The ODYSSEY OUTCOMES Trial: Topline Results

Alirocumab in Patients After Acute Coronary Syndrome

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On behalf of the ODYSSEY OUTCOMES Investigators and Committees

American College of Cardiology – 67th Scientific Sessions
March 10, 2018

ODYSSEY OUTCOMES

ClinicalTrials.gov: NCT01663402

Disclosures

- The trial was funded by **Sanofi** and **Regeneron Pharmaceuticals**
- **Ph. Gabriel Steg** discloses the following relationships:

- Research grants from Bayer, Merck, Sanofi, and Servier

- Speaking or consulting fees from Amarin, Amgen, AstraZeneca, Bayer/Janssen, Boehringer Ingelheim, Bristol-Myers Squibb, Lilly, Merck, Novartis, Novo-Nordisk, Pfizer, Regeneron Pharmaceuticals, Sanofi, and Servier

- **Gregory G. Schwartz** discloses research support to his institution

Residual Risk After Acute Coronary Syndrome

- Remains high despite evidence-based preventive therapies
- Is related, in part, to levels of low-density lipoprotein cholesterol (LDL-C)
- Is reduced when LDL-C is lowered by
  - Statin therapy, compared with placebo[1]
  - High-intensity, compared with moderate-intensity statin therapy[2]
  - Ezetimibe, compared with placebo, added to statin[3]

1. Schwartz GG, et al. JAMA 2001;285:1711-8. 2. Cannon CP, et al. NEJM 2004;350:1495-504.
3. Cannon CP, et al. NEJM 2015;372:2387-97.

Alirocumab

- PCSK9 is a validated target for risk reduction in stable atherosclerotic cardiovascular disease[1–3]
- A fully human monoclonal antibody against PCSK9
- Produces substantial and sustained reductions in LDL-C and other atherogenic lipoproteins[2]
- Has been safe and well-tolerated in studies to date[4]

PCSK9, proprotein convertase subtilisin/kexin type 9

1. Sabatine et al, NEJM 2017;376:713-22. 2. Robinson JG et al. NEJM 2015;372:1489-99.
3. Ridker PM et al. NEJM 2017;376:1527-39. 4. Robinson JG et al. JACC 2017;69:471-82.

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Study Hypothesis

Alirocumab, versus placebo, reduces cardiovascular (CV) morbidity and mortality after recent acute coronary syndrome (ACS) in patients with elevated levels of atherogenic lipoproteins despite intensive or maximum-tolerated statin therapy

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

Main Inclusion Criteria

- **Age** ≥40 years
- **ACS**
  - 1 to 12 months prior to randomization
  - Acute myocardial infarction (MI) or unstable angina
- **High-intensity statin therapy***
  - Atorvastatin 40 to 80 mg daily or
  - Rosuvastatin 20 to 40 mg daily or
  - Maximum tolerated dose of one of these agents for ≥2 weeks
- **Inadequate control of lipids**
  - LDL-C ≥70 mg/dL (1.8 mmol/L) or
  - Non-HDL-C ≥100 mg/dL (2.6 mmol/L) or
  - Apolipoprotein B ≥80 mg/dL

*Patients not on statins were authorized to participate if tolerability issues were present and documented

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

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Key Exclusion Criteria

- Uncontrolled hypertension
- NYHA class III or IV heart failure;

  LVEF <25% if measured
- History of hemorrhagic stroke
- Fasting triglycerides >400 mg/dL

  (4.52 mmol/L)
- Use of fibrates other than fenofibrate or fenofibric acid
- Recurrent ACS within 2 weeks prior to randomization visit
- Coronary revascularization performed within 2 weeks prior to randomization visit, or planned after randomization
- Liver transaminases >3 × ULN;

  hepatitis B or C infection
- Creatine kinase >3 × ULN
- eGFR <30 mL/min/1.73 m^2
- Positive pregnancy test

eGFR, estimated glomerular filtration rate; ULN, upper limit of normal

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

Primary Efficacy Outcome

Time of first occurrence of:

- **Coronary heart disease (CHD) death, or**
- **Non-fatal MI, or**
- **Fatal or non-fatal ischemic stroke, or**
- **Unstable angina requiring hospitalization***

All outcomes adjudicated by the Clinical Events Committee, under the auspices of the Duke Clinical Research Institute (DCRI). Members were unaware of treatment assignment and lipid levels

*Required all of the following:

1. Hospital admission >23 h for MI symptoms, ↑ tempo in prior 48 hours and/or ≥20 min of chest discomfort at rest
2. New ECG findings consistent with ischemia or infarction
3. Angiographically significant obstructive coronary disease

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

Major Secondary Efficacy Endpoints

Tested in the following hierarchical sequence:

- **CHD event**: CHD death, non-fatal MI, unstable angina requiring hospitalization, or ischemia-driven coronary revascularization*
- **Major CHD event**: CHD death or non-fatal MI
- **CV event:** CV death, non-fatal CHD event, or non-fatal ischemic stroke
- **All-cause death, non-fatal MI, non-fatal ischemic stroke**
- **CHD death**
- **CV death**
- **All-cause death**

*Revascularization performed because of recurrent ACS, new or progressive symptoms of myocardial ischemia or new or progressive abnormalities on functional testing, except revascularization due to restenosis at a prior coronary intervention site.

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Other Secondary and Safety Endpoints

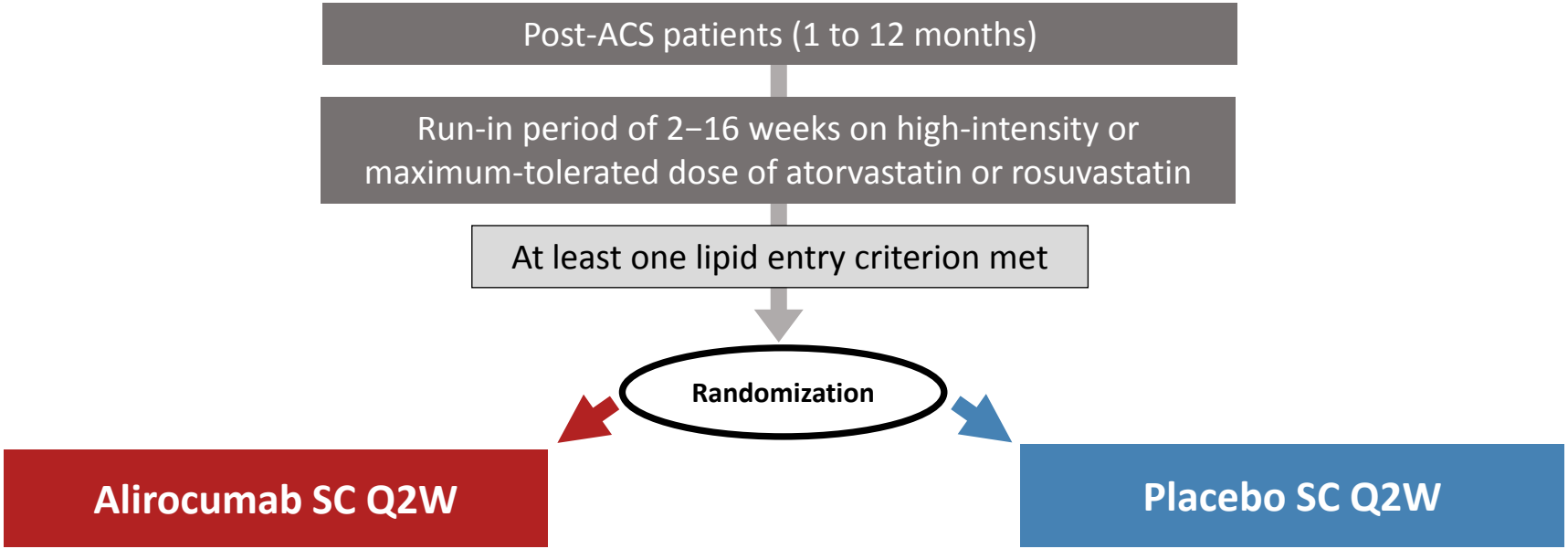
Other secondary endpoints

- Components of the primary endpoint considered individually:
  - CHD death
  - Non-fatal MI
  - Fatal and non-fatal ischemic stroke
  - Unstable angina requiring hospitalization
- Ischemia-driven coronary revascularization
- Congestive heart failure requiring hospitalization

