Alirocumab Treatment Effect Did Not Differ Between Patients With and Without Low HDL-C or High Triglyceride Levels in Phase 3 trials

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Industry Relationships and Institutional Affiliations

Author	Disclosure
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Background and Aims

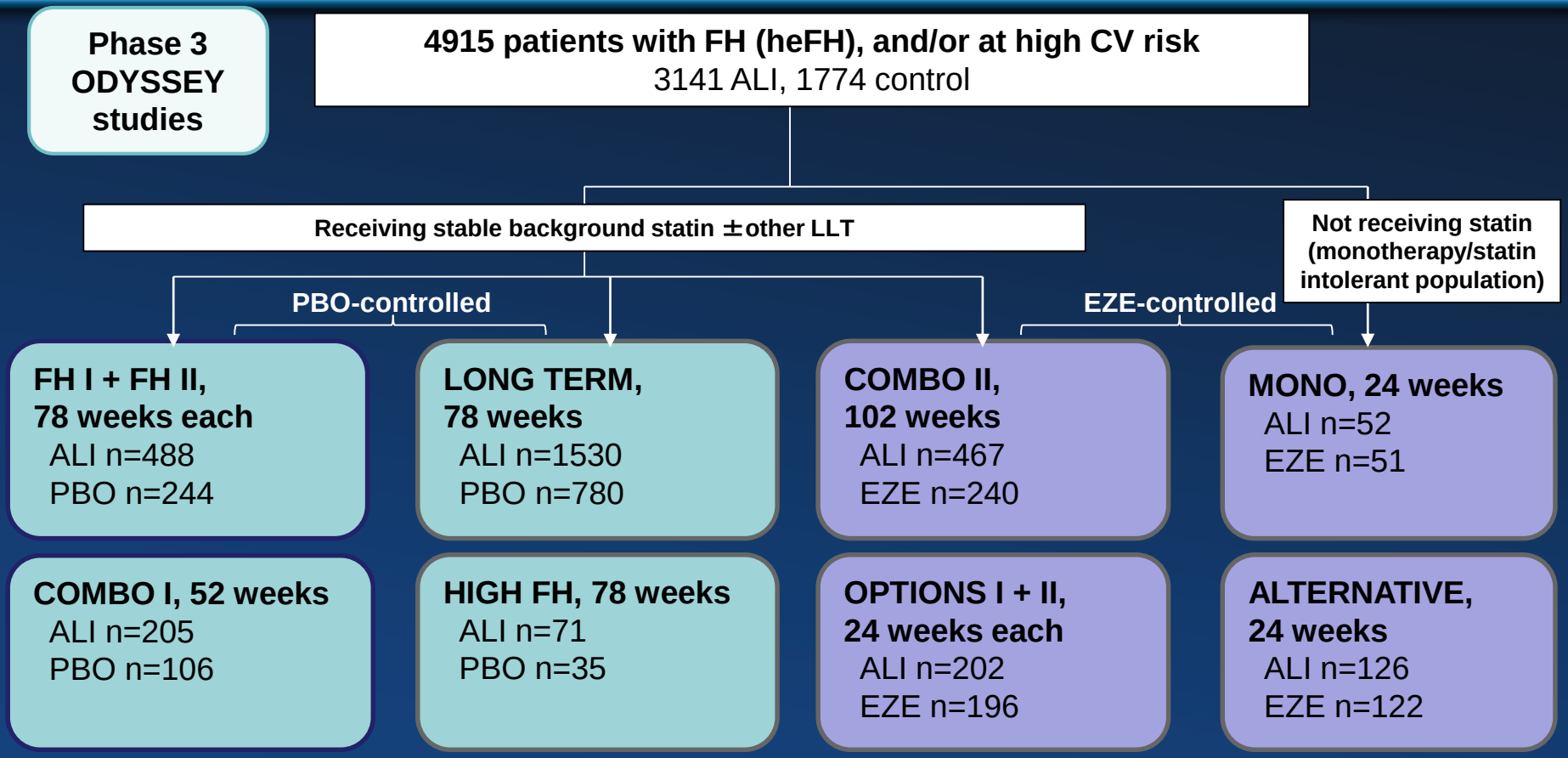
- High TG and low HDL-C levels are associated with increased risk of CVD[1,2]
- Patients with high TG/low HDL-C may have elevations in LDL particle number and non-LDL atherogenic lipoproteins for a given LDL-C level[3]
  - Apo B or non-HDL-C may be a better estimate of risk in such cases
- Alirocumab is a fully human monoclonal antibody to PCSK9 which has shown significant LDL-C reductions in Phase 2 and 3 trials[4-8]

