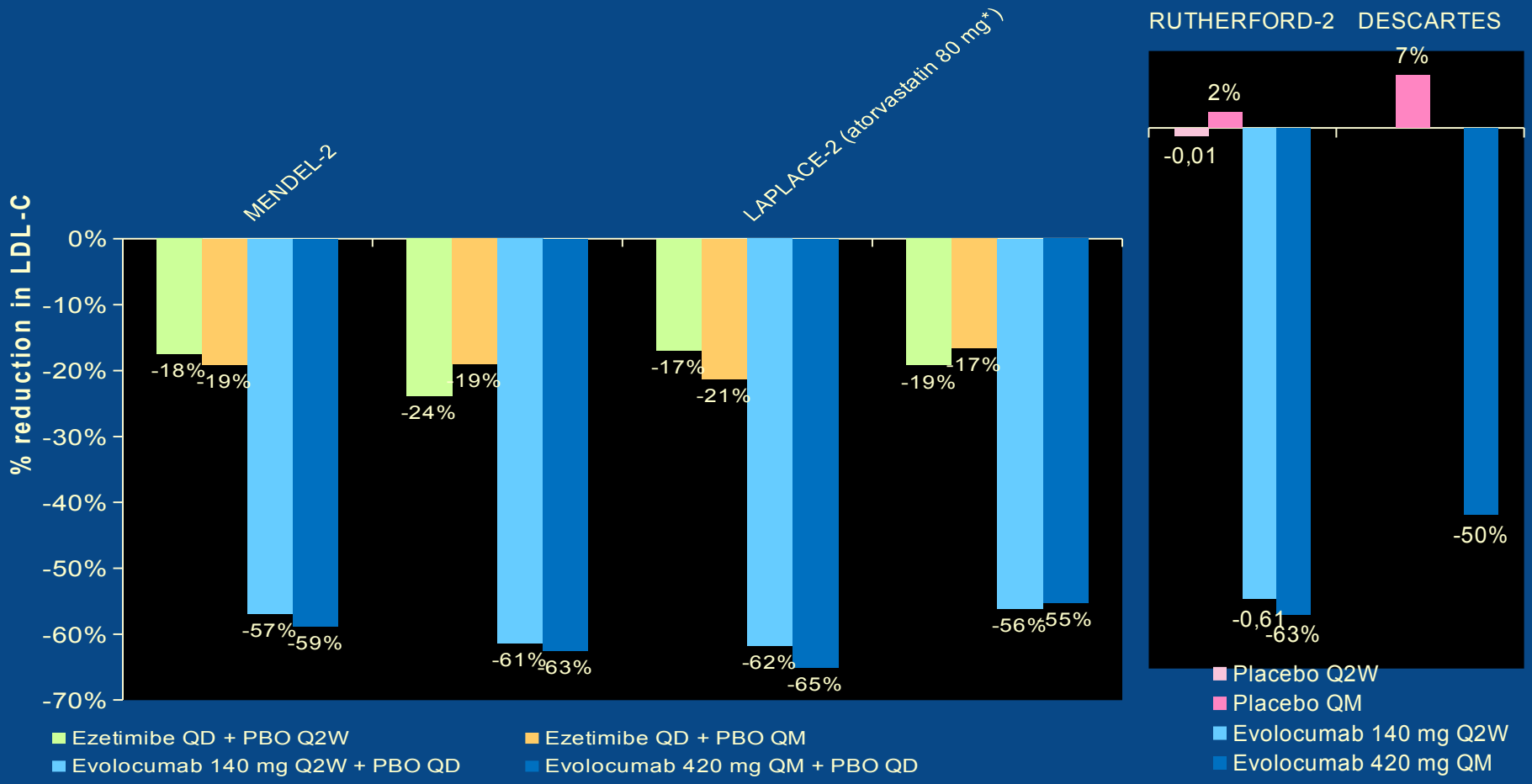
Evolocumab Phase III Clinical Trials Overview