Safety endpoints

- Adverse events
- Laboratory assessments

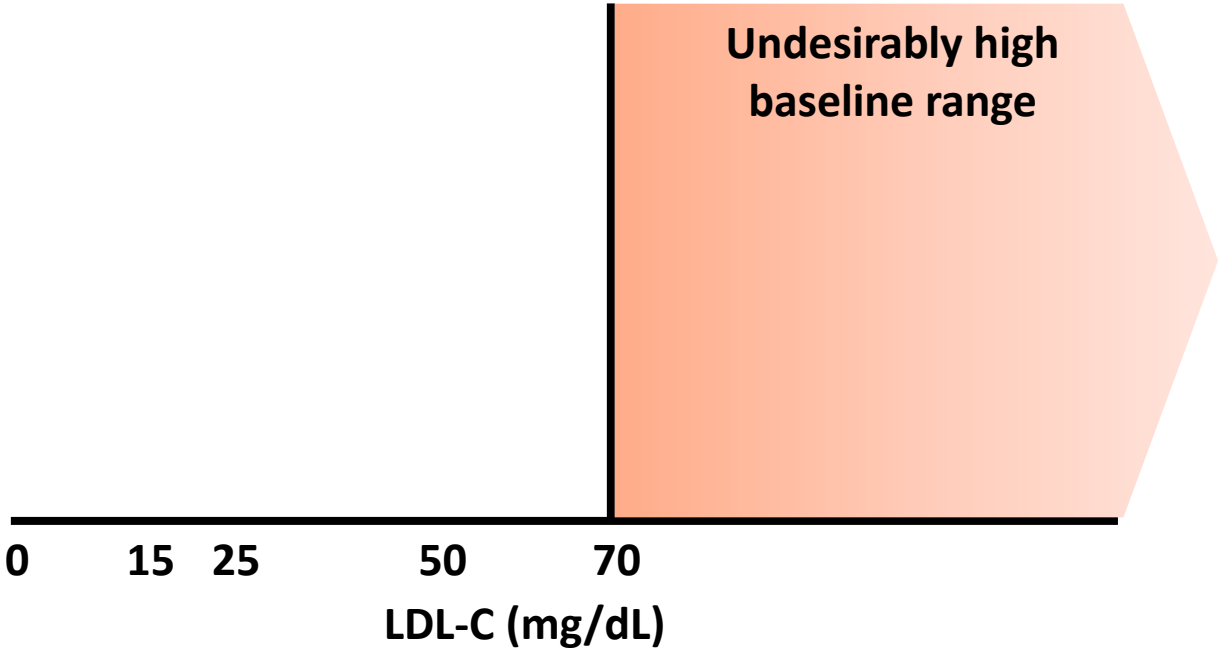
Treatment Assignment



Patient and investigators remained blinded to treatment and lipid levels for the entire duration of the study

Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

A Target Range for LDL-C



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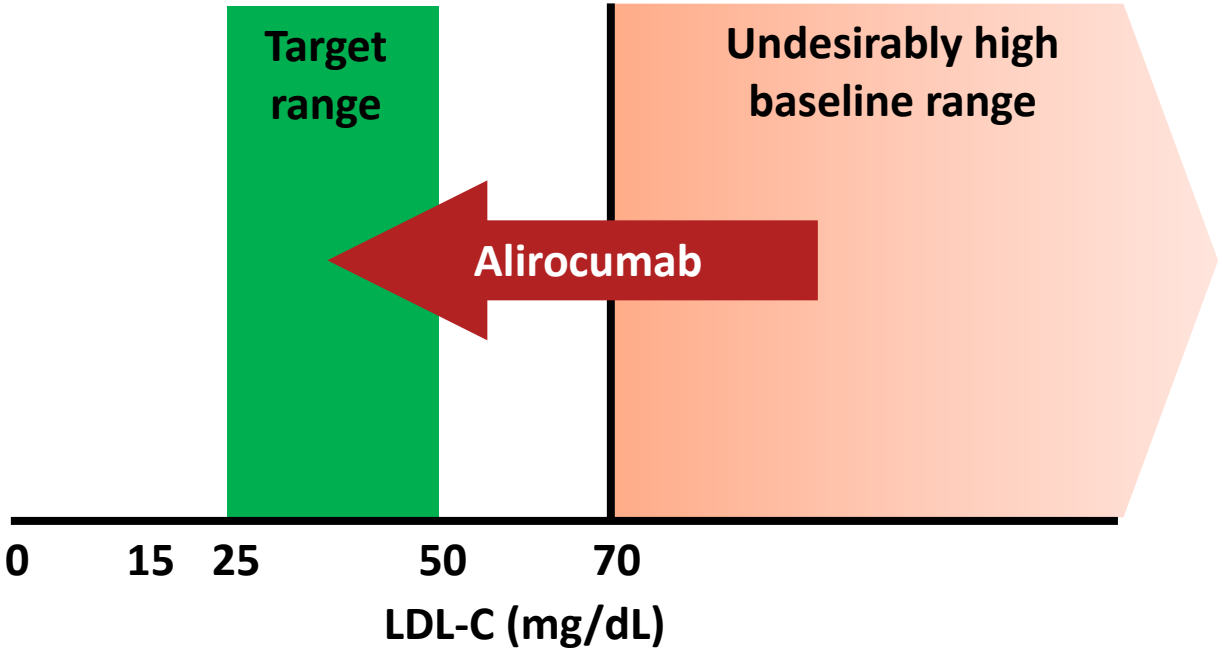
A Target Range for LDL-C