The aim of this analysis of 10 Phase 3 trials was to determine potential treatment differences in alirocumab lipid- and lipoprotein-lowering efficacy and safety between patients with baseline TG levels < or ≥150 mg/dL (1.69 mmol/L) or baseline HDL-C levels < or ≥40 mg/dL (1.03 mmol/L)

TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9;.

1. Assmann G. et al. *Eur Heart J*. 1998;19(suppl M):M8–M14. 2. Gordon DJ et al. *Circulation*. 1989;79:8–15. 3. Bays HE et al. *J Clin Lipidol*. 2014;8, S1-S36; 4. Koren MJ et al. *Postgrad Med*. 2015;127:125–132; 5. Roth EM et al. *Int J Cardiol*. 2014;176:55–61; 6. Cannon CP et al. *Eur Heart J*. 2015; 36:1186-1194; 7. Robinson JG et al. *N Eng J Med*. 6;372:1489–1499; 8. Kereiakes DJ et al. *Am Heart J*. 2015 [Epub ahead of print].

Pooled Analysis of Ten Phase 3 Alirocumab Trials



Primary endpoint in each study: % change from baseline to Week 24 in LDL-C based on an ITT approach.
In LONG TERM and HIGH FH, ALI was dosed at 150 mg Q2W, whereas in COMBO I and II, FH I and II, OPTIONS I and II, MONO and ALTERNATIVE, the initial 75 mg Q2W dose regimen was increased to 150 mg Q2W at week 12 if Week 8 LDL-C was ≥70 mg/dL.

*Includes all lipid data throughout the duration of the study irrespective of adherence to the study treatment.
ALI, alirocumab; CV, cardiovascular; EZE, ezetimibe; FH, familial hypercholesterolemia; heFH, heterozygous familial hypercholesterolemia; ITT, intent-to-treat; LLT, lipid-lowering therapy; PBO, placebo.

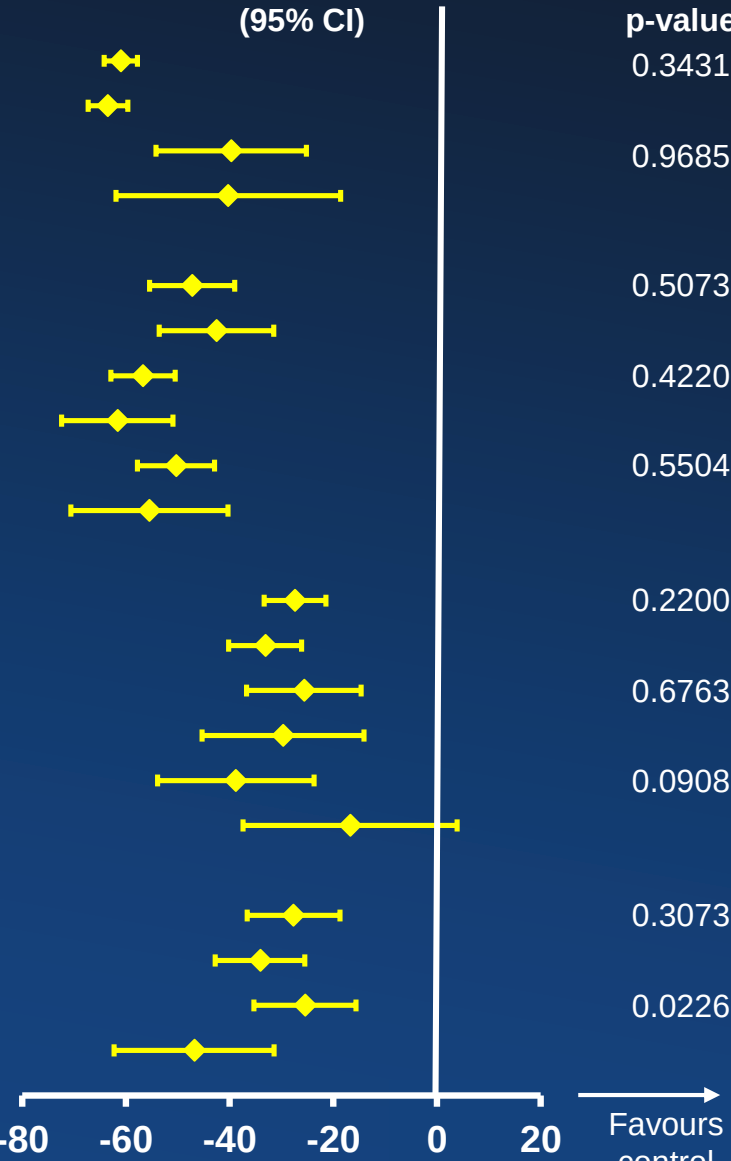
Baseline Characteristics by Baseline TG Levels (Pooled Randomized Population)