Study	Monotherapy	Combotherapy	Statin intolerant population	HeFH population	Long-term safety and efficacy
Acronym	mendel-2	laplace-2	gauss-2	rutherford-2	descartes
N (enrolled)	615	2067	307	331	905
Background lipid lowering therapy	None	Different statins/doses ± ezetimibe	No statin or lowest weekly dose statin	Stable statin dose ± other approved lipid-modifying therapy	No statin, low dose atorvastatin or high dose atorvastatin ± ezetimibe
Treatment duration	12 weeks	12 weeks	12 weeks	12 weeks	52 weeks
Comparator(s)	Placebo and ezetimibe	Placebo and ezetimibe	Ezetimibe	Placebo	Placebo
Evolocumab doses	140 mg Q2W 420 mg QM	140 mg Q2W 420 mg QM	140 mg Q2W 420 mg QM	140 mg Q2W 420 mg QM	420 mg QM
Reference	Koren MJ et al. *JACC* 2014;63:2531–40	Robinson JG et al. *JAMA* 2014;311:1870–82	Stroes E et al. *JACC* 2014;63:2541–8	Raal FJ et al. *Lancet* 2015;385:331–40	Blom DJ et al. *N Engl J Med* 2014;370:1809–19

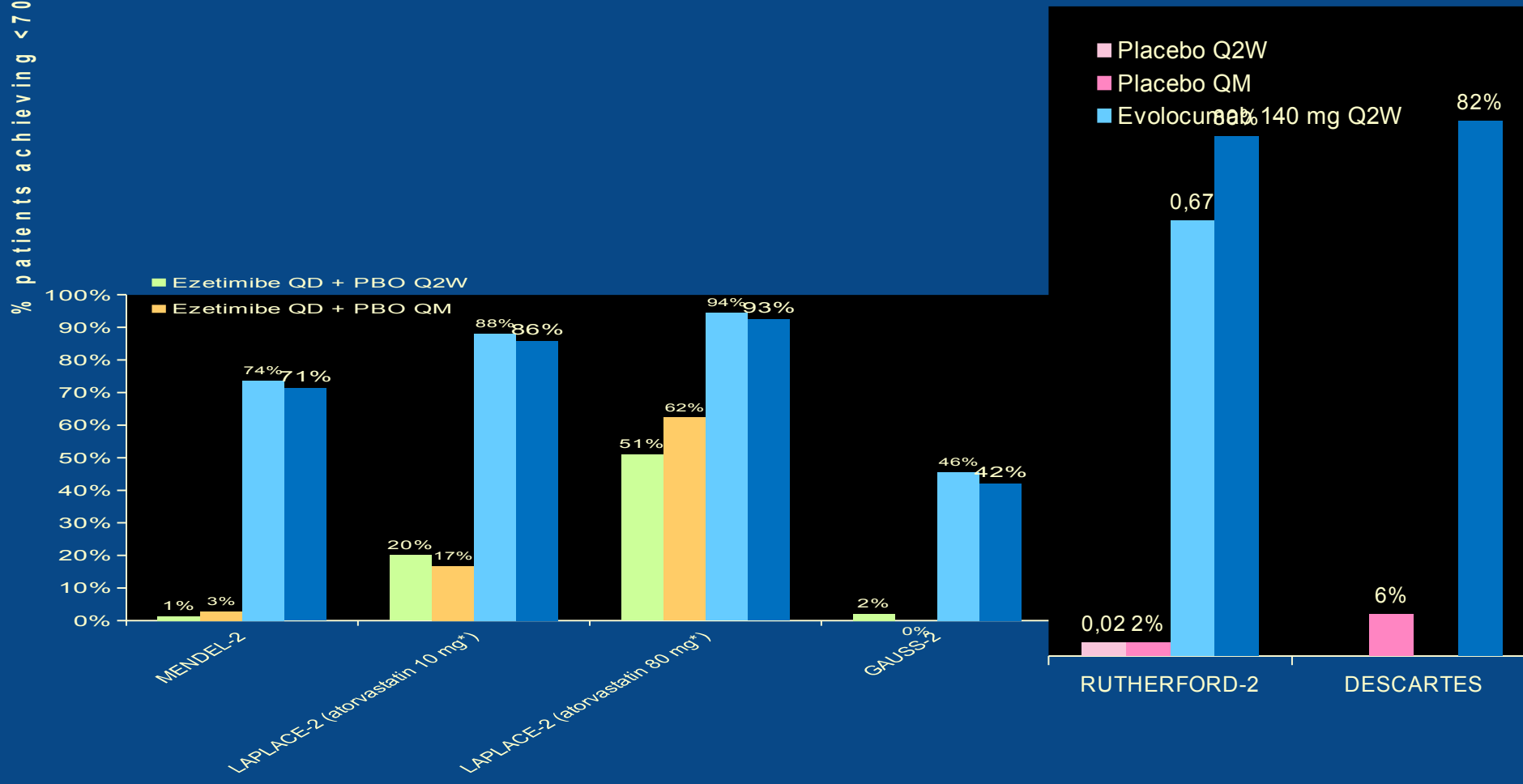
Disclaimer: Evolocumab has been approved for use by the EMA