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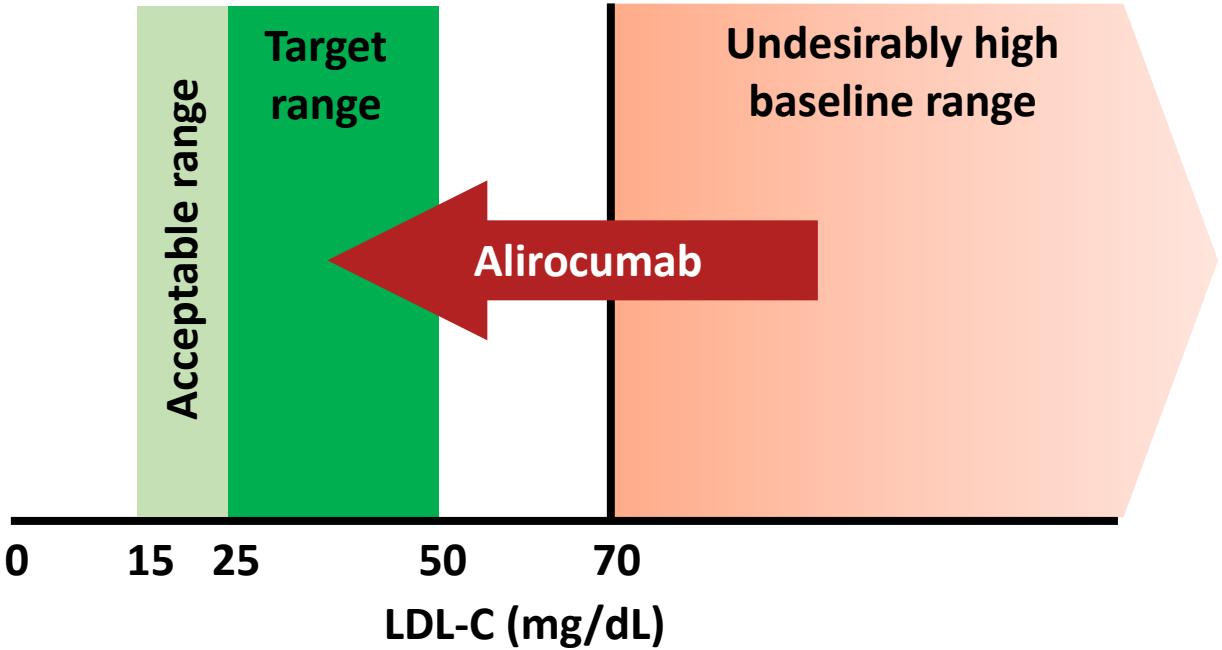
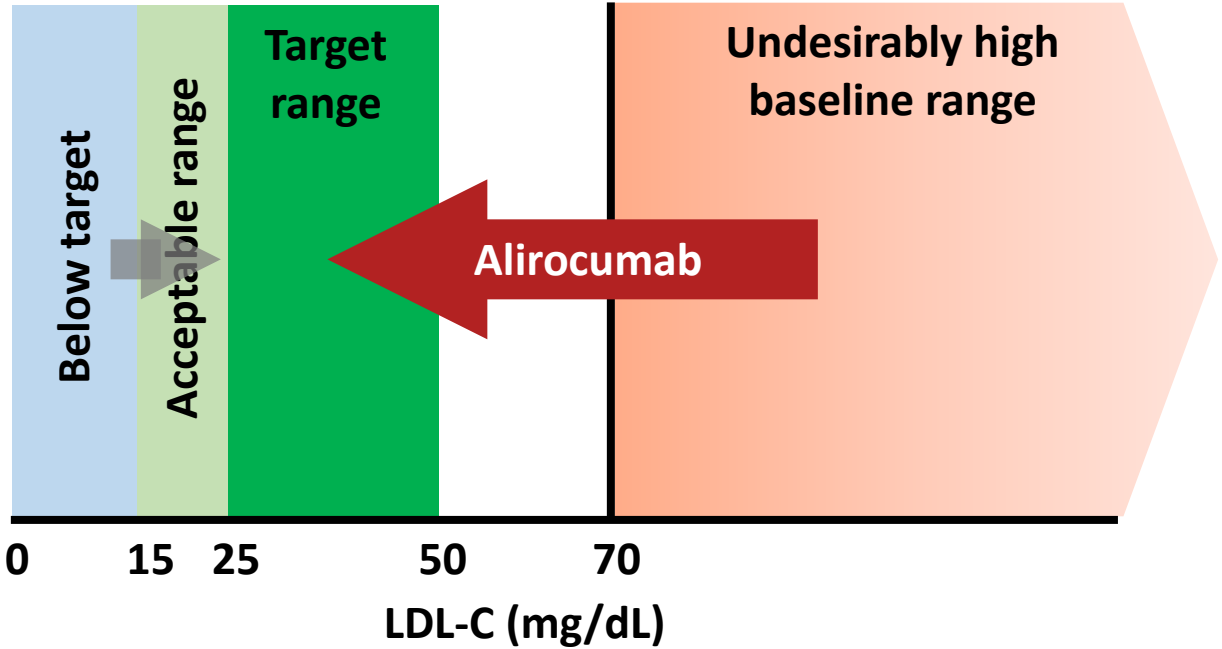
A Target Range for LDL-C



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.



Schwartz GG, et al. Am Heart J 2014;168:682-689.e1.

Statistical Considerations

- All analyses conducted by independent academic statistical team at State University of New York (SUNY) Downstate School of Public Health, in parallel with the sponsor
- Efficacy analysis by intention-to-treat (ITT)

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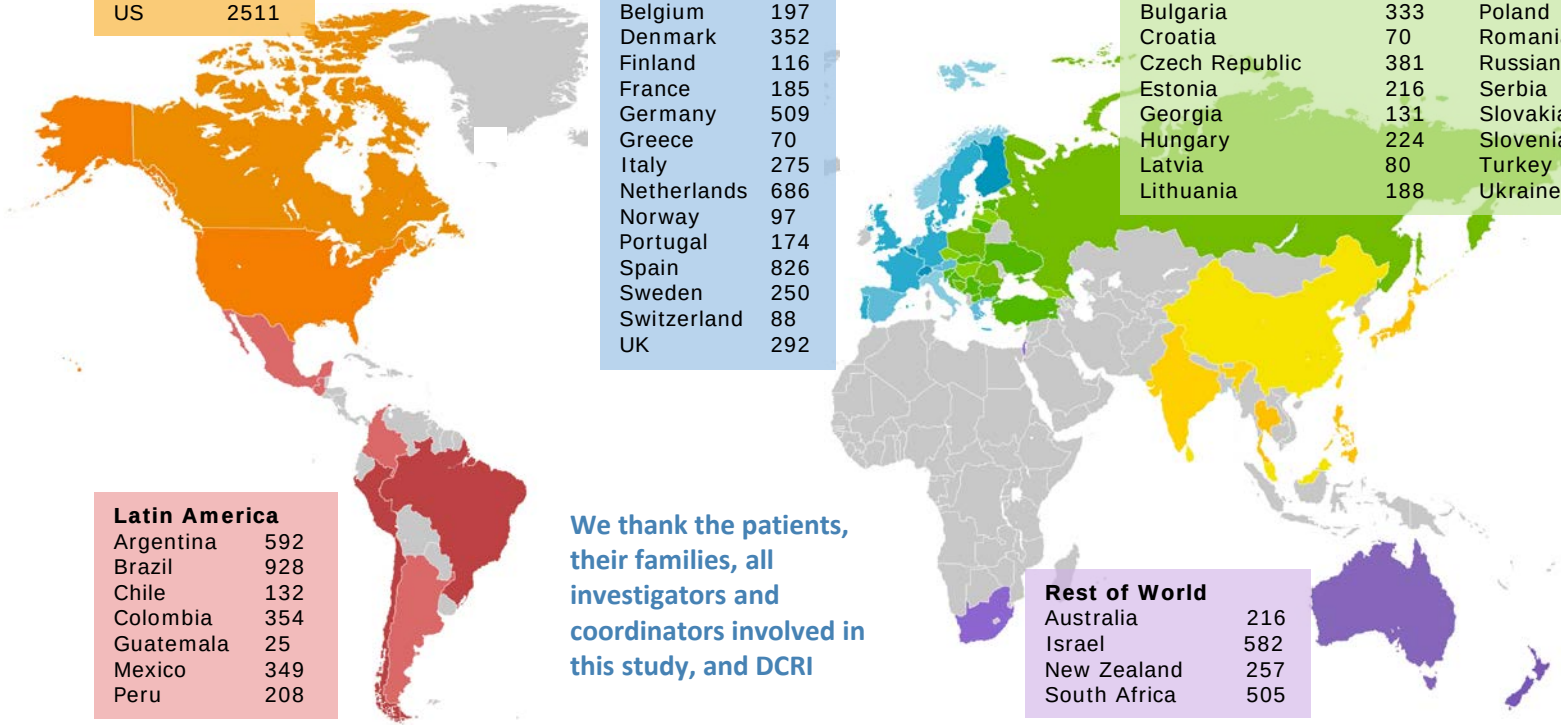
- All analyses conducted by independent academic statistical team at State University of New York (SUNY) Downstate School of Public Health, in parallel with the sponsor
- Efficacy analysis by intention-to-treat (ITT)
- Assumptions
  - Cumulative incidence of primary endpoint in placebo group 11.4% at 48 months
  - Baseline LDL-C 90 mg/dL; reduction to 45 mg/dL with alirocumab
  - **15% expected hazard reduction for primary endpoint**
  - Loss to follow-up at 24 months: 1%
  - Log-rank test with 1-sided 2.5% significance level
  - Continuation of the trial until **1613** patients with a primary endpoint (for 90% power) **AND** all surviving patients followed for **≥2 years** (for adequate safety assessments), **whichever came later***

