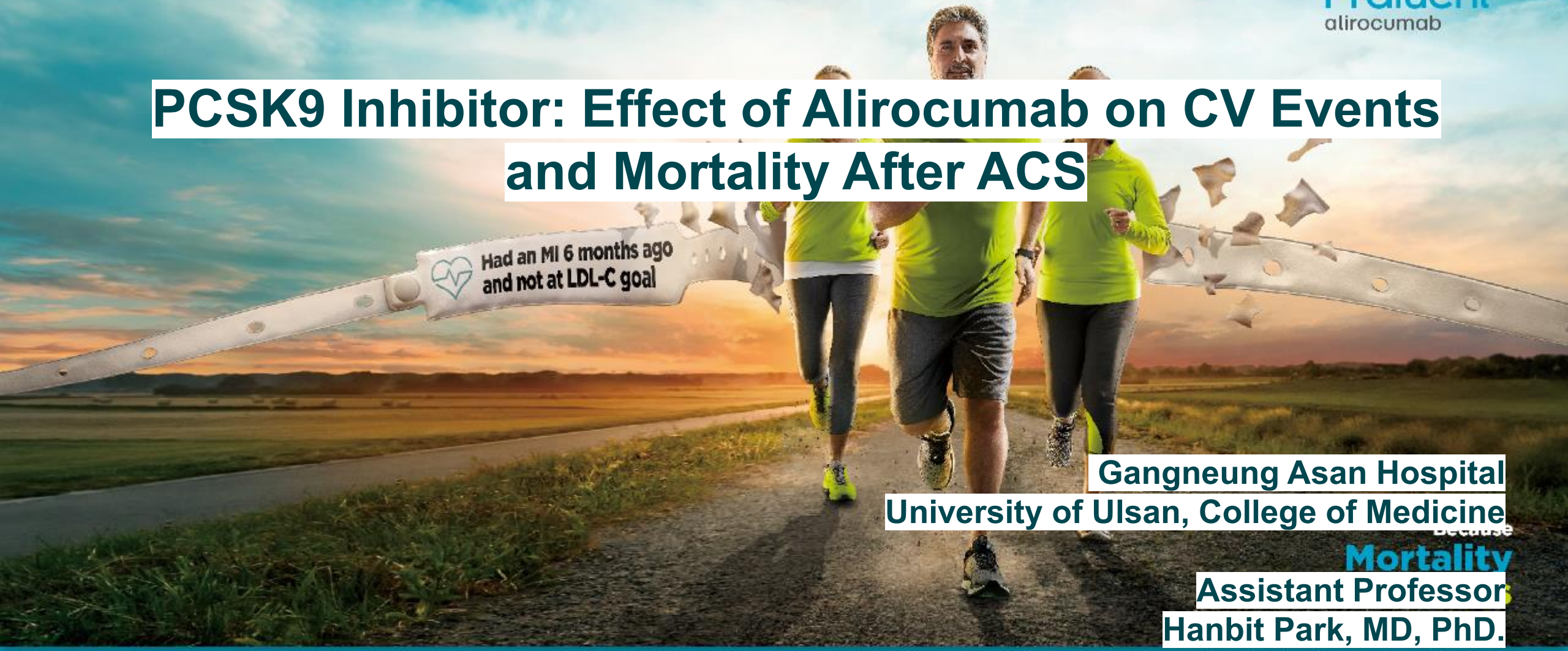
Session II

Praluent®
alirocumab

PCSK9 Inhibitor: Effect of Alirocumab on CV Events and Mortality After ACS



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SANOFI

Praluent® alirocumab

An overview of the ODYSSEY clinical trial programme

HeFH/HoFH population

Add-on to max tolerated statin (± other LMT)

- **ODYSSEY ESCAPE** (R727-CL-1216) N=63 — Patients undergoing LDL-apheresis therapy — 4 months
- **ODYSSEY OLE** (LTS13463) N=985 — Patients with HeFH from 1 of 4 parent studies — 30 months
- **ODYSSEY FH I** (EFC12492) N=486 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 18 months
- **ODYSSEY FH II** (CL1112) N=249 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 18 months
- **ODYSSEY HIGH FH** (EFC12732) N=107 — LDL-C ≥160 mg/dL — 18 months
- **ODYSSEY LONG TERM** (LTS11717) N=2341 — LDL-C ≥70 mg/dL — 18 months
- **ODYSSEY JAPAN** (EFC13672) N=216 — LDL-C ≥100 mg/dL OR LDL-C ≥120 mg/dL — 12 months
- **ODYSSEY APPRISE** (LPS14245) N=994 — LDL-C ≥100 mg/dL OR LDL-C ≥130 mg/dL OR LDL-C ≥160 mg/dL — 3-30 months
- **ODYSSEY KIDS (NCT02890992)** N=42 — Patients aged 8-17 years with HeFH and LDL-C >130 mg/dL at screening; phase 2
- **ODYSSEY HoFH (NCT03156621)** N=69 — Adults ≥18 years with HoFH — Phase 3
- **ODYSSEY HoFH KIDS (EFC14660)** N=18 — Patients aged 8-17 years with HoFH and LDL-C >130 mg/dL at screening; phase 3
- **ODYSSEY HeFH KIDS (EFC14643)** N=150 — Patients aged 8-17 years with HeFH and LDL-C >130 mg/dL at screening; phase 3 **[Ongoing]**

HC in high CV risk population

Add-on to max tolerated statin (± other LMT)

- **ODYSSEY OUTCOMES**[1] (EFC11570) N=18,924 — LDL-C ≥70 mg/dL; Event-driven; Conducted in 57 countries — 2-year min. follow-up
- **ODYSSEY COMBO I** (EFC11568) N=316 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 12 months
- **ODYSSEY COMBO II** (EFC11569) N=720 — LDL-C ≥70 mg/dL — 24 months
- **ODYSSEY EAST** (EFC13389) N=615 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 6 months
- **ODYSSEY KT** (EFC14074) N=199 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 6 months
- **ODYSSEY DM – Insulin** (LPS14355) N=500 — LDL-C ≥70 mg/dL — 6 months
- **ODYSSEY DM – Dyslipidemia** (LPS14354) N=420 — Non–HDL-C ≥100 mg/dL — 6 months
- **ODYSSEY J-IVUS** N=206 — LDL-C ≥100 mg/dL at ACS; imaging 9 months; phase 4 — 9 months

Additional populations/studies

- **ODYSSEY MONO** (EFC11716) N=103 — No background LLTs with LDL-C ≥100 mg/dL — 6 months
- **ODYSSEY ALTERNATIVE** (CL1119) N=314 — LDL-C ≥70 mg/dL or LDL-C ≥100 mg/dL — 6 months (+OLE)
- **ODYSSEY OPTIONS I** (CL1110) N=355 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 6 months
- **ODYSSEY OPTIONS II** (CL1118) N=305 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL — 6 months
- **ODYSSEY CHOICE II** (EFC13786) N=233 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; 150 mg Q4W dosing — 6 months (+OLE)
- **ODYSSEY NIPPON** (EFC14305) N=159 — LDL-C ≥100 mg/dL OR LDL-C ≥120 mg/dL — 3 months (+OLE)
- **ODYSSEY CHOICE I** (CL1308) N=803 — LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL; 300 mg Q4W dosing, < — 12 <months

28 global trials, including more than 32,100 patients over 3,000 study centres

1ACS, acute coronary syndrome; CV, cardiovasvular; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; HC, high cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; LMT, lipid-modifying therapy; OLE, open-label extension; Q4W, every 4 weeks

The ODYSSEY trials led to an expanded CV outcomes indication for PRALUENT®

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Primary hypercholesterolaemia and mixed dyslipidaemia[1]

Adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- In combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or,
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated

CV indication[1]: Established atherosclerotic cardiovascular disease

Adults with established atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- In combination with the maximum-tolerated dose of a statin with or without other lipid-lowering therapies, or,
- Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contr aindicated

Reference 1. PRALUENT (Alirocumab) Summary of Product Characteristics. Aug 2020.

PRALUENT® clinical data

1. **ODYSSEY OUTCOMES**
   - MACE
   - All cause mortality
2. **ODYSSEY KT**

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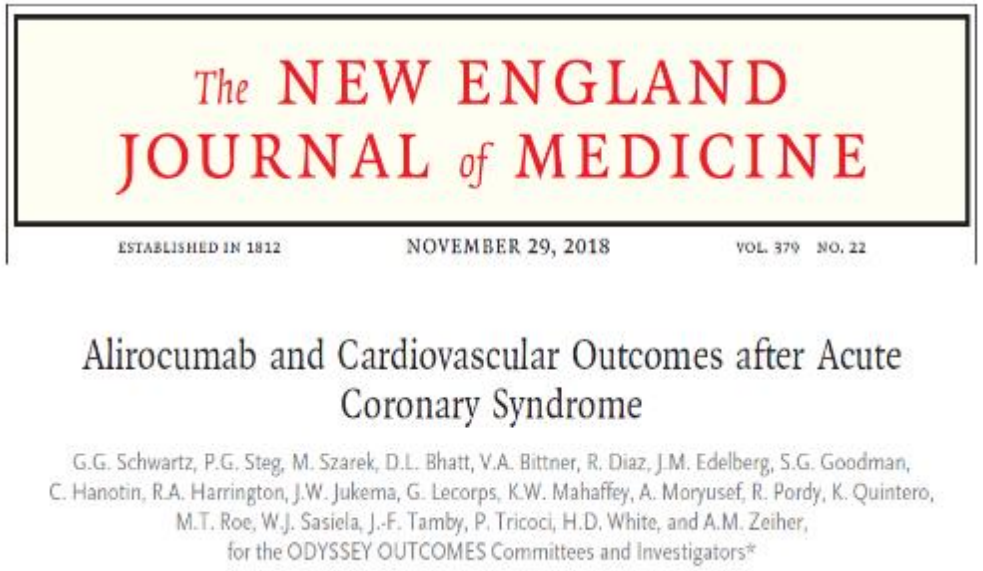
ODYSSEY OUTCOMES