	Baseline TGs <150 mg/dL (1.69 mmol/L)		Baseline TGs ≥150 mg/dL (1.69 mmol/L)	
	Alirocumab n=1989	Control n=1103	Alirocumab n=1199	Control n=690
Age, years, mean (SD)	**59.4** (11.8)	**60.2** (11.3)	**59.8** (10.1)	**59.6** (10.1)
Males, % (n)	**62.2** (1237)	**60.5** (667)	**63.3** (759)	**62.6** (432)
Race, white, % (n)	**90.1** (1792)	**90.3** (996)	**91.1** (1092)	**90.1** (622)
BMI, kg/m^2, mean (SD)	**29.4** (5.7)	**29.5** (5.6)	**31.4** (5.6)	**31.4** (5.5)
Calculated LDL-C, mmol/L [mg/dL], mean (SD)	**3.20** (1.2) [123.5 (46.3)]	**3.21** (1.2) [123.8 (47.0)]	**3.36** (1.3) [129.8 (49.9)]	**3.37** (1.4) [130.3 (52.5)]
Non HDL-C, mmol/L [mg/dL], mean (SD)	**3.72** (1.2) [143.7 (47.0)]	**3.73** (1.2) [144.0 (47.4)]	**4.52** (1.4) [174.5 (53.6)]	**4.54** (1.5) [175.1 (59.1)]
Apo B, mg/dL, mean (SD)	**96.7** (26.3)	**96.6** (25.9)	**115.0** (31.0)	**114.4** (32.3)
HDL-C, mmol/L [mg/dL], mean (SD)	**1.36** (0.4) [52.7 (14.1)]	**1.37** (0.4) [53.0 (13.7)]	**1.15** (0.3) [44.5 (10.4)]	**1.15** (0.3) [44.6 (11.3)]
Fasting TGs, mmol/L [mg/dL], median (Q1:Q3)	**1.14** (0.9:1.4) [101.0 (79.6:123.9)]	**1.14** (0.9:1.4) [101.0 (79.6:123.0)]	**2.3** (1.9:2.8) [203.5 (171.7:251.3)]	**2.27** (2.0:2.9) [201.0 (171.0:249.0)]
Lp(a), mg/dL, median (Q1:Q3)	**25.3** (9.0:70.2)	**26.1** (9.0:70.0)	**21.9** (7.0:65.1)	**18.2** (6.0:55.0)

Apo, apolipoprotein; BMI, body mass index; Lp(a), lipoprotein (a); SD, standard deviation.