* Except for patients enrolled in China (enrollment started on May 5, 2016)

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



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

We thank the patients, their families, all investigators and coordinators involved in this study, and DCRI

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Monitoring of safety in patients with low LDL-C values

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Academic and Contract Research Organizations

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Independent Statistical Team

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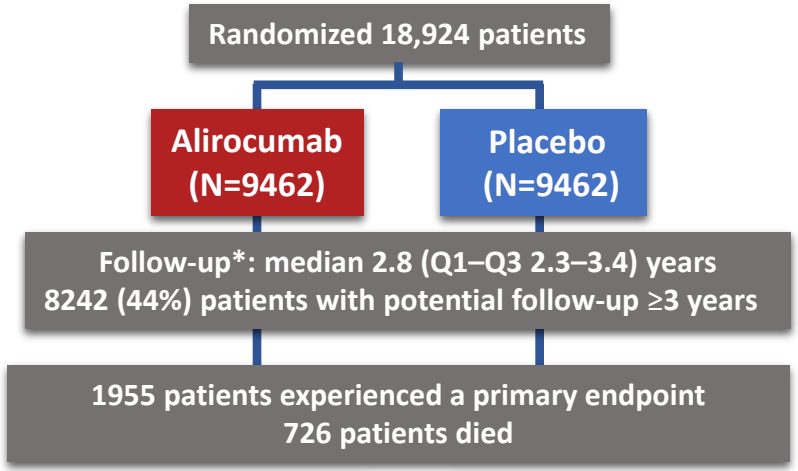
Patient Disposition



• **Premature treatment discontinuation**	1343 (14.2%)	1496 (15.8%)
• **Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)**	730 (7.7%)	Not applicable
• **Patients lost to follow-up (vital status)**	14	9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

Baseline Demographics

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Age, years, median (Q1–Q3)	58 (52–65)	58 (52–65)
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)
Current tobacco smoker	2282 (24.1)	2278 (24.1)
Prior MI	1790 (18.9)	1843 (19.5)

Baseline Index Events

Characteristic	Alirocumab (N=9462)	Placebo (N=9462)
Time from index ACS to randomization, months, median (Q1–Q3)	2.6 (1.7–4.4)	2.6 (1.7–4.3)
ACS type, n (%)		
NSTEMI	4574 (48.4)	4601 (48.7)
STEMI	3301 (35.0)	3235 (34.2)
Unstable angina	1568 (16.6)	1614 (17.1)
Revascularization for index ACS, n (%)	6798 (71.8)	6878 (72.7)

Baseline Lipid Characteristics

Characteristic, mg/dL, median (Q1–Q3)	Alirocumab (N=9462)	Placebo (N=9462)
LDL-C	87 (73–104)	87 (73–104)
Non-HDL-C	115 (99–136)	115 (99–137)
Apolipoprotein B	79 (69–93)	80 (69–93)
HDL-C	43 (37–50)	42 (36–50)
Triglycerides	129 (94–181)	129 (95–183)
Lipoprotein(a)	21 (7–59)	22 (7–60)

92.5% of patients qualified on the basis of LDL-C ≥70 mg/dL

Baseline Lipid-Lowering Therapy

Therapy, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
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)

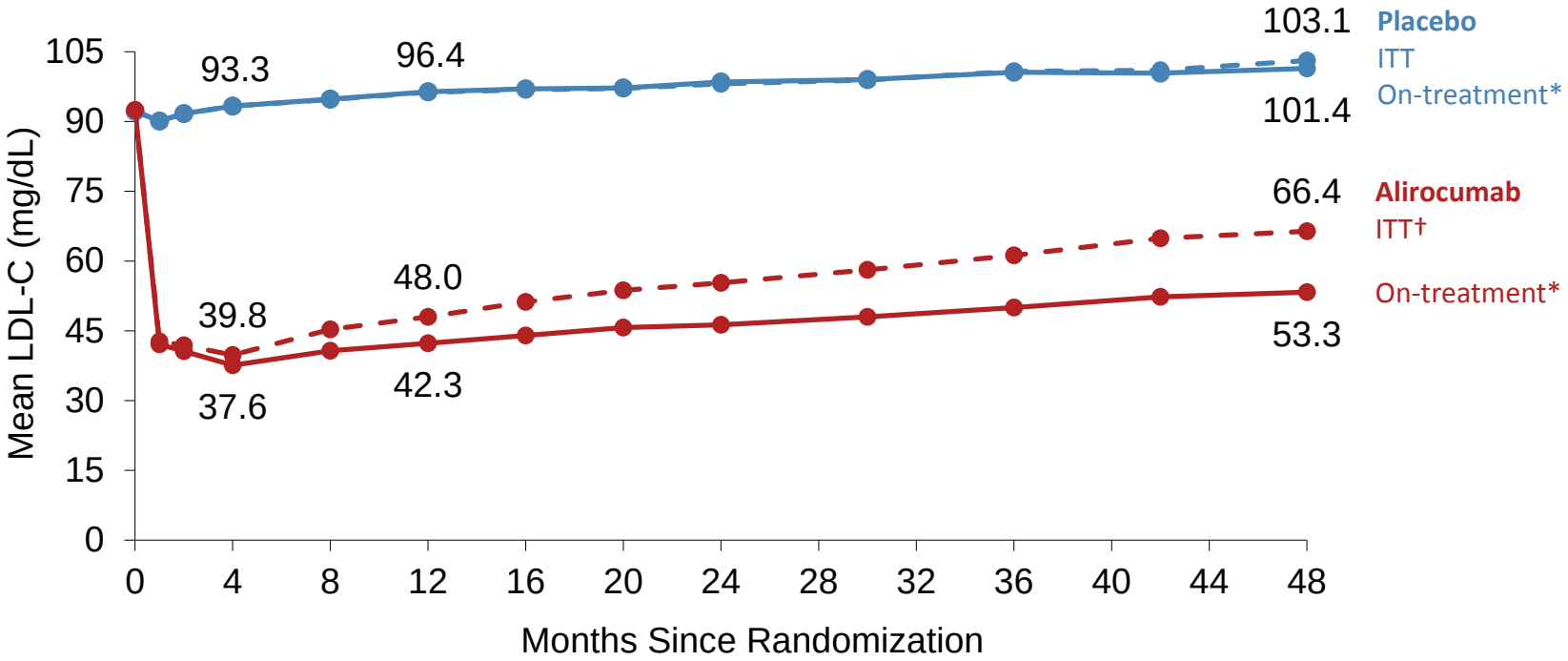
*Patients not on statins were authorized to participate if tolerability issues were present and documented