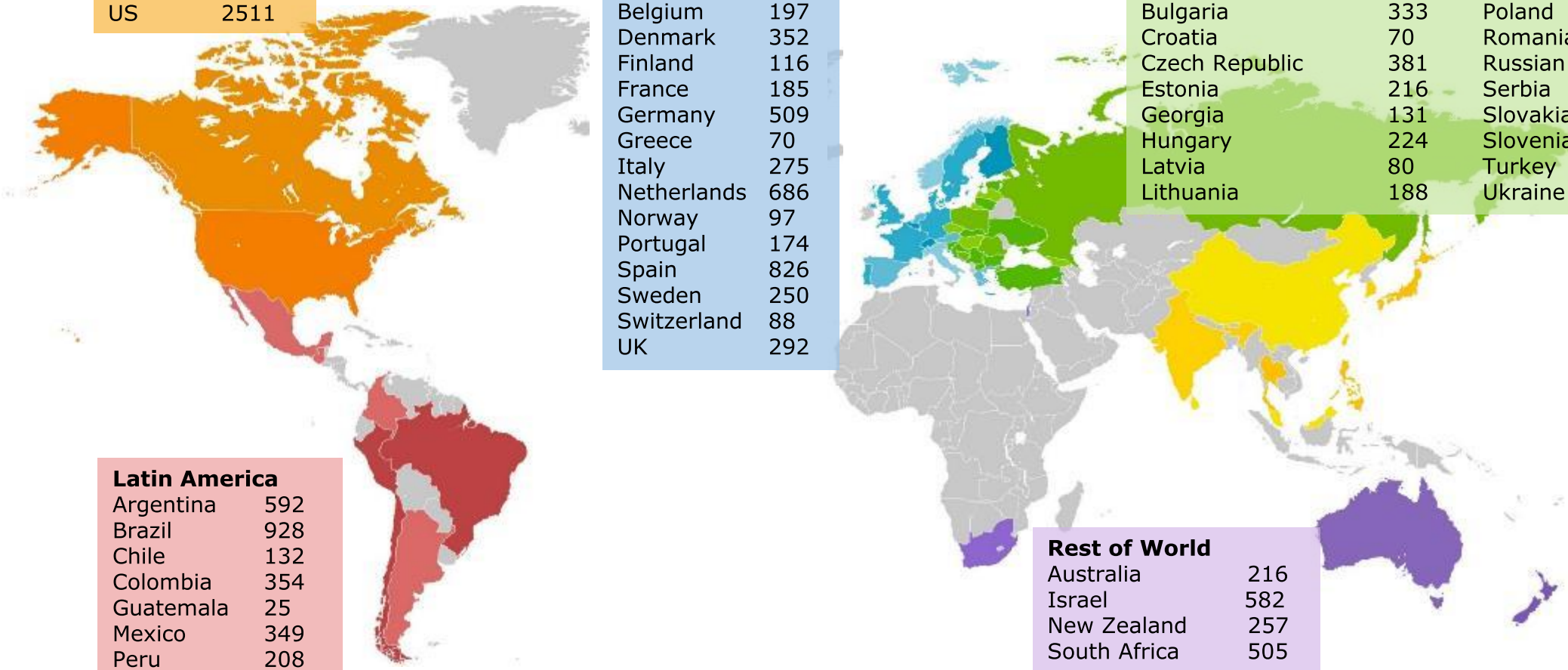


Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome

- Schwarz GG, et al. N Engl J Med. 2018;379:2097–107.

ODYSSEY OUTCOMES: 18,924 patients randomized at 1315 sites in 57 countries, Nov 2, 2012 – Nov 11, 2017

Praluent® alirocumab



Canada/USA	
Canada	361
US	2511

Western Europe	
Austria	58
Belgium	197
Denmark	352
Finland	116
France	185
Germany	509
Greece	70
Italy	275
Netherlands	686
Norway	97
Portugal	174
Spain	826
Sweden	250
Switzerland	88
UK	292

Central/Eastern Europe			
Bosnia–Herzegovina	156	Macedonia	132
Bulgaria	333	Poland	926
Croatia	70	Romania	145
Czech Republic	381	Russian Federation	1109
Estonia	216	Serbia	255
Georgia	131	Slovakia	340
Hungary	224	Slovenia	36
Latvia	80	Turkey	78
Lithuania	188	Ukraine	639

Asia	
China	614
Hong Kong	17
India	521
Japan	204
Korea	94
Malaysia	110
Philippines	116
Singapore	49
Sri Lanka	314
Taiwan	93
Thailand	161

Latin America	
Argentina	592
Brazil	928
Chile	132
Colombia	354
Guatemala	25
Mexico	349
Peru	208

Rest of World	
Australia	216
Israel	582
New Zealand	257
South Africa	505

ODYSSEY OUTCOMES was carried out in a high-risk population, all of whom had experienced a previous CV event (MI or unstable angina)

Praluent® alirocumab

100% had a previous MI or unstable angina

2.6 months median time post-index event to randomisation

~90% were receiving high-intensity statins

Atorvastatin 40 or 80 mg/day or Rosuvastatin 20 or 40 mg/day

MI, myocardial infarction

Reference. 1. Schwarz GG, *et al*. N Engl J Med. 2018;379:2097–107.

Nearly all participants(89%) were taking high-intensity statins such as 40-80 mg/day atorvastatin or 20-40 mg/day rosuvastatin

Praluent® alirocumab

Baseline characteristic	PRALUENT® (N=9462)	Placebo (N=9462)
Age, years, median (Q1, Q3)	58.5±9.3	58.6±9.4
Female, n (%)	2390 (25.3)	2372 (25.1)
Medical history, n (%)		
Hypertension	6205 (65.6)	6044 (63.9)
Diabetes mellitus	2693 (28.5)	2751 (29.1)
Myocardial infarction	1790 (18.9)	1843 (19.5)
Percutaneous coronary intervention	1626 (17.2)	1615 (17.1)
Coronary-artery bypass grafting	521 (5.5)	526 (5.6)
Stroke	306 (3.2)	305 (3.2)
Peripheral artery disease	373 (3.9)	386 (4.1)
Congestive heart failure	1365 (14.4)	1449 (15.3)
Index ACS type, n (%)		
NSTEMI	4574 (48.3)	4601 (48.6)
STEMI	3301 (34.9)	3235 (34.2)
Unstable angina	1568 (16.6)	1614 (17.1)
Time from index ACS to randomisation, months, median (Q1, Q3)	2.6 (1.7, 4.4)	2.6 (1.7, 4.3)
Revascularisation for index ACS, n (%)	6798 (71.8)	6878 (72.7)
Therapy, n (%)		
High-dose atorvastatin/rosuvastatin	8380 (88.6)	8431 (89.1)
Low-/moderate-dose atorvastatin/rosuvastatin	830 (8.8)	777 (8.2)
Other statin	19 (0.2)	27 (0.3)
Ezetimibe, with or without statin	269 (2.8)	285 (3.0)
No lipid-lowering therapy	87 (0.9)	91 (1.0)

ACS, acute coronary syndrome; CAD, coronary artery disease; CeVD, cerebrovascular disease; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NSTEMI, non-ST-segment elevation MI; PAD, peripheral artery disease

Reference 1. Schwartz GG, et al. N Engl J Med 379 2097-2107.

ODYSSEY OUTCOMES is a long-term study of CV outcomes in 18,924 patients[1,2]

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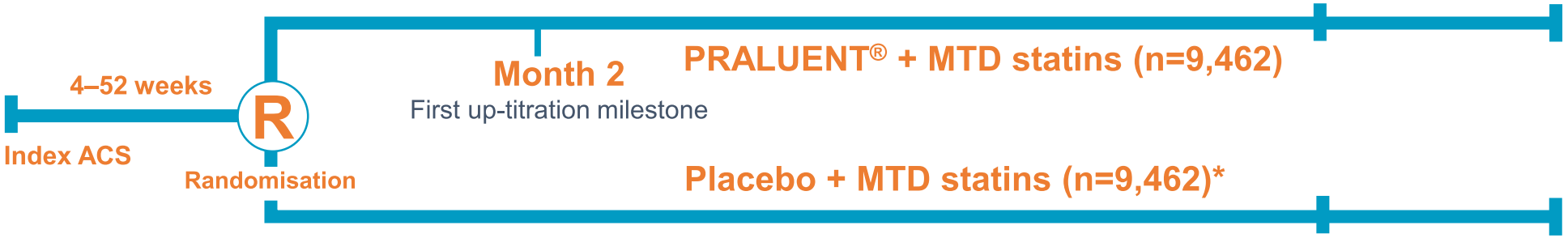
Run-in period (up to 16 weeks)	Double-blind treatment period* (≈2 to 5 years)		Post-treatment follow-up
Optimise statin†: practise self-injection with placebo; complete planned vascularisation >2 weeks befor randomisation	**Until Month 2** 75 mg every 2 weeks	**At Month 2 and beyond** 75 mg or 150 mg every 2 weeks *Dose adjusted in blind fashion to maximize the number of patents to achieve target LDL-C of 25-50 mg/dL (0.65-1.29 mmol/L)$*	2 weeks after end of treatment



The only double-blind, randomized PCSK9i CV outcomes study with treat-to-target LDL-C approach, **2.8 years median follow-up**, and **44 %** of patients eligible to be followed for **3-5 years**.