Phase III Evolocumab Trial Summary – Reduction in LDL-C



*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C reductions seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin
Percentage reduction in LDL-C for each trial at mean of Week 10 and Week 12; DESCARTES reduction at Week 52.
LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy.

Phase III Evolocumab Trial Summary – LDL-C Goal Fulfilment

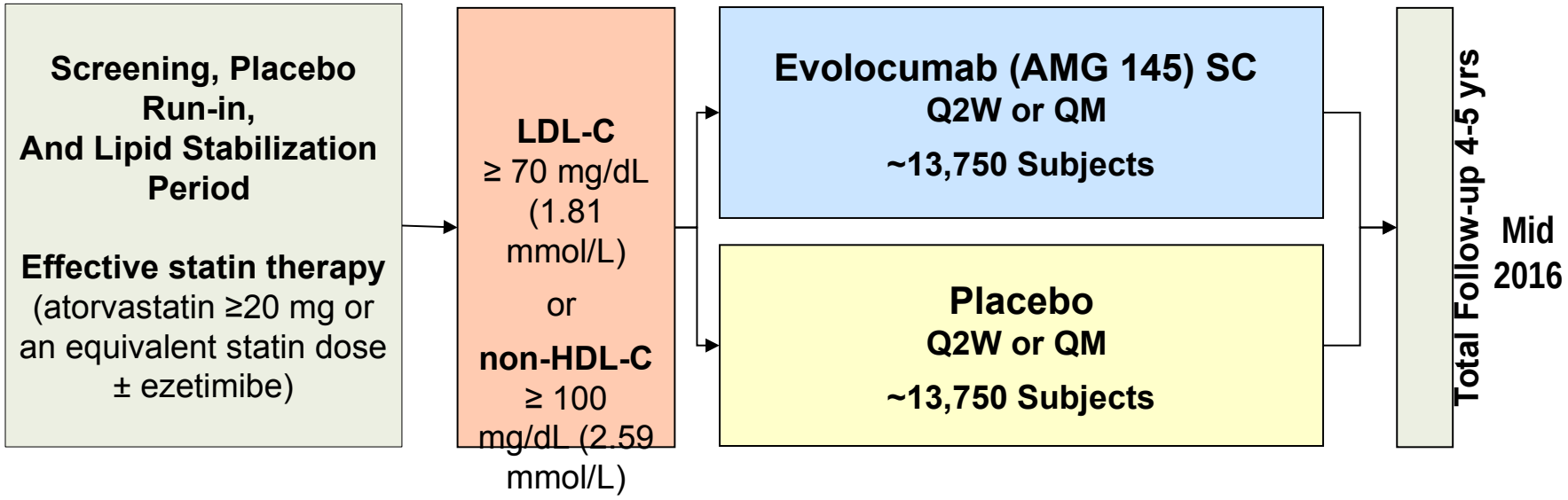


*Only 2 statin dose groups are shown for the LAPLACE-2 study; these indicate the level of LDL-C goal fulfilment seen with moderate intensity (atorvastatin 10 mg) and high intensity (atorvastatin 80 mg) statin