Guideline-Recommended Post-ACS Medications

Medication, n (%)	Alirocumab (N=9462)	Placebo (N=9462)
Aspirin	9050 (95.6)	9036 (95.5)
$P2Y_{12}$ antagonist	8296 (87.7)	8245 (87.1)
ACE-I/ARB	7356 (77.7)	7360 (77.8)
Beta-blocker	7998 (84.5)	7992 (84.5)

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

LDL-C: ITT and On-Treatment Analyses



*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

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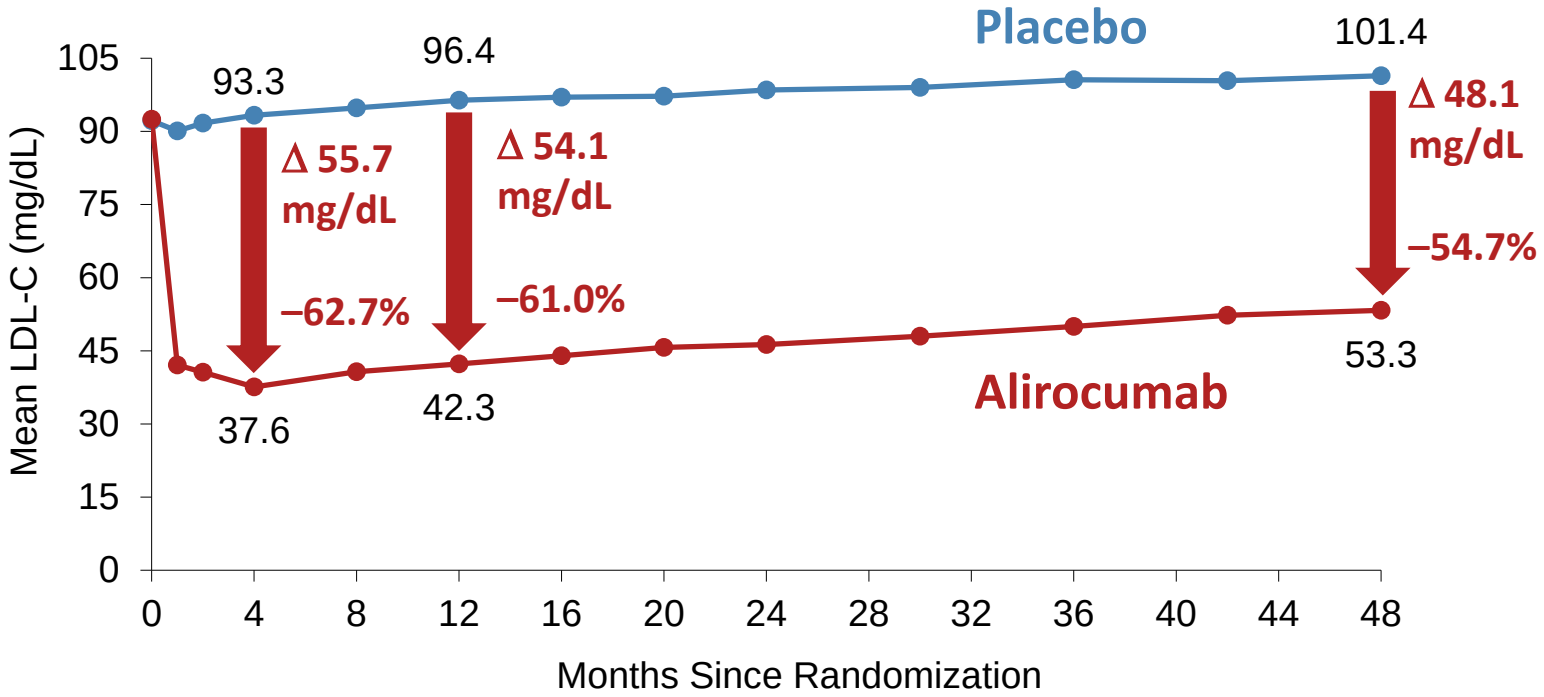
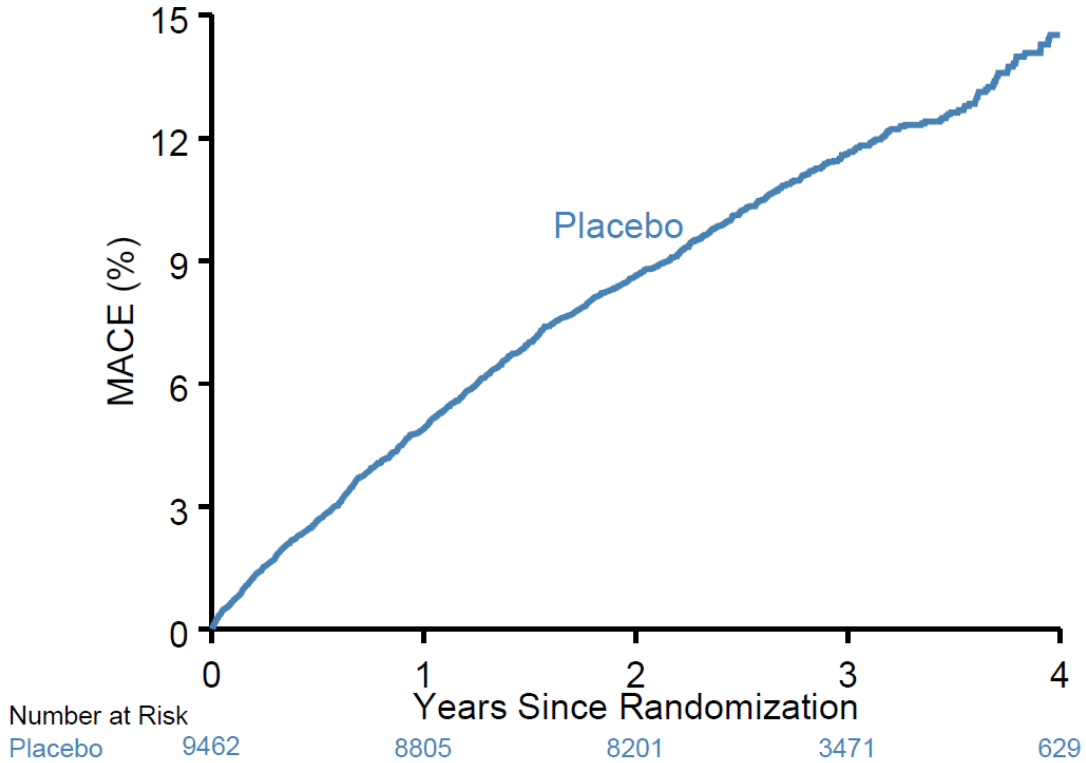
LDL-C: On-Treatment Analysis