Clinically stable **high-risk patients with prior CHD event of ACS**, likely to derive high absolute benefit

Patients with residual cardiovascular risk (despite moderate/ intensive statins) **most likely to be modified** by further reduction of LDL-C lipoproteins ‡

***Background therapy:** 96% aspirin; 88% P2Y12 inhibitor; 85% beta blocker.
†**Optimal statin treatment:** atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg, or maximal tolerated dose of one of these statins, with or without non-statin lipid treatments. NCEP-ATP III therapeutic lifestyle changes or equivalent throughout study. Other CV prevention therapies not excluded (other than PCI within 2 weeks of start of trial). ‡**Inadequate control of atherogenic lipoproteins.** At least one of the following: LDL-C ≥70 mg/dL (1.81 mmol/L), non HDL-C ≥100 mg/dL (2.59 mmol/L), or apo B ≥80 mg/dL.
$Dose was up-titrated from 75 mg Q2W to 150 mg Q2W at month 2 if LDL-C was ≥50 mg/dL at month 1. Dose was down-titrated from 150 mg Q2W to 75 mg Q2W if LDL-C was <25 mg/dL on 2 consecutive measures. Patients on the 75 mg Q2W dose were blindly switched to placebo if LDL-C was <15 mg/dL on 2 consecutive measures.

ACS, acute coronary syndrome; apo B, apolipoprotein B; HDL-C, high density lipoprotein cholesterol; MTD, maximally tolerated dose; NCEP-ATP III, National Cholesterol Education Program - Adult Treatment Panel III.

References 1. Schwartz GG, et al. Am Heart J. 2014;168:682–689. 2. Schwartz GG, et al. N Engl J Med. 2018;379:2097–2b107.

ODYSSEY OUTCOMES studied the effect of PRALUENT® on CV outcomes[1,2]

Endpoint	Further details
Primary endpoint (MACE)	
• CHD death • Nonfatal MI • Ischaemic stroke • UA	**Major CV events** Composite of CHD death, non-fatal MI, fatal or non-fatal ischaemic stroke, UA requiring hospitalisation Estimate of 1,613 primary endpoint events to provide 90% power to detect a 15% hazard reduction with PRALUENT® co mpared with placebo
Secondary endpoints (in order of hierarchical testing)	
• CHD event • Major CHD event • CV event • Composite of all-cause mortality, nonfatal MI, nonfatal ischaemic stroke • CHD death • CV death • All-cause mortality	**CHD event:** CHD death, non-fatal MI, unstable angina requiring hospitalisation, or ischaemia-driven coronary revasculari sation **Major CHD event:** CHD death or non-fatal MI **CV event:** CV death, non-fatal CHD event, or non-fatal ischaemic stroke
Other secondary endpoints	Components of the primary endpoint considered individually: CHD death, non-fatal MI, fatal and non-fatal ischaemic stro ke, unstable angina requiring hospitalisation Ischaemia-driven coronary revascularisation Congestive heart failure requiring hospitalisation
Safety data	Adverse events, laboratory tests
Other	Development of anti-alirocumab antibodies

CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction

References 1. Schwartz GG, et al. Am Heart J. 2014;168:682–689. 2. Schwartz GG, et al. N Engl J Med. 2018;379:2097–107.

ODYSSEY OUTCOMES had a treat-to-target approach to reach the ‘maximum tolerated dose’ of statin

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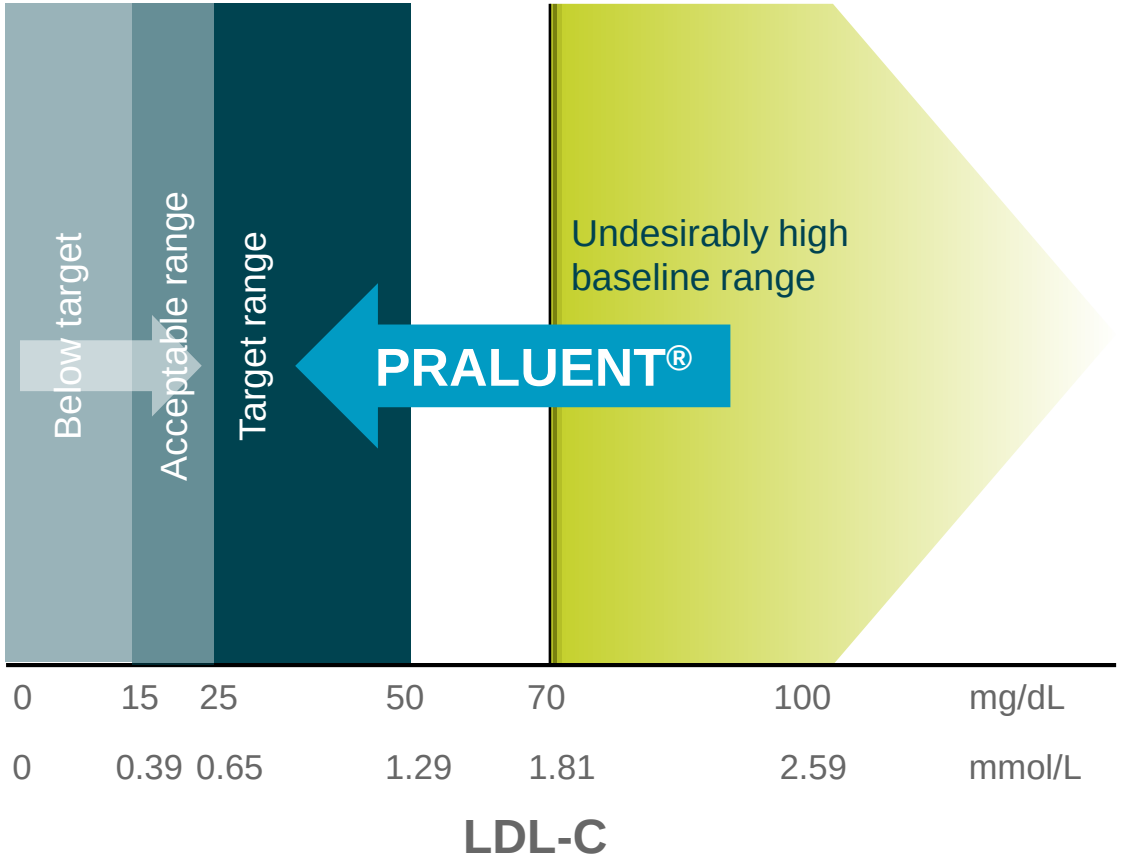
Aim: to maximise the number of patients in the target range (25-50 mg/dL) (0.65-1.29 mmol/L), and minimise those below target by titrating PRALUENT® dose (75 or 150 mg SC Q2W) or switching to placebo

If two consecutive measurements of LDL cholesterol were < 15 mg/dL on the 75 mg dose treatment with alirocumab was blindly switched to placebo for the remaining duration of the trial.



Treat-to-target reflected clinical practice at time of trial design

The 75mg dose of Praluent® was used 78% of the time in the study

Dose adjusted based on response

Trial not designed to explore safety of sustained, very low LDL-C levels[1]

Dose adjustment was used to achieve LDL-cholesterol levels in a low, but physiologic range (25-50 mg/dL, [0.65-1.29 mmol/L]) and avoid sustained very low levels[2] ODYSSEY OUTCOMES is the only trial to use a blinded dose-adjustment strategy to achieve a target range of LDL-cholesterol with PCSK9 inhibition[2]

PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; SC, subcutaneous

References 1. Schwartz GG, et al. Am Heart J. 2014;168:682–689. 2. Schwartz GG, et al. N Engl J Med. 2018;379:2097–107.

Praluent® alirocumab

Summary: ODYSSEY OUTCOMES trial design

Patient population

Recent ACS (4–52 weeks) including patients with diabetes, prior CAD, recurrent events, prior stroke or PAD

LDL-C reduction

Background 'Maximum tolerated dose' of statin with treat-to-target approach

PRALUENT® dosing titrated up and down according to LDL-C response

Follow up

2–5 years

Management of low LDL-C

Downtitration/uptitration

Statin dose

Maximum tolerated dose

(89% high intensity statin at baseline)

Endpoints

Powered by primary endpoint events

CHD death endpoint

ACS, acute coronary syndrome; CAD, coronary artery disease; PAD, peripheral artery disease; LDL-C, low-density lipoprotein cholesterol

References 1. Schwartz GG, et al. Am Heart J. 2014;168:682–689. 2. Schwartz GG, et al. N Engl J Med. 2018;379:2097–107.

ODYSSEY OUTCOMES: LDL-C by ITT & On-Treatment Analyses
LDL-C reduction for PRALUENT® vs placebo