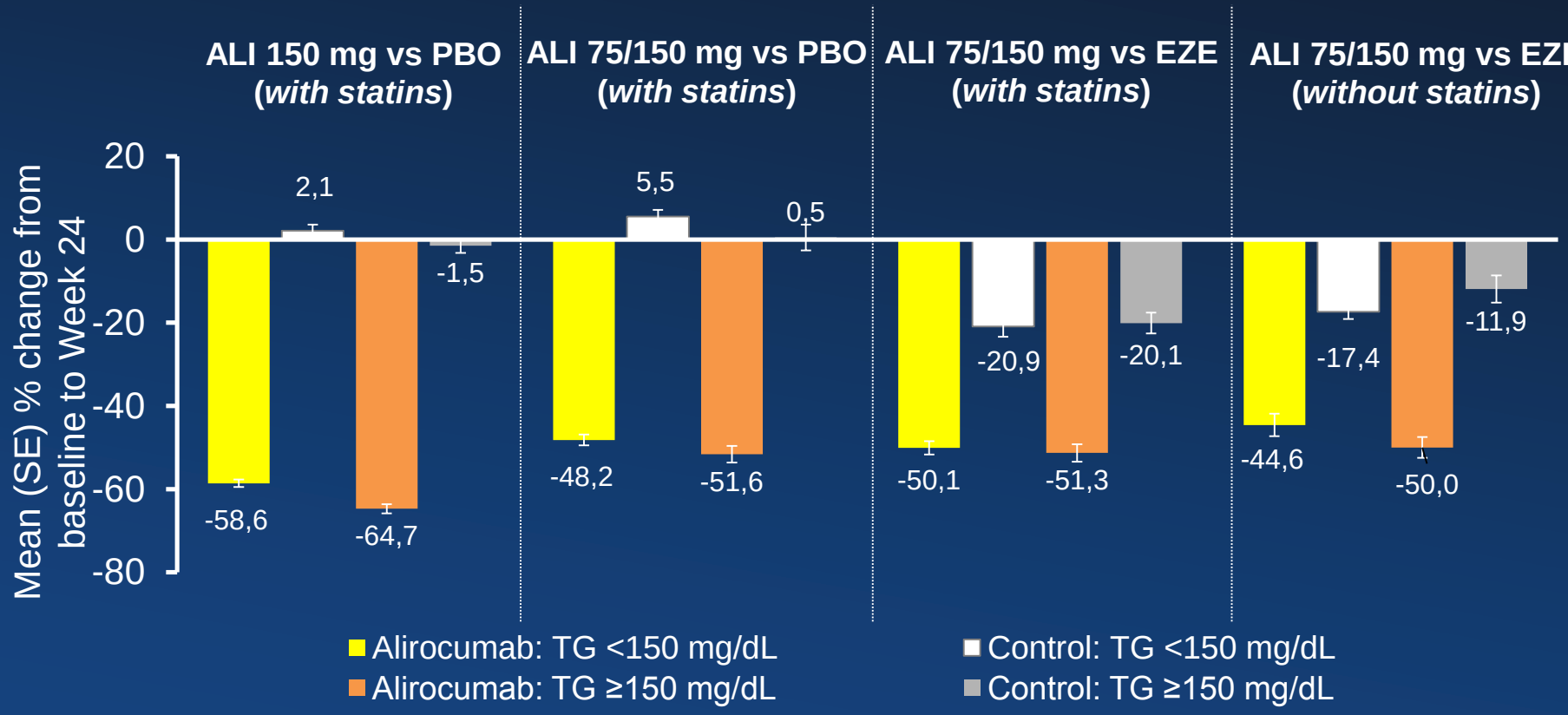
LDL-C Reduction with Alirocumab vs Control was Generally Consistent Across Phase 3 Trials Regardless of Baseline TG

	Study	Baseline TG	N	% change from baseline* Control	% change from baseline* Alirocumab	Interaction p-value
ALI 150 vs PBO (+ statin)	Long Term	<150 mg/dL	1378	2.2 (1.3)	-58.8 (0.9)	0.3431
		≥150 mg/dL	931	-1.1 (1.6)	-64.5 (1.2)	
	High FH	<150 mg/dL	76	-3.3 (6.0)	-43.1 (4.1)	0.9685
		≥150 mg/dL	30	-13.1 (8.4)	-53.4 (6.9)	
ALI 75/150 vs PBO (+ statin)	COMBO I	<150 mg/dL	190	0.2 (3.3)	-46.9 (2.5)	0.5073
		≥150 mg/dL	120	-7.6 (4.7)	-50.1 (3.1)	
	FH I	<150 mg/dL	356	8.6 (2.6)	-48.1 (1.8)	0.4220
		≥150 mg/dL	129	10.7 (4.5)	-50.9 (3.1)	
	FH II	<150 mg/dL	194	2.9 (3.1)	-47.4 (2.2)	0.5504
		≥150 mg/dL	53	2.4 (6.4)	-53.1 (4.2)	
ALI 75/150 vs EZE (+ statin)	COMBO II	<150 mg/dL	409	-22.8 (2.5)	-50.2 (1.8)	0.2200
		≥150 mg/dL	298	-17.9 (2.9)	-51.0 (2.1)	
	OPTIONS I	<150 mg/dL	130	-24.1 (4.)	-49.8 (4.0)	0.6763
		≥150 mg/dL	70	-16.2 (5.7)	-45.9 (5.4)	
	OPTIONS II	<150 mg/dL	128	-7.4 (5.7)	-46.2 (5.1)	0.0908
		≥150 mg/dL	70	-17.5 (6.8)	-34.2 (8.0)	
ALI 75/150 vs EZE (no statin)	ALTERNATIVE	<150 mg/dL	119	-18.3 (3.0)	-46.0 (3.4)	0.3073
		≥150 mg/dL	129	-10.0 (3.3)	-44.2 (2.9)	
	MONO	<150 mg/dL	73	-16.4 (3.5)	-41.9 (3.5)	0.0226
		≥150 mg/dL	30	-13.3 (5.6)	-60.1 (5.4)	