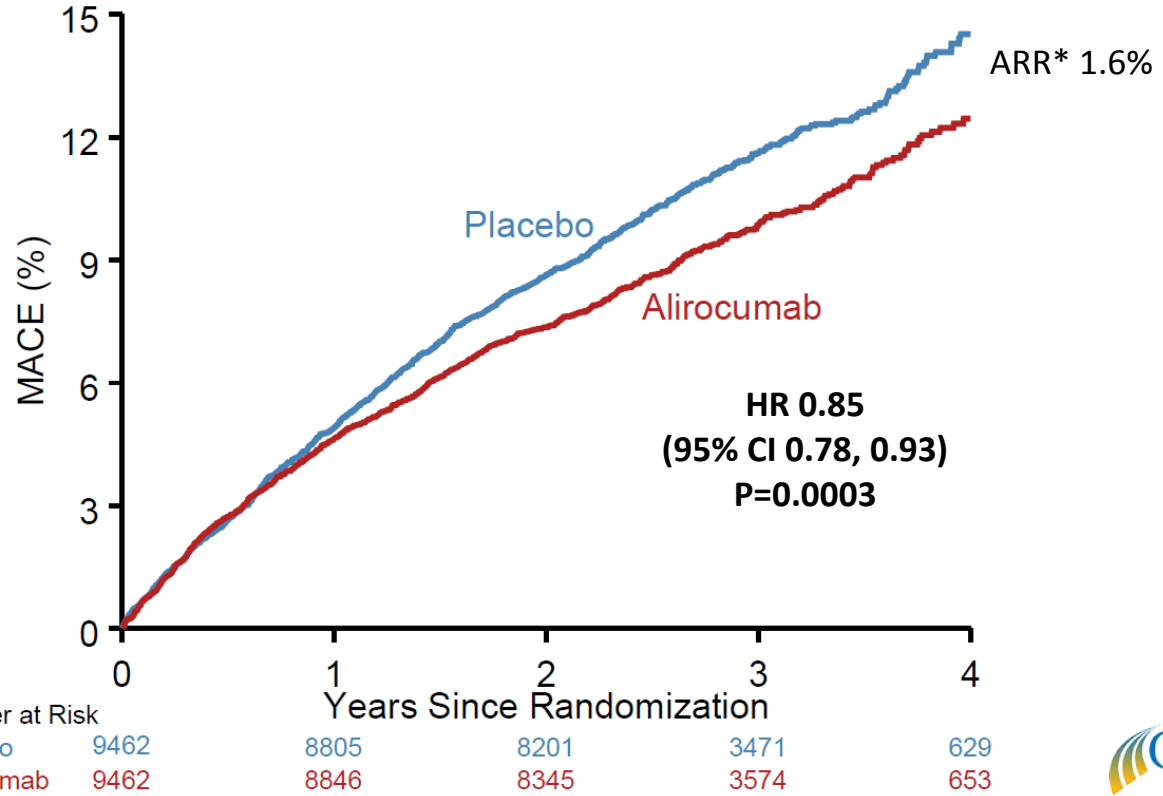
Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo
Approximately 75% of months of active treatment were at the 75 mg dose

Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization



Primary Efficacy Endpoint: MACE



MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

*Based on cumulative incidence

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Primary Efficacy and Components

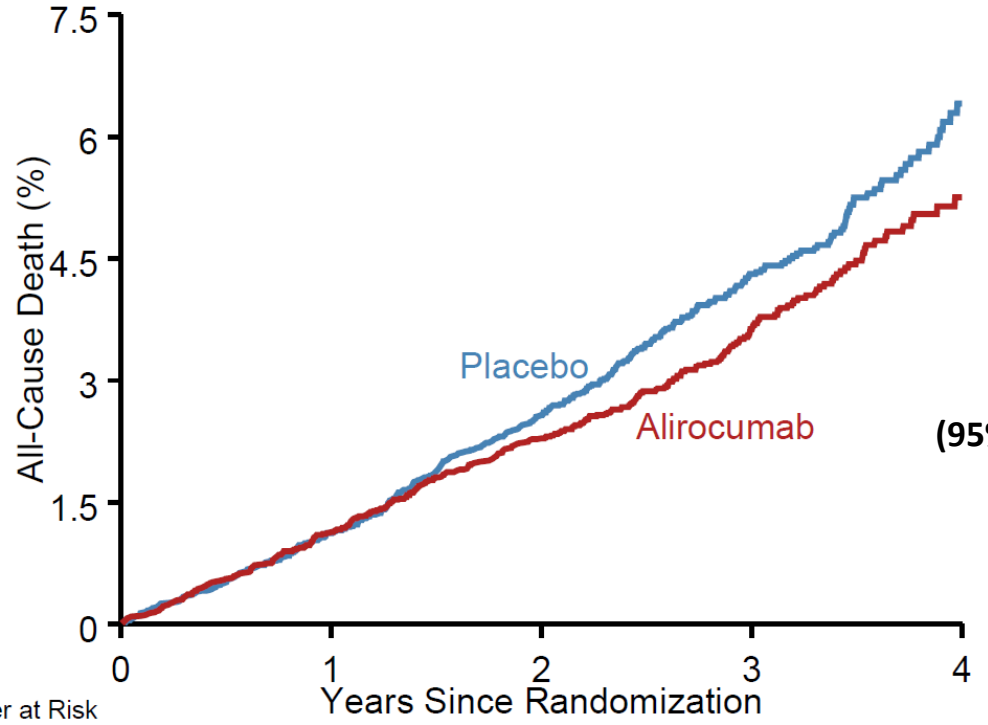
Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
MACE	**903 (9.5)**	**1052 (11.1)**	**0.85 (0.78, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
Non-fatal MI	**626 (6.6)**	**722 (7.6)**	0.86 (0.77, 0.96)	0.006
Ischemic stroke	**111 (1.2)**	**152 (1.6)**	0.73 (0.57, 0.93)	0.01
Unstable angina	**37 (0.4)**	**60 (0.6)**	0.61 (0.41, 0.92)	0.02

Main Secondary Efficacy Endpoints:
Hierarchical Testing

Endpoint, n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
CHD event	**1199 (12.7)**	**1349 (14.3)**	**0.88 (0.81, 0.95)**	**0.001**
Major CHD event	**793 (8.4)**	**899 (9.5)**	**0.88 (0.80, 0.96)**	**0.006**
CV event	**1301 (13.7)**	**1474 (15.6)**	**0.87 (0.81, 0.94)**	**0.0003**
Death, MI, ischemic stroke	**973 (10.3)**	**1126 (11.9)**	**0.86 (0.79, 0.93)**	**0.0003**
CHD death	**205 (2.2)**	**222 (2.3)**	0.92 (0.76, 1.11)	0.38
CV death	**240 (2.5)**	**271 (2.9)**	0.88 (0.74, 1.05)	0.15
All-cause death	**334 (3.5)**	**392 (4.1)**	**0.85 (0.73, 0.98)**	**0.026***