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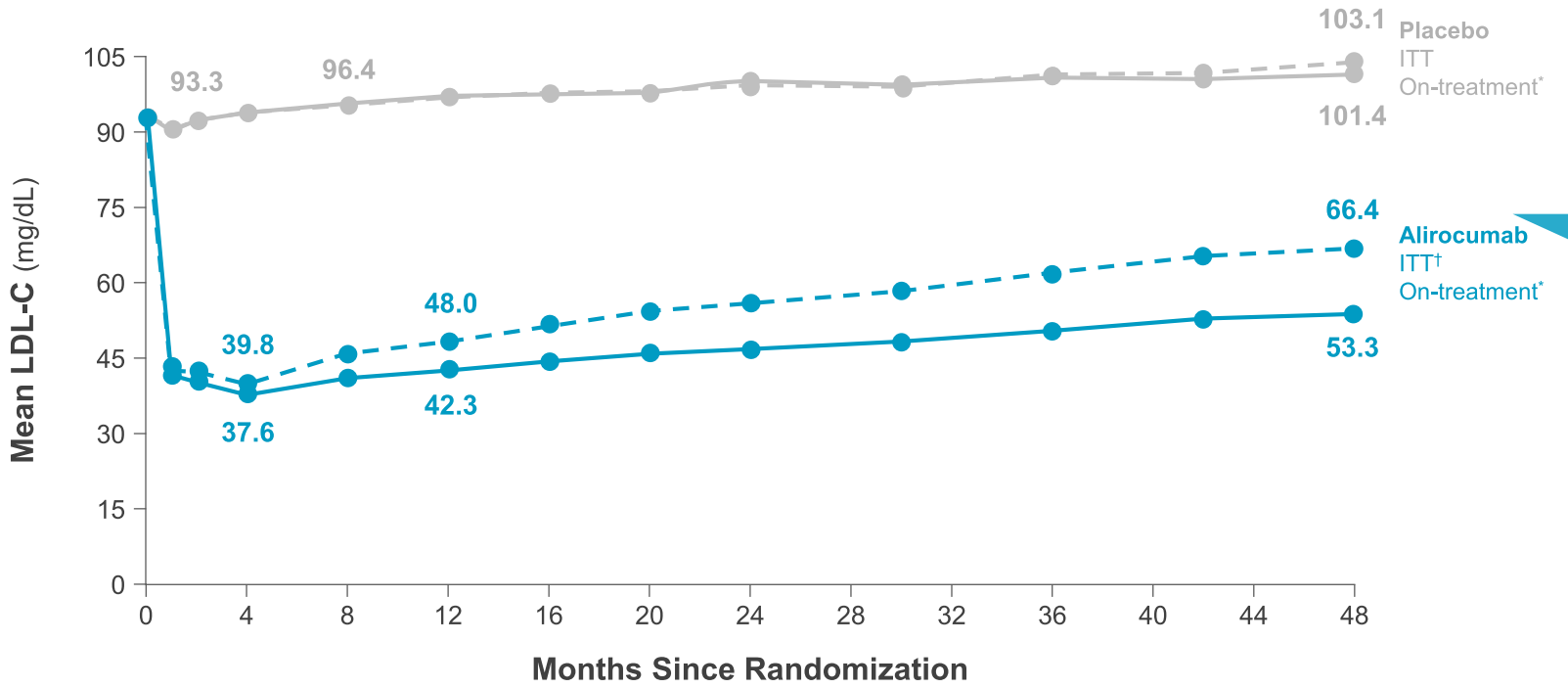
Rapid LDL-C reduction sustained over 48 months

LDL Cholesterol Levels during the Trial



54.7% mean LDL-C reduction at 4 years

*Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
†All LDL-C values, including those after premature treatment discontinuation, blinded down titration, or blinded switch to placebo

Reference 1. Schwartz GG, et al. N Engl J Med. 2018;379:2097–107.

ODYSSEY OUTCOMES

Primary Efficacy Endpoint: MACE
PRALUENT® significantly reduces relative risk of MACE by 15%

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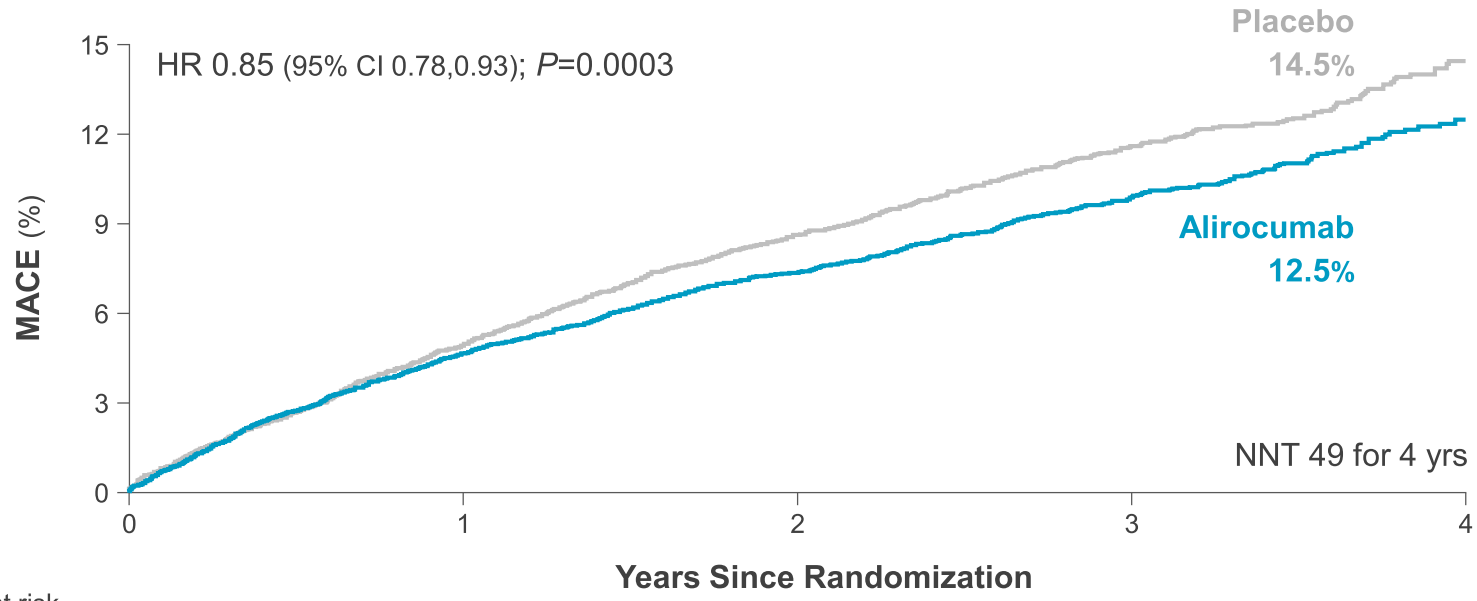
NNT 49 for 4 yrs



Number at risk

Placebo	9,462	8,805	8,201	3,471	629
Alirocumab	9,462	8,846	8,345	3,574	653

15% RRR*

HR 0.85 (95% CI: 0.78 to 0.93)
P<0.001

Based on cumulative incidence.
*Observed cumulative incidence of events over a median of 2.8 years.
MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Reference 1. Schwartz GG, et al. N Engl J Med. 2018;379:2097–107.

ODYSSEY OUTCOMES

PRALUENT® reduces MACE by 24% in patients with LDL-C ≥100 mg/dL[2]

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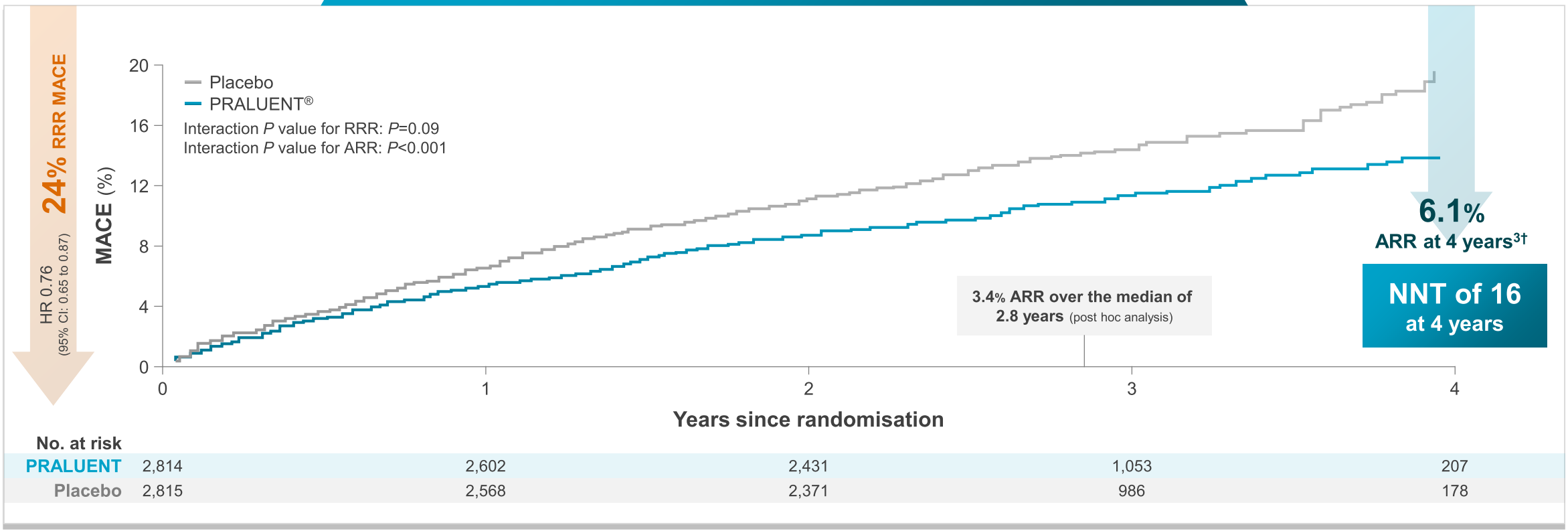
Pre-specified sub-group: MACE in patient with LDL-C ≥100 mg/dL[2*]



No. at risk					
PRALUENT	2,814	2,602	2,431	1,053	207
Placebo	2,815	2,568	2,371	986	178

*In the subgroup of patients with baseline LDL-C ≥100 mg/dL (2.6 mmol/L): higher incidence of primary MACE in placebo and greater absolute risk reduction (significant interaction P value, nonprespecified analysis).
†The NNT of 16 is calculated in accordance with the formula NNT=1/ARR, with a 4-year Kaplan-Meier estimate ARR of 6.1%.

Reference. 1. Schwarz GG, *et al*. N Engl J Med. 2018;379:2097–107. 2. Schwarz GG, *et al*. N Engl J Med. 2018;379:2097–107. Supplementary Appendix. 3. Data on file. Clinical study report. Sanofi. June 2018.