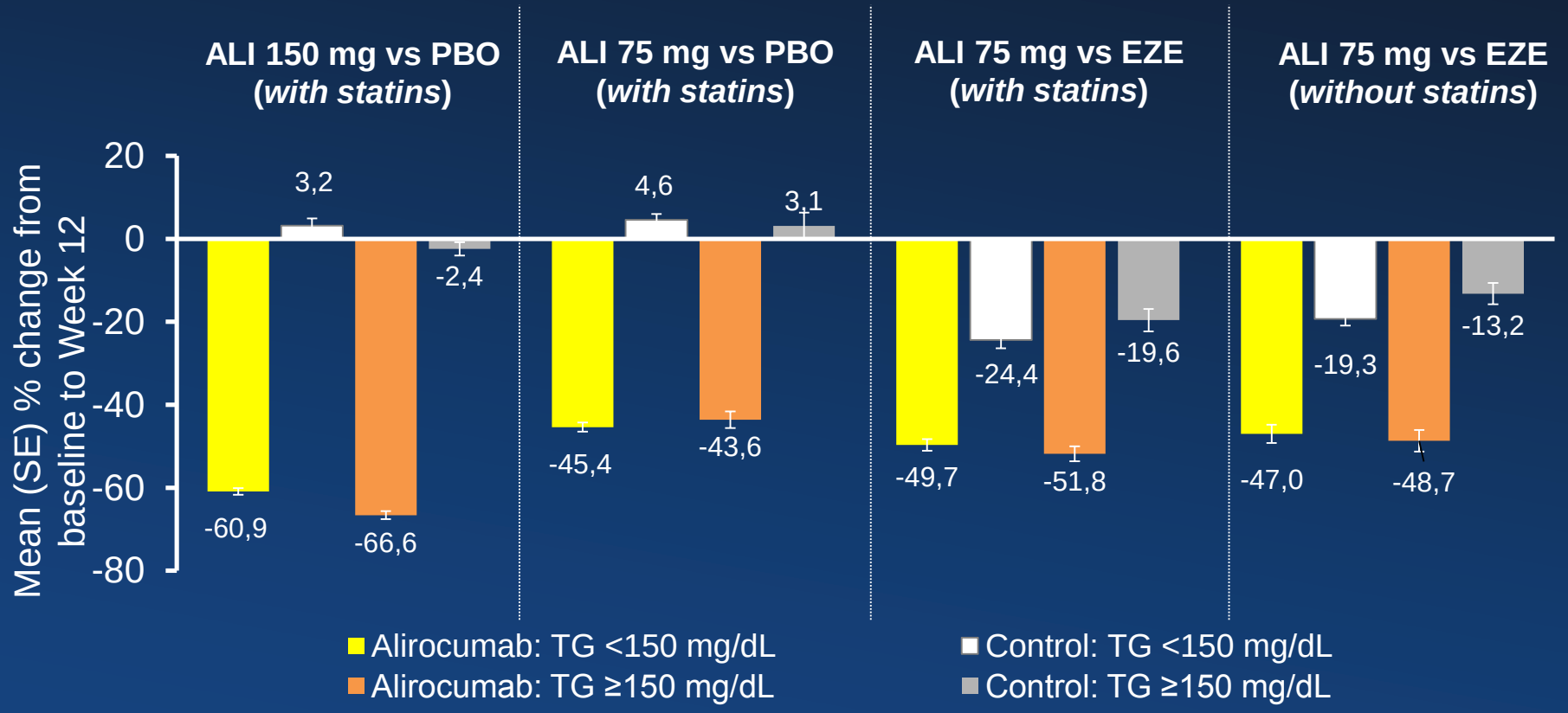
*Least square mean (SE). ITT analysis.
ALI, alirocumab, EZE, ezetimibe, PBO, placebo.