*Nominal P-value

All-Cause Death



*Nominal P-value
†Based on cumulative incidence

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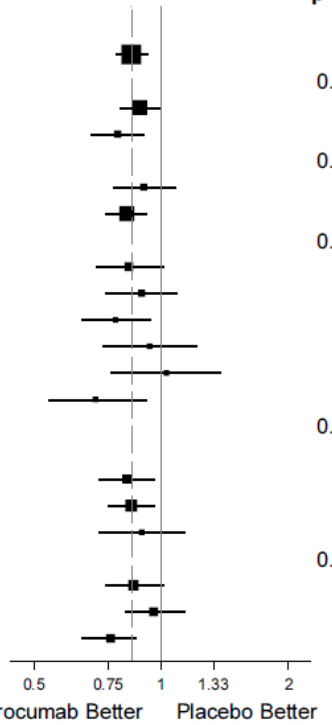
Other Efficacy Endpoints

Endpoint n (%)	Alirocumab (N=9462)	Placebo (N=9462)	HR (95% CI)	Log-rank P-value
Ischemia-driven coronary revascularization	731 (7.7)	828 (8.8)	0.88 (0.79, 0.97)	0.009
Hospitalization for CHF	176 (1.9)	179 (1.9)	0.98 (0.79, 1.20)	0.84

Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
Overall	18924	9.5	11.1	0.85 (0.78, 0.93)	
Age					0.19
< 65 Yr	13840	8.5	9.5	0.89 (0.80, 0.99)	
≥ 65 Yr	5084	12.4	15.5	0.79 (0.68, 0.91)	
Sex					0.35
Female	4762	10.7	11.8	0.91 (0.77, 1.08)	
Male	14162	9.2	10.9	0.83 (0.74, 0.92)	
Region					0.40
Eastern Europe	5437	7.9	9.3	0.84 (0.70, 1.01)	
Western Europe	4175	9.1	10.0	0.90 (0.74, 1.09)	
North America	2871	13.7	17.1	0.78 (0.65, 0.94)	
South America	2588	9.1	9.7	0.94 (0.73, 1.21)	
Asia	2293	7.7	7.6	1.03 (0.76, 1.38)	
Rest of World	1560	12.2	16.7	0.70 (0.54, 0.92)	
Time from Index Event to Randomization					0.85
<2 Months	6178	10.3	12.3	0.83 (0.71, 0.96)	
2 - <6 Months	9518	9.6	11.1	0.85 (0.75, 0.96)	
≥6 Months	3228	8.0	8.7	0.90 (0.71, 1.14)	
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



*P-values for interaction

Primary Efficacy in Main Prespecified Subgroups

Subgroup	Patients	Incidence (%) Alirocumab	Incidence (%) Placebo	HR (95% CI)	p-value*
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
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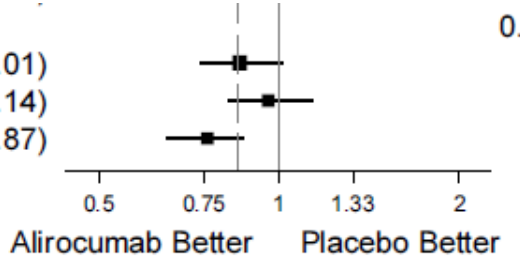

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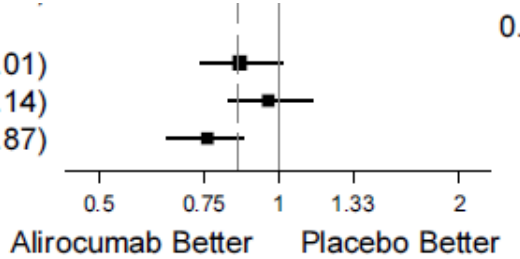

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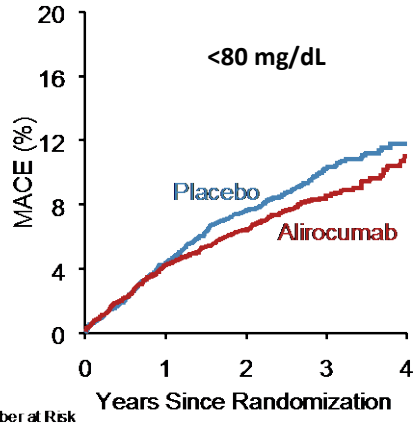

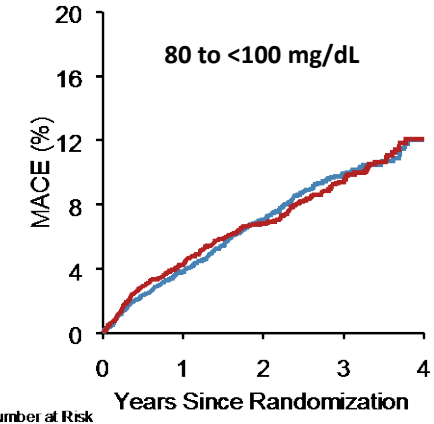

Number at Risk					
Placebo	3583	3347	3122	1290	256
Alirocumab	3581	3365	3183	1327	233

Number at Risk					
Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

ODYSSEY OUTCOMES

Primary Efficacy in Main Prespecified Subgroups

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<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
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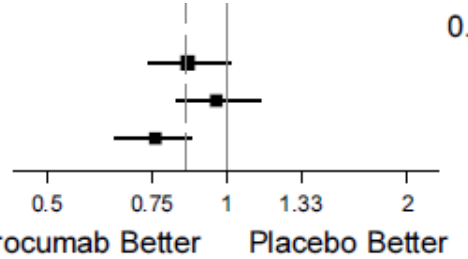

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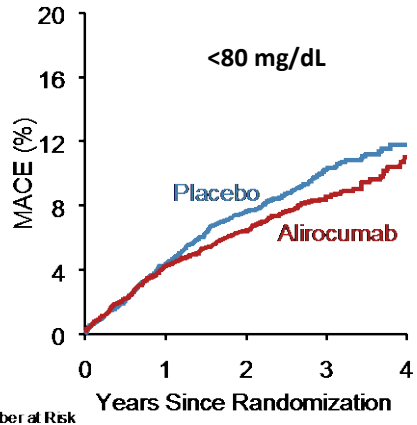