All Patients vs Patients with ≥3 Years of Follow-Up
Fewer deaths occurred in the alirocumab group vs the placebo group

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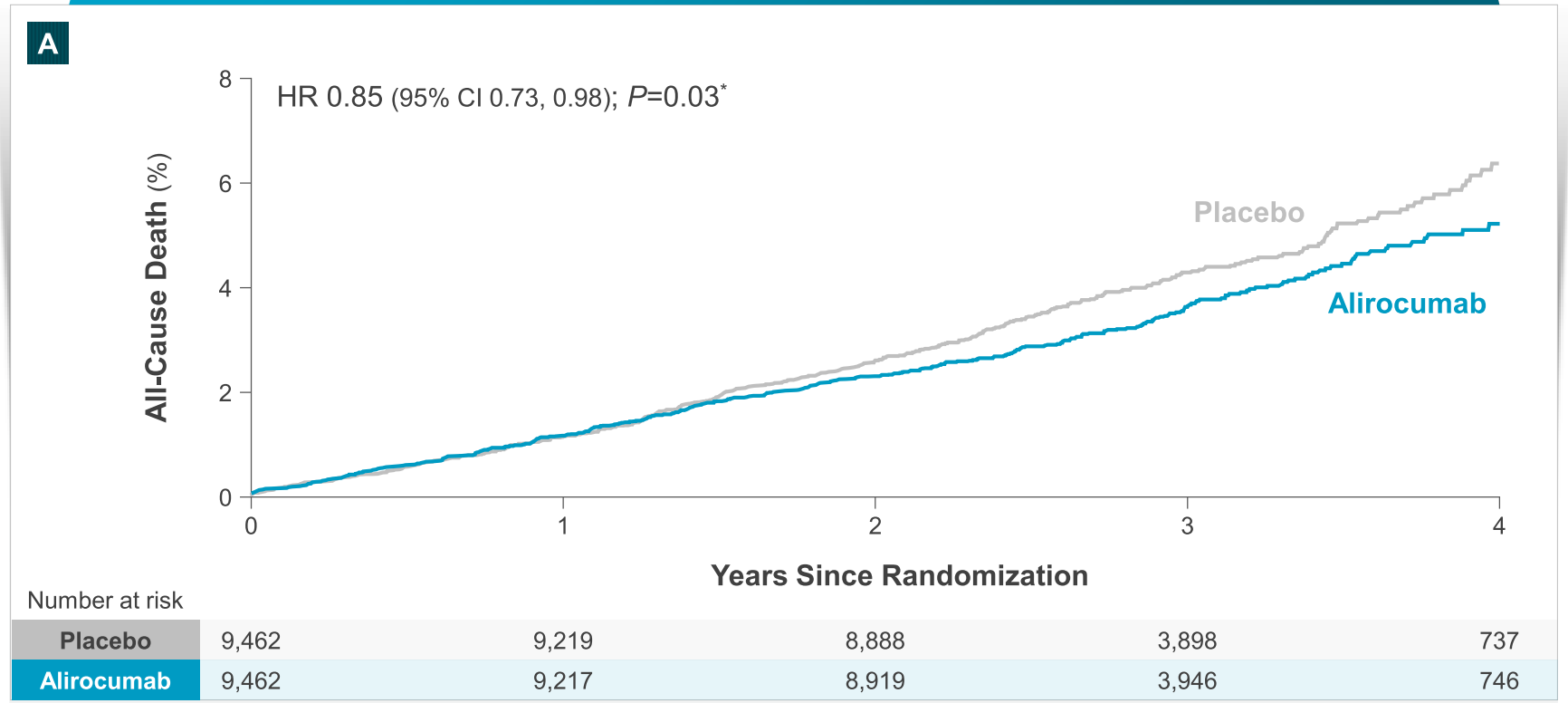
All patients (N=18,924)



Number at risk

Placebo	9,462	9,219	8,888	3,898	737
Alirocumab	9,462	9,217	8,919	3,946	746

*Nominal P-value due to hierarchical position of all-cause death among secondary endpoints

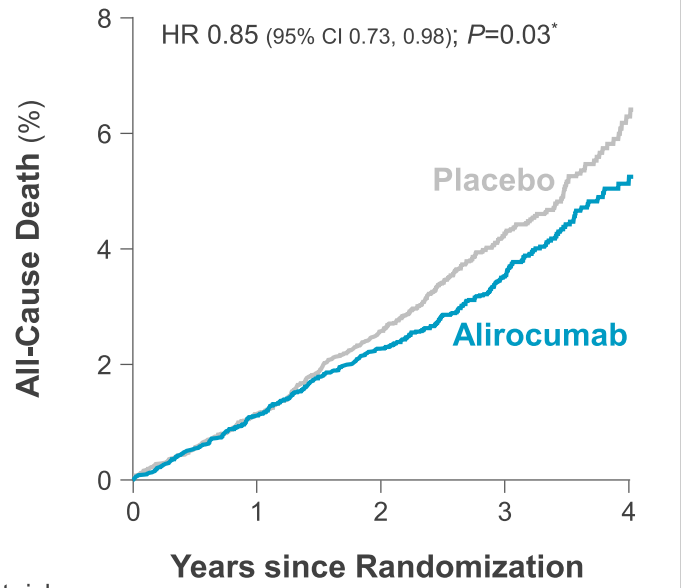
Reference 1. Steg PG, et al. Circulation 2019; 140(2):103-112.

The benefit of alirocumab on all-cause death appeared more pronounced than in the overall trial population.

Praluent® alirocumab

All patients (N=18,924)

A

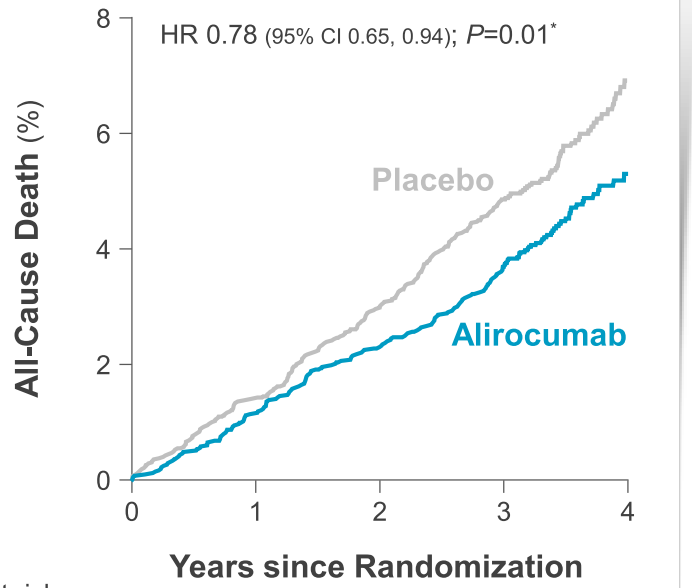


Number at risk

Placebo	9,462	9,219	8,888	3,898	737
Alirocumab	9,462	9,217	8,919	3,946	746

Eligible for ≥3 years follow-up (N=8,242, pre-specified)

B



Number at risk

Placebo	4,126	4,061	3,987	3,898	737
Alirocumab	4,116	4,059	4,007	3,946	746

*Nominal P-value due to hierarchical position of all-cause death among secondary endpoints

Reference 1. Steg PG, et al. Circulation 2019; 140(2):103-112.

ODYSSEY OUTCOMES

PRALUENT® reduced risk of MACE and was associated with a reduction of all-cause mortality which was observed in a CV outcomes trial

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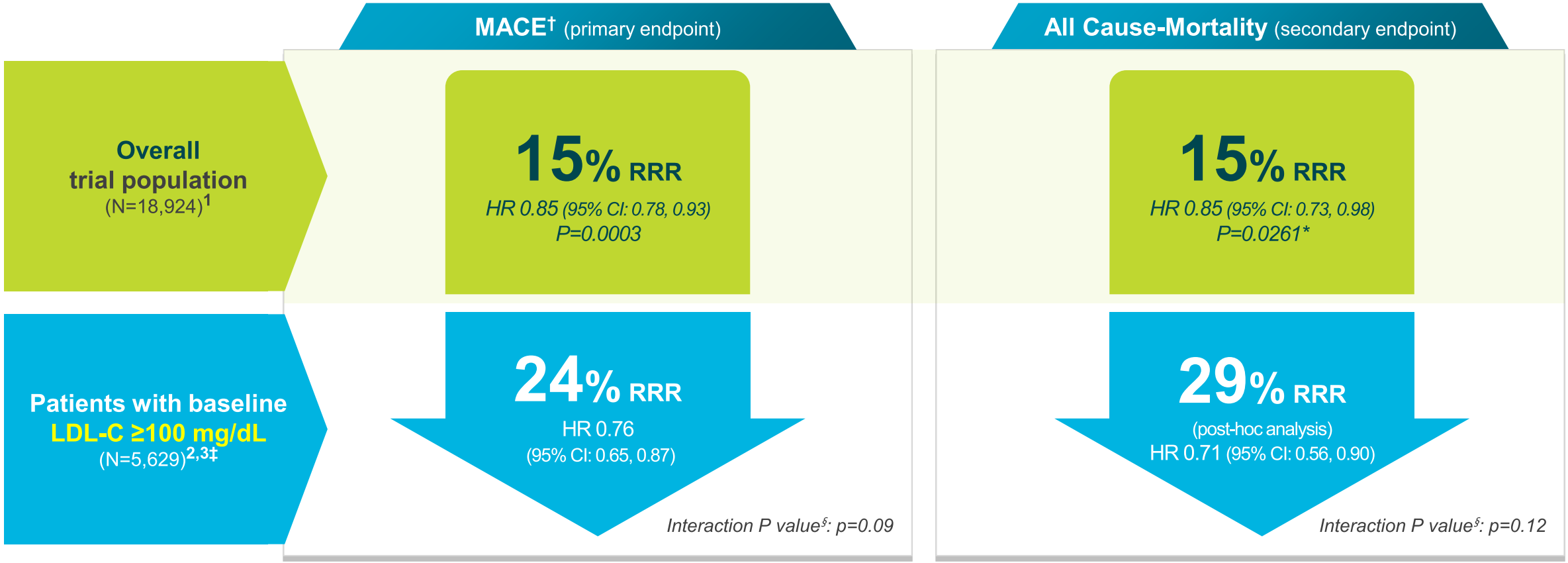

*With only nominal statistical significance by hierarchical testing (HR 0.85, 95% CI 0.73, 0.98).[2]
†Major adverse cardiovascular events (MACE)=primary composite endpoint of CHD death, nonfatal myocardial infarction, fatal and nonfatal ischaemic stroke, or unstable angina requiring hospitalisation.
‡From prespecified subgroup analysis according to baseline LDL-C ≥100 mg/dL (N=5,629).; §Interaction *P* value to assess interaction between treatment and baseline LDL-C level.