Percentage Change from Baseline in Calculated LDL-C Level at Week 24 Subgroup Analysis According to TG baseline



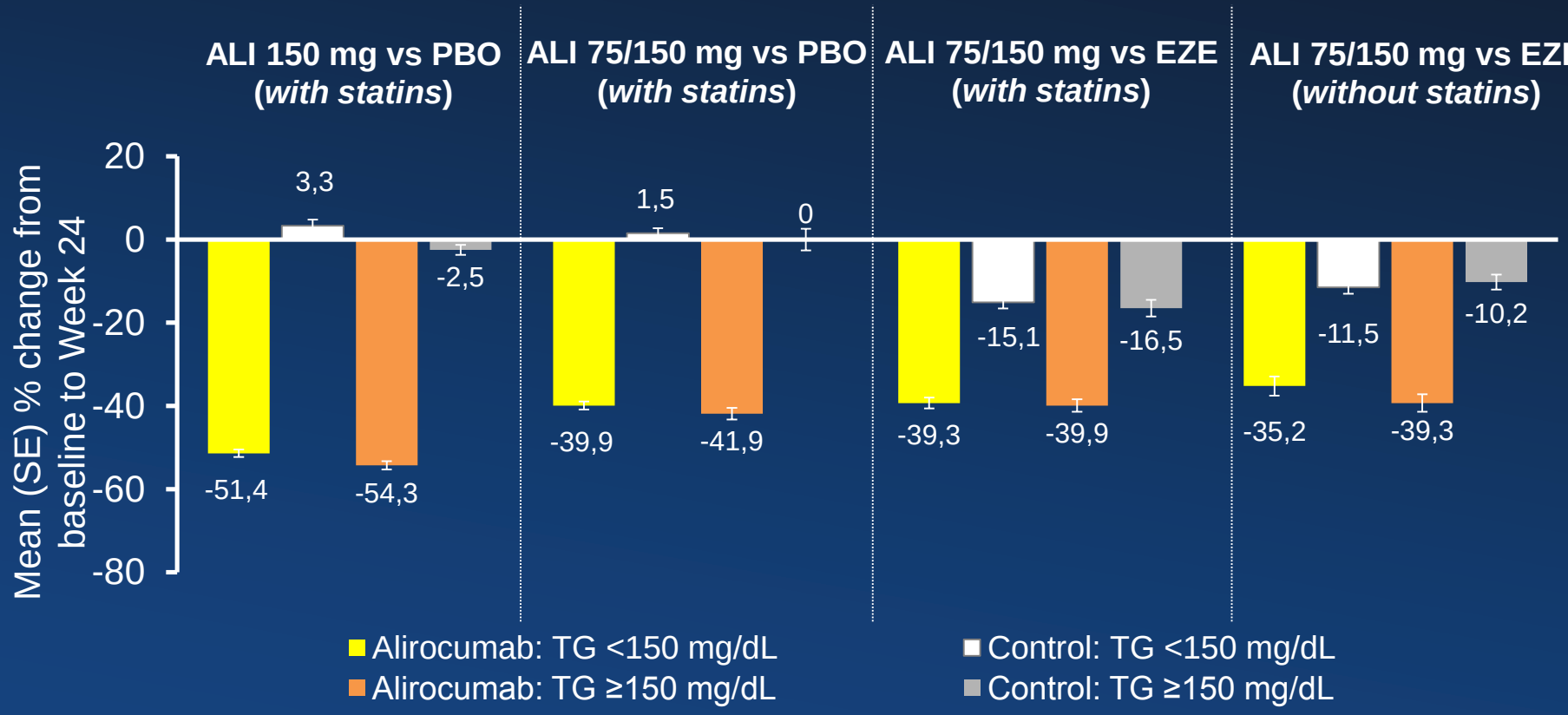
All *P*<0.0001 versus placebo

Percentage Change from Baseline in Calculated LDL-C Level at Week 12 Subgroup Analysis According to TG baseline