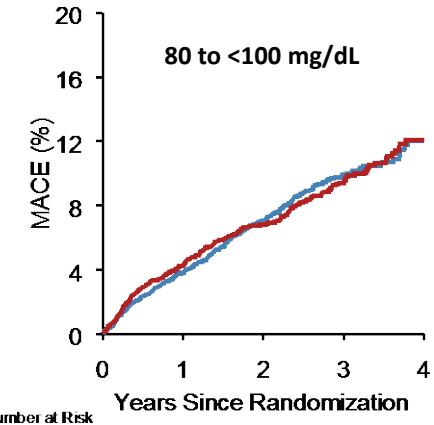

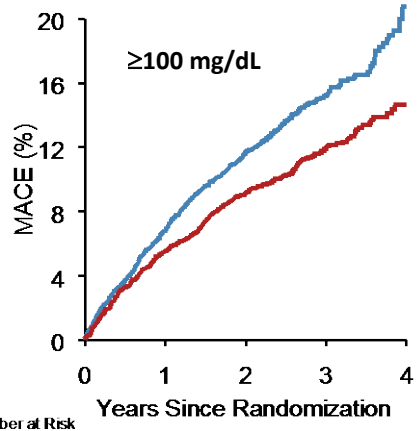

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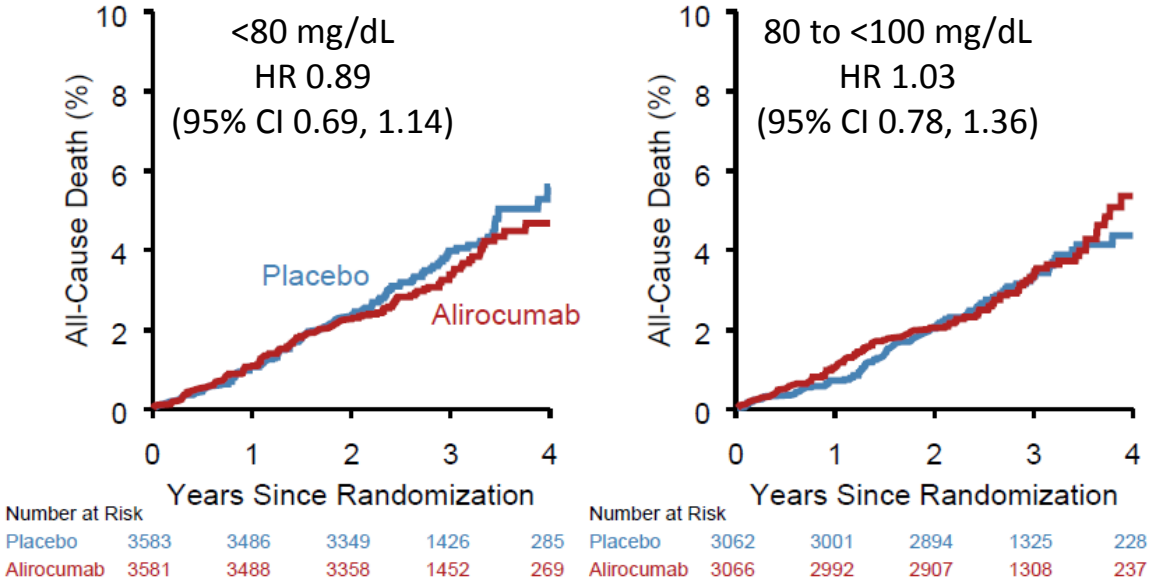
Number at Risk					
Placebo	3062	2889	2708	1195	195
Alirocumab	3066	2880	2732	1194	213

Number at Risk					
Placebo	2815	2568	2371	986	178
Alirocumab	2814	2602	2431	1053	207

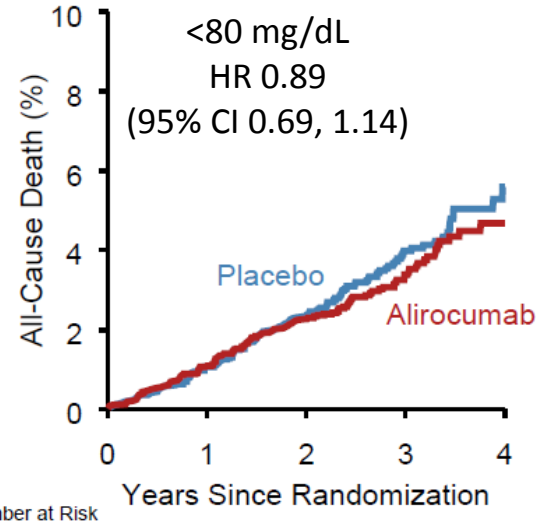
ODYSSEY OUTCOMES

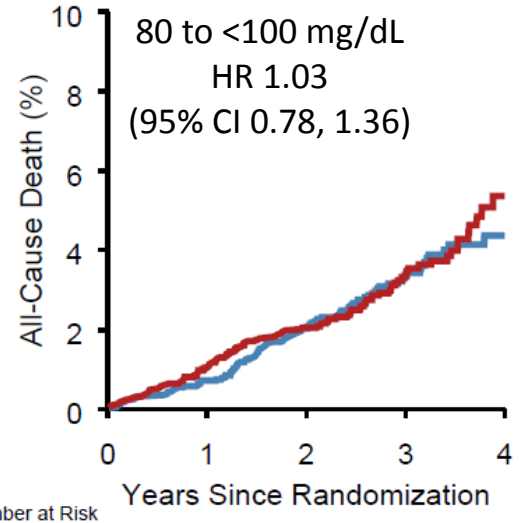
Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

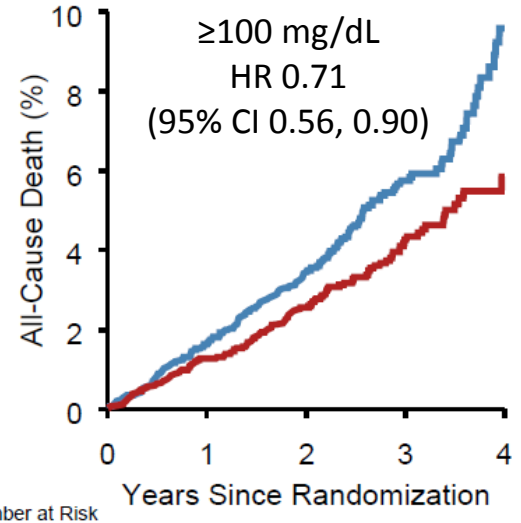


Post Hoc Analysis: All-Cause Death by Baseline LDL-C Subgroups

ARR* 1.7% $P_{interaction}$=0.12







Number at Risk					
Placebo	3583	3486	3349	1426	285
Alirocumab	3581	3488	3358	1452	269

Number at Risk					
Placebo	3062	3001	2894	1325	228
Alirocumab	3066	2992	2907	1308	237

Number at Risk					
Placebo	2815	2732	2645	1147	224
Alirocumab	2814	2739	2655	1186	240

*Based on cumulative incidence

ODYSSEY OUTCOMES

Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

Safety (1)

Treatment-emergent adverse events, n (%)	Alirocumab (N=9451)	Placebo (N=9443)
Any	7165 (75.8)	7282 (77.1)
Serious	2202 (23.3)	2350 (24.9)

Laboratory value	Alirocumab	Placebo
ALT >3 × ULN, n/N (%)	212/9369 (2.3)	228/9341 (2.4)
Creatine kinase >10 × ULN, n/N (%)	46/9369 (0.5)	48/9338 (0.5)

Safety (2)

Event	Alirocumab (N=9451)	Placebo (N=9443)
Diabetes worsening or diabetic complications: *pts w/DM at baseline*, n/N (%)	506/2688 (18.8)	583/2747 (21.2)
New onset diabetes; *pts w/o DM at baseline*, n/N (%)	648/6763 (9.6)	676/6696 (10.1)
General allergic reaction, n (%)	748 (7.9)	736 (7.8)
Hepatic disorder, n (%)	500 (5.3)	534 (5.7)
Local injection site reaction, n (%)*	360 (3.8)	203 (2.1)
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

Conclusions

Compared with placebo in patients with recent ACS, alirocumab 75 or 150 mg subcutaneous Q2W targeting LDL-C levels 25–50 mg/dL, and allowing levels as low as 15 mg/dL:

1. Reduced MACE, MI, and ischemic stroke
2. Was associated with a lower rate of all-cause death
3. Was safe and well-tolerated over the duration of the trial

Clinical Perspective

- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions

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- In this nearly 19,000-patient placebo-controlled trial, including many patients treated for ≥3 years, there was no safety signal with alirocumab other than injection site reactions
- Among patients with ACS and baseline LDL-C ≥100 mg/dL, alirocumab reduced MACE by 24% (ARR 3.4%) and all-cause death by 29% (ARR 1.7%) compared with placebo
  - ➢These are the patients who may benefit most from treatment

ARR, absolute risk reduction