Reference. 1. PRALUENT (alirocumab) Summary of Product Characteristics. Paris, France: sanofi-aventis groupe; Aug 2020. 2. Schwarz GG, et al. N Engl J Med. 2018;379:2097–107. 3. Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes: an analysis of the Odyssey Outcomes randomized clinical trial. Circulation. 2019;140(2):103-112, 1-35.

ODYSSEY OUTCOMES

All-Cause mortality was less frequent among PRALUENT® -treated patients compared with those receiving placebo*

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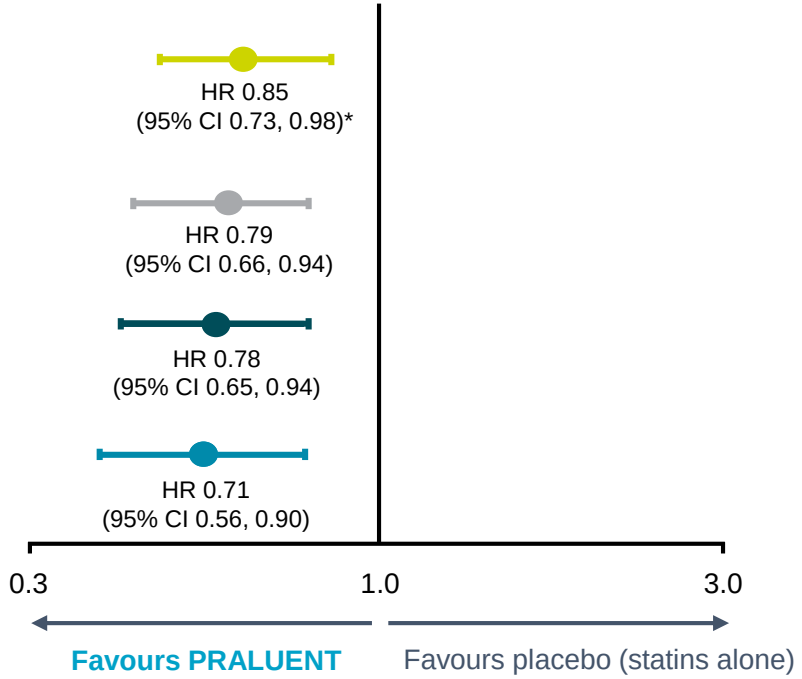
All-cause mortality in patients treated with PRALUENT® (plus statins) vs placebo (plus statins)[4,5†]

Overall trial population*	15% RRR; *P*=0.03
Treatment effect after 1 year	21% RRR; *P*=0.0073
Patients followed over 3 years ‡	22% RRR; *P*=0.01
Patients with baseline LDL-C ≥100 mg/dL §	29% RRR; Interaction *P* value: *P*=0.12



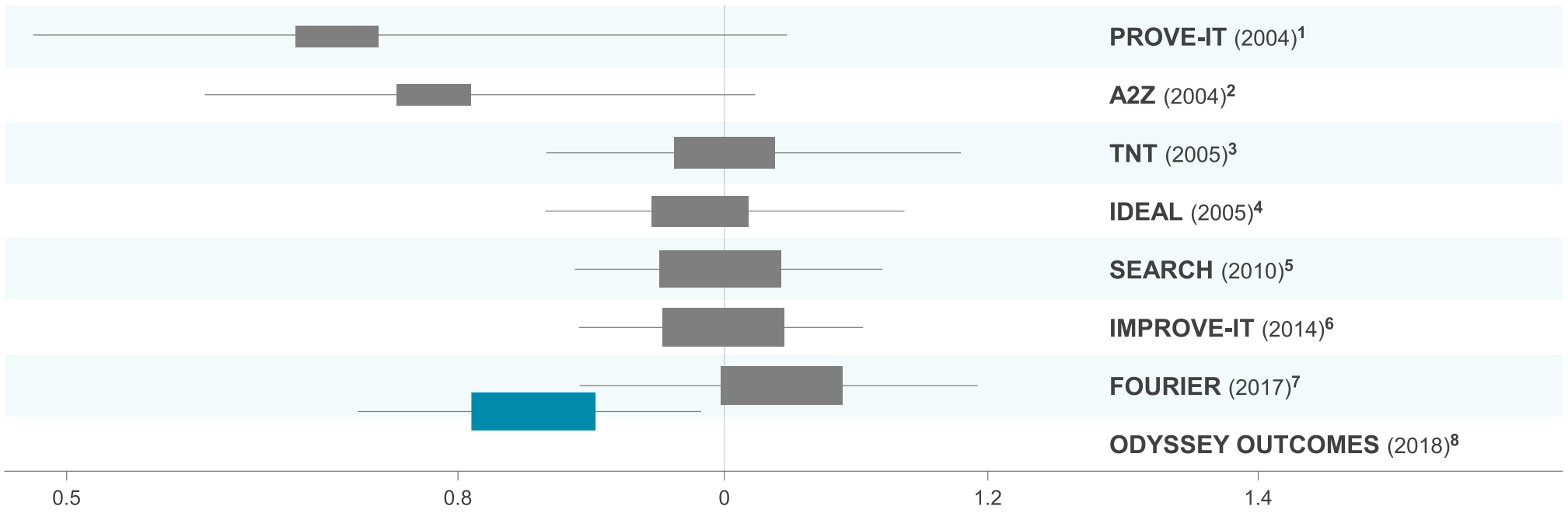
*With only nominal statistical significance by hierarchical testing.
†Because all-cause death followed CHD death and cardiovascular death in the prespecified hierarchy of main secondary endpoints, the P value for all-cause mortality was considered nominal.
‡Prespecified analysis. First year: HR 1.01 (95% CI 0.77, 1.32); <3 years of follow-up: HR 0.96 (95% CI 0.76, 1.21).
§Post hoc analysis.

References 1. Schwarz GG, et al. N Engl J Med. 2018;379:2097–107. 2. Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes: an analysis of the Odyssey Outcomes randomized clinical trial. Circulation. 2019;140(2):103-112, 1-35.

ODYSSEY OUTCOMES is the first published PCSK9 inhibitor study with a lower rate of deaths in the treatment arm

Praluent® alirocumab

All-cause death in secondary prevention lipid-lowering therapy trials



Pedro-Botet, J., López-Miranda, J., Badimón, L. *et al*. Overall Mortality and LDL Cholesterol Reduction in Secondary Prevention Trials of Cardiovascular Disease. Am J Cardiovasc Drugs (2019). https://doi.org/10.1007/s40256-019-00376-y

Reference. 1. Cannon CP, *et al*. N Engl J Med. 2004;350:1495–504; 2. de Lemos JA, *et al*. JAMA. 2004;292:1307–16; 3. LaRosa JC, *et al*. N Engl J Med. 2005;352:1425–35; 4. Pedersen TR, *et al*. JAMA. 2005;294:2437–45; 5. SEARCH Collaborative Group, *et al*. Lancet. 2010;376:1658–69; 6. Cannon CP, *et al*. N Engl J Med. 2015;372:2387–97; 7. Sabatine MS, *et al*. N Engl J Med. 2017;376:1713–22; 8. Schwarz GG, *et al*. N Engl J Med. 2018;379:2097–107.

All CV events were consistently lower in the PRALUENT® group than the placebo group

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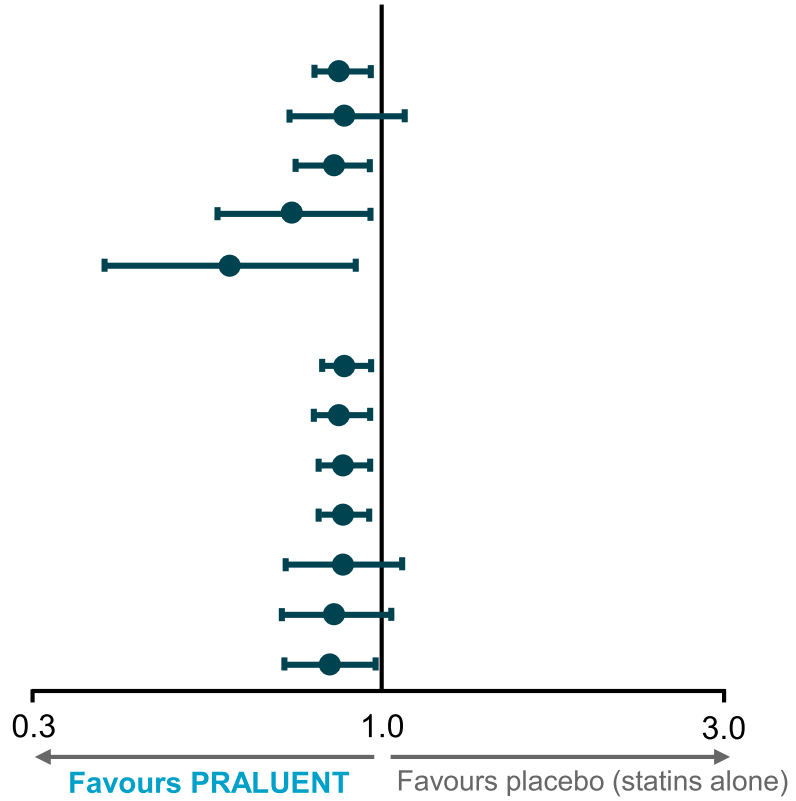
Endpoint, n (%)	HR (95% CI)	P-value
Primary endpoint (MACE)	0.85 (0.78, 0.93)	0.0003
CHD death	0.92 (0.76, 1.11)	0.38
Nonfatal MI	0.86 (0.77, 0.96)	0.006¶
Ischaemic stroke	0.73 (0.57, 0.93)	0.01¶
Unstable angina	0.61 (0.41, 0.92)	0.02¶
Secondary endpoints		
CHD event	0.88 (0.81, 0.95)	0.0013
Major CHD event	0.88 (0.80, 0.96)	0.0060
CV event	0.87 (0.81, 0.94)	0.0003
All-cause mortality, nonfatal MI, nonfatal ischaemic stroke	0.86 (0.79, 0.93)	0.0003
CHD death	0.92 (0.76, 1.11)	0.3824
CV death	0.88 (0.74, 1.05)	0.1528
All-cause mortality	0.85 (0.73, 0.98)	0.0261¶



¶Shows nominal significance.