Percentage of patients achieving LDL-C treatment goal of <70 mg/dL at a mean of Weeks 10 and 12; DESCARTES patients at Week 52. LAPLACE-2 patients are grouped by moderate- or high-intensity statin combination therapy.

FOURIER (20110118) Trial Ongoing

27,500 patients with cardiovascular disease (prior MI, stroke or PAD)
Age 40 to 85 years
≥1 other high-risk feature



Primary Endpoint: CV death, MI, hosp for UA, stroke, coronary revascularization

NCT01764633

www.clinicaltrialsregister.eu EudraCT Number: 2012-001398-97
https://clinicaltrials.gov/ct2/show/NCT01764633?term=NCT01764633&rank=1

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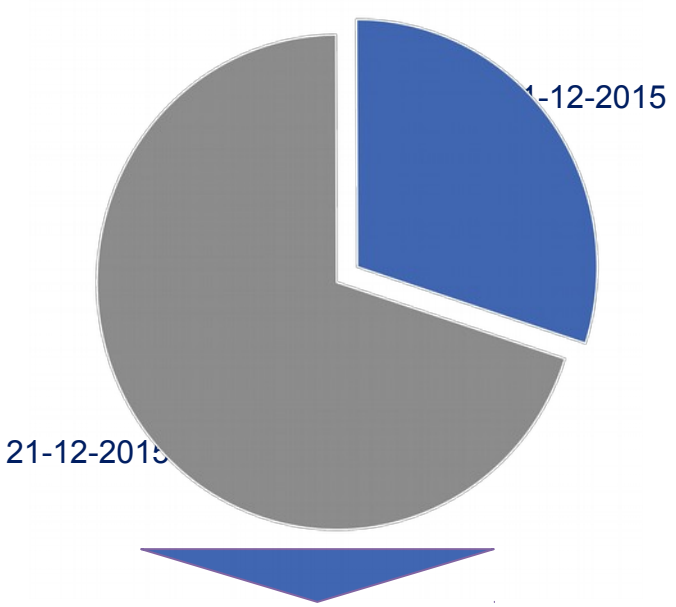
Elaborated from Sabatine et al. N Engl J Med. 2015 Apr 16;372(16):1500-9 (Suppl.):1-21

Burden of Disease delle Malattie Cardiovascolari in Italia

Morti totali



- **Le malattie CV causano** approssimativamente185.000 morti **in Italia** ogni anno, e rappresentano il **30% di tutte le cause di morte**
- Il tasso di mortalità per le malattie CV è **6.1 / 1,000 uomini** and **1.6 / 1,000 donne**

Costi cardiovascoalari

- Nel 2014 le malattie CV hanno generato costi pari a **€18,3 miliardi** (11% della spesa sanitaria nazionale complessiva)
- Un evento CV maggiore può costare oltre **€3,900**
- Un intervento di bypass ha un costo fino a **€18,500**

Source: TARIFFE MINISTERIALI, Centre for Economics and Business Research, Italy Factsheet, 2014, ISTAT data 2012, Sito: http://www.salute.gov.it/imgs/C_17_navigazioneSecondariaRelazione_1_listaCapitoli_capitoliItemName_1_scarica.pdf - ultima visita 21/05/2015, De Smedt et al, 2013, L'uso dei farmaci in Italia gennaio - settembre 2014