Reference 1. Schwartz GG, et al. N Engl J Med 379 2097-2107.

Praluent® alirocumab

PCSK 9 inhibitors meta-analysis of RCTs

Figure 1. primary efficacy endpoints for PCSK9 inhibitors vs. control. Results are reported as risk ratios and 95% confidence intervals estimated using random-effect models.

	PCSK9-I (n/N)	Control (n/N)	PCSK9 better / Control better	Incidence rates Per 100 Patient-year		Risk Ratio	95% CI	I^2	*P*-value	P-int
				PCSK9-I	Control					
Overall	810/35,896	851/30,582		1.03	1.15	0.89	0.75-1.04	13%	0.15	
Evolocumab	454/21,257	437/18,124		1.31	1.31	1.03	0.90-1.17	0%	0.70	0.03
Alirocumab	**356/14,639**	**414/12,458**		**0.81**	**1.01**	**0.83**	**0.72-0.95**	**0%**	**0.008**	
Overall	509/34,839	528/29,868		0.66	0.73	0.94	0.84-1.06	0%	0.34	
Evolocumab	258/20,773	244/17,640		0.76	0.76	1.04	0.87-1.23	0%	0.68	0.13
Alirocumab	251/14,066	284/12,228		0.58	0.70	0.86	0.73-1.02	0%	0.08	
Overall	1,154/32,947	1,411/28,837		1.49	1.93	0.80	0.74-0.86	0%	<0.0001	
Evolocumab	492/19,369	659/16,860		1.44	2.04	0.73	0.66-0.82	0%	<0.0001	0.86
Alirocumab	662/13,578	752/11,977		1.53	1.84	0.76	0.54-1.06	10%	0.10	
Overall	337/31,852	425/28,476		0.44	0.58	0.78	0.67-0.89	0%	0.0005	
Evolocumab	213/18,847	268/16,728		0.63	0.83	0.79	0.66-0.94	0%	0.009	0.77
Alirocumab	124/13,005	157/11,748		0.29	0.39	0.75	0.60-0.95	0%	0.02	

CI, confidence interval; PCSK9-I, proprotein convertase subtilisin-kexin type 9 inhibitors; p-int, p-interaction.

Reference. 1. European Heart Journal (2019)0, 1-9

The incidence of AE was similar in the alirocumab and the placebo, with the exception of local injection-site reaction

Praluent® alirocumab

- Injection-site reactions (itching, redness, or swelling) were usually mild and self-limited.

Event	Alirocumab (N=9,451)	Placebo (N=9,443)
Local injection site reaction, n (%)*	**360** (3.8)	**203** (2.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Neurocognitive disorder, n (%)	143 (1.5)	167 (1.8)
Cataracts, n (%)	120 (1.3)	134 (1.4)
Hemorrhagic stroke, n (%)	9 (<0.1)	16 (0.2)

*HR vs. placebo 1.82 (95% CI 1.54, 2.17)

ODYSSEY OUTCOMES

PRALUENT® treatment has shown a favourable safety profile

Praluent® alirocumab

When comparing patients receiving PRALUENT vs. placebo

No increased risk of new onset diabetes or adverse effect on glycaemic parameters[1]

No increased risk of haemorrhagic stroke, whilst reducing risk of any stroke and ischaemic stroke[2]

No increased risk of neurocognitive disorder[3]
(1.5% [n=9451] vs. 1.8% [n=9443], respectively)

The safety profile of PRALUENT® has now been evaluated in 28 global trials, including all phase 2 and 3 trials and more than 32,100 patients across 3,000 study centres

CVOT, cardiovascular outcomes trial; LDL-C, low-density lipoprotein cholesterol; PCSK9i, PCSK9, proprotein convertase subtilisin/kexin type 9

Reference. 1. Ray KK, *et al*. Lancet Diabetes Endocrinol. 2019;7:618–28; 2. Jukema JW, *et al*. Circulation. 2019;140:2054–62; 3. Schwarz GG, *et al*. N Engl J Med. 2018;379:2097–107.

Praluent® alirocumab

Summary: ODYSSEY OUTCOMES results

Primary endpoint: MACE

PRALUENT significantly reduced the risk of MACE by 15%

LDL-C ≥100 mg/dL

A greater absolute benefit in MACE was shown in patients with baseline LDL-C ≥100 mg/dL

Safety

PRALUENT demonstrated a favourable safety and tolerability profile

All-cause mortality

PRALUENT was associated with a reduction in all-cause mortality†

LDL-C reduction

PRALUENT demonstrated a 54.7% LDL-C reduction at 4–years

Dosing

78% of PRALUENT administrations in the study were at the 75-mg dose

†With only nominal statistical significance by hierarchical testing (HR 0.85, 95% CI 0.73, 0.98)

LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event

Reference 1. Schwartz GG, et al. N Engl J Med. 2018;379:2097–107.

Praluent®
alirocumab

ODYSSEY KT

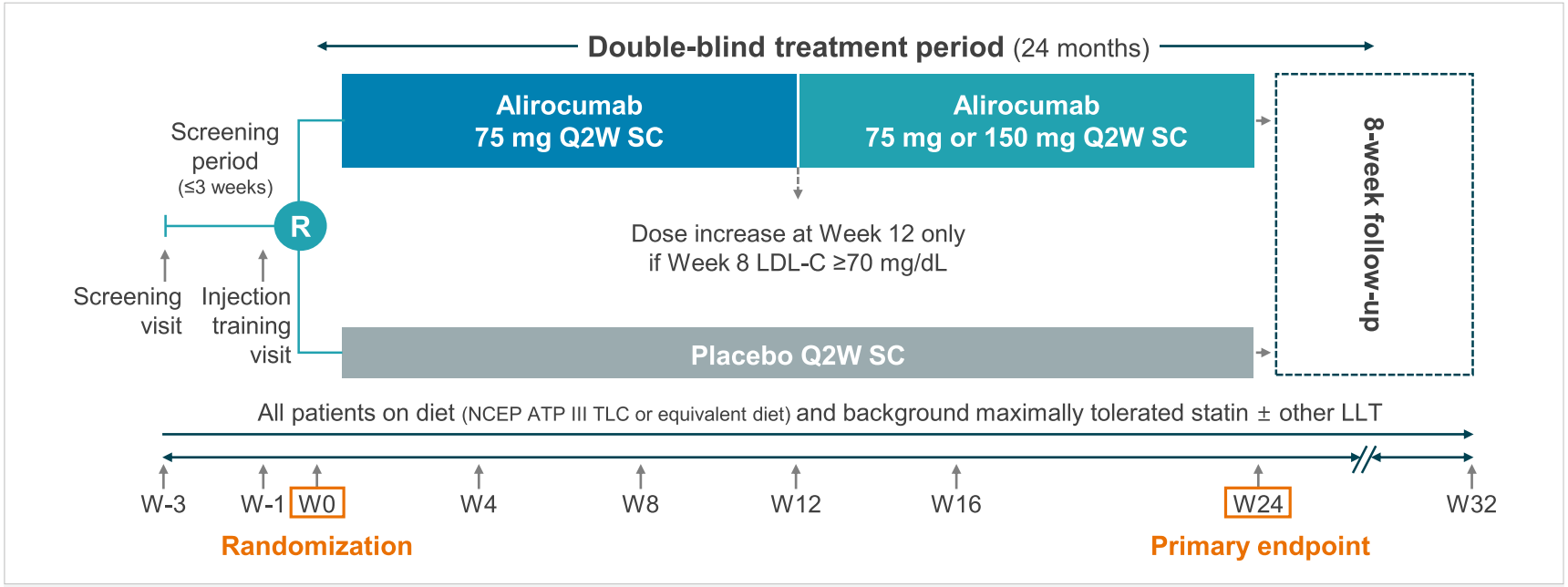
A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan

1. Koh KK, *et al*. J Clin Lipidol. 2017 Oct 19. pii: S1933-2874(17)30463-4.

ODYSSEY KT assessed the efficacy and safety of alirocumab in patients from South Korea and Taiwan

Praluent® alirocumab

- Patients: with hypercholesterolemia at high cardiovascular risk who were on maximally tolerated statin
- ODYSSEY KT assessed the efficacy and safety of alirocumab in patients from South Korea and Taiwan.



LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; Q2W, once every 2 weeks; SC, subcutaneous; TLC, therapeutic lifestyle changes; W, week

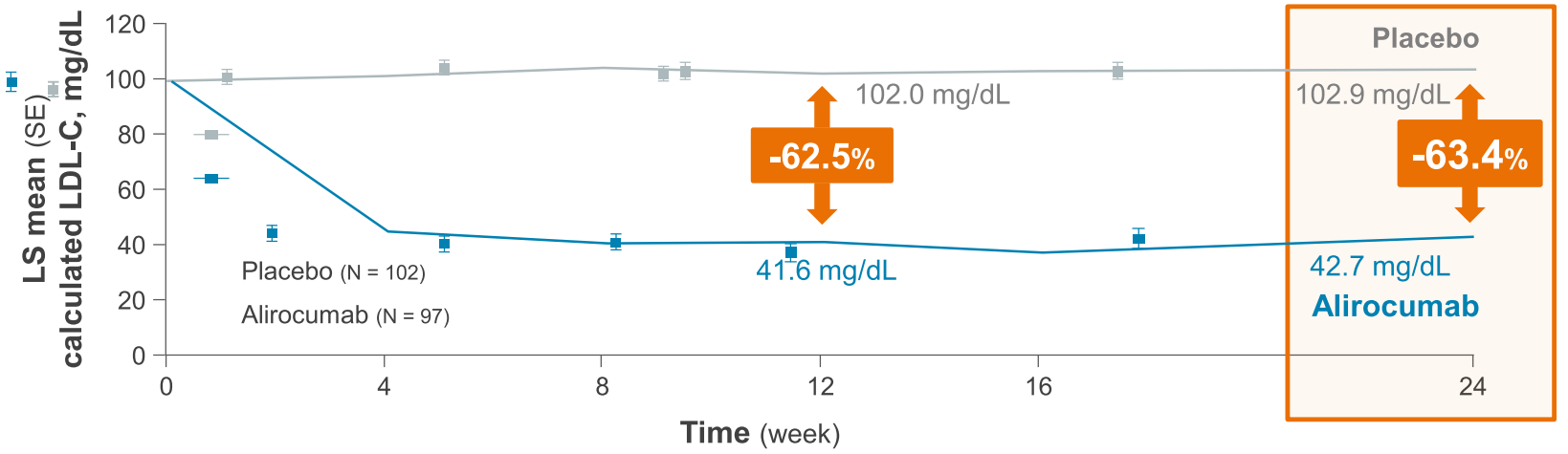
1. Koh KK, *et al*. Journal of Clinical Lipidology. 2017 Oct 19. pii: S1933-2874(17)30463-4.

LDL-C reductions were observed from week 4 and maintained until week 24

Praluent® alirocumab

- The difference in LDL-C levels from baseline between two groups was statistically significant at week 24 (-63.4%, $p<0.0001$)
- At week 24, 85.8% of patients in the alirocumab group reached LDL-C <70 mg/dL (placebo: 14.2%; $p<0.0001$ vs. placebo)

Calculated LDL-C levels over time (ITT)



ITT, intent to treat; LDL-C, Low-density lipoprotein cholesterol; LS, least square; SE, standard error

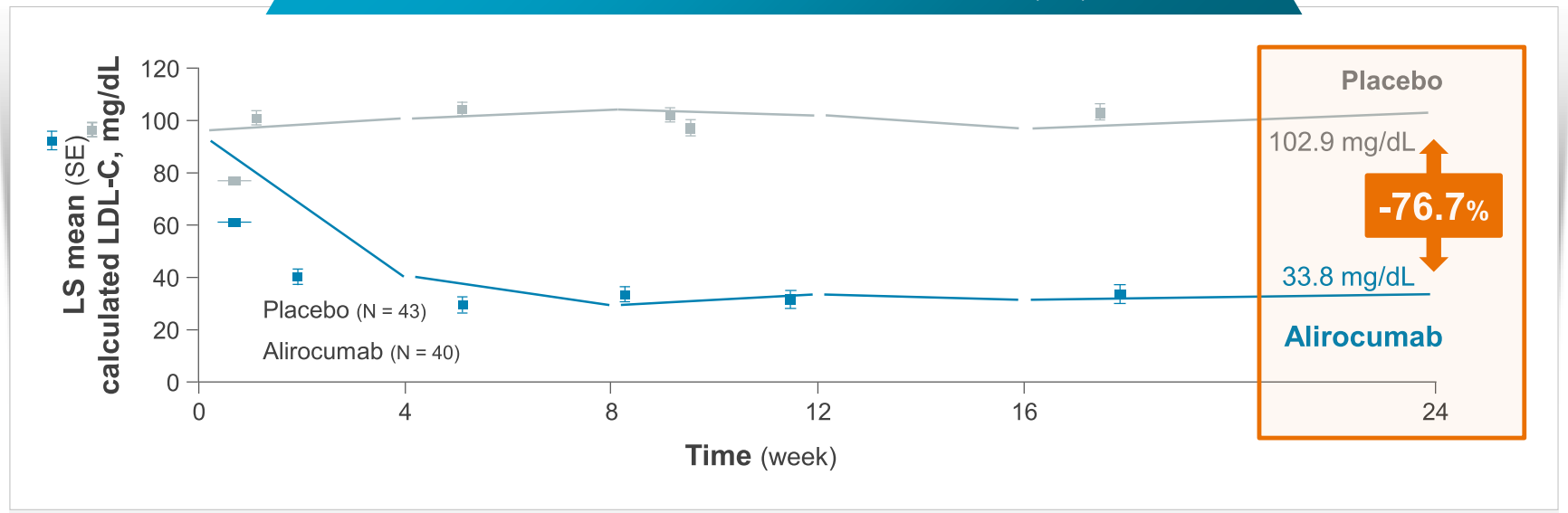
1. Koh KK, *et al*. Journal of Clinical Lipidology. 2017 Oct 19. pii: S1933-2874(17)30463-4.

ODYSSEY KT

Results from Korean Sub-data : Alirocumab has demonstrated to be effective in improvement of LDL-C level in Korean

- The difference in LDL-C levels from baseline between two groups reached -76.7% at week 24 (p<0.0001)
- At week 24, 92.0% of patients in the alirocumab group reached LDL-C <70 mg/dL
  (placebo: 12.7%; p<0.0001 vs. placebo)

Calculated LDL-C levels over time (ITT)



1. Nam CW, *et al*. Korean J Intern Med. 2019;34(6):1252-1262.

Safety in Korean Sub-data
: Alirocumab was generally well tolerated with no significant safety signals

Praluent® alirocumab

Alirocumab showed a comparable safety profile to placebo consistent with the whole KT population

n (%)	Alirocumab (n=40)	Placebo (n=43)
TEAEs	18 (45.0%)	22 (51.2)
Treatment-emergent SAEs	5 (12.5)	5 (11.6)
TEAEs leading to death	0	0
TEAEs leading to treatment discontinuation	0	0
TEAEs occurring in ≥5% of patients		
Headache	4 (10.0)	0
Nasopharyngitis	3 (7.5)	2 (4.7)
Fall	2 (5.0)	0

1. Nam CW, *et al*. Korean J Intern Med. 2019;34(6):1252-1262.

Patient profile*

Praluent® alirocumab

ASCVD very high risk patient with prior ACS, Stroke, CABG

Patients such as Sophie†
Age: 52 / Former smoker

입원 시 환자의 프로파일

Clinical considerations	Details
Patient demographics	• 52-year old • female
Clinical history	• Hospitalisation for **ACS** (first event) CV 초고위험군
CV risk factors	• Smoker, treated hypertension • Poor lifestyle habits
Lipid profile at admission (on Rosuvastatin 40 mg)	• **LDL-C 116 mg/dL** (3.0 mmol/L) • HDL-C 35 mg/dL (0.9 mmol/L) • TG 175 mg/dL (2.0 mmol/L) LDL-C 목표: 70 mg/dL 이하 (기저치보다 50% 이상 감소) • Ezetimibe 10 mg/day • Rosuvastatin 20 mg/day 고강도 스타틴으로 치료 중

2019 ESC 가이드라인 권고사항[1]

	Class[a]	Level[b]
초고위험군 환자에서 이차 예방으로서 LDL-C을 기저치 대비 50% 이상 낮추면서 **LDL-C을 55 mg/dL 이하**로 감소할 것을 권고하고 있습니다.	I	A
초고위험군 환자에서 최대가용량 스타틴과 에제티미브 치료에도 불구하고 LDL-C 치료 목표에 도달하지 못하는 경우, **PCSK9 억제제 추가를 권고**하고 있습니다.	I	A

[a] Class of recommendation: Class I Definition: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.
[b] Level of evidence: A Data derived from multiple randomized clinical trials or meta-analyses.

2018 국내 이상지질혈증 가이드라인 권고사항[2]

	저위험군	중등도 위험군	고위험군	초고위험군
CV Risk	주요 위험인자[†] 1개 이하	주요 위험인자[†] 2개 이하	• 경동맥질환[‡] • 복부동맥류 • 당뇨병[§]	• **관상동맥질환** • **죽상경화성 허혈뇌졸중 및 일과성 뇌허혈발작** • 말초동맥질환 (**기존에 심혈관 질환이 있었던 환자의 경우, 심혈관 질환 재발을 방지하기 위해 LDL-C <70 mg/dL 또는 기저치보다 50%이상 감소**)
LDL-C 치료 목표	<160 mg/dL	<130 mg/dL	<100 mg/dL	**< 70 mg/dL**

[†]연령(남≥45세, 여≥55세), 관상동맥질환 조기발병 가족력, 고혈압, 흡연, Low HDL-C
[‡]무증상 경동맥 협착이 확인된 경우 [§]표적장기손상 혹은 심혈관질환의 주요 위험인자를 가지고 있는 경우 환자에 따라서 목표치를 하향조정할 수 있음

*hypothetical patient

†Very high risk: • ASCVD (clinical/imaging): Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, PCI, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. • SCORE 10%. • FH with ASCVD or with another major risk factor • Severe CKD (eGFR <30 mL/min) • DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years).

References 1. Mach F, et al. Eur Heart J. 2020;41:111-188. 2. 한국지질·동맥경화학회. 2018 이상지질혈증 치료지침 제4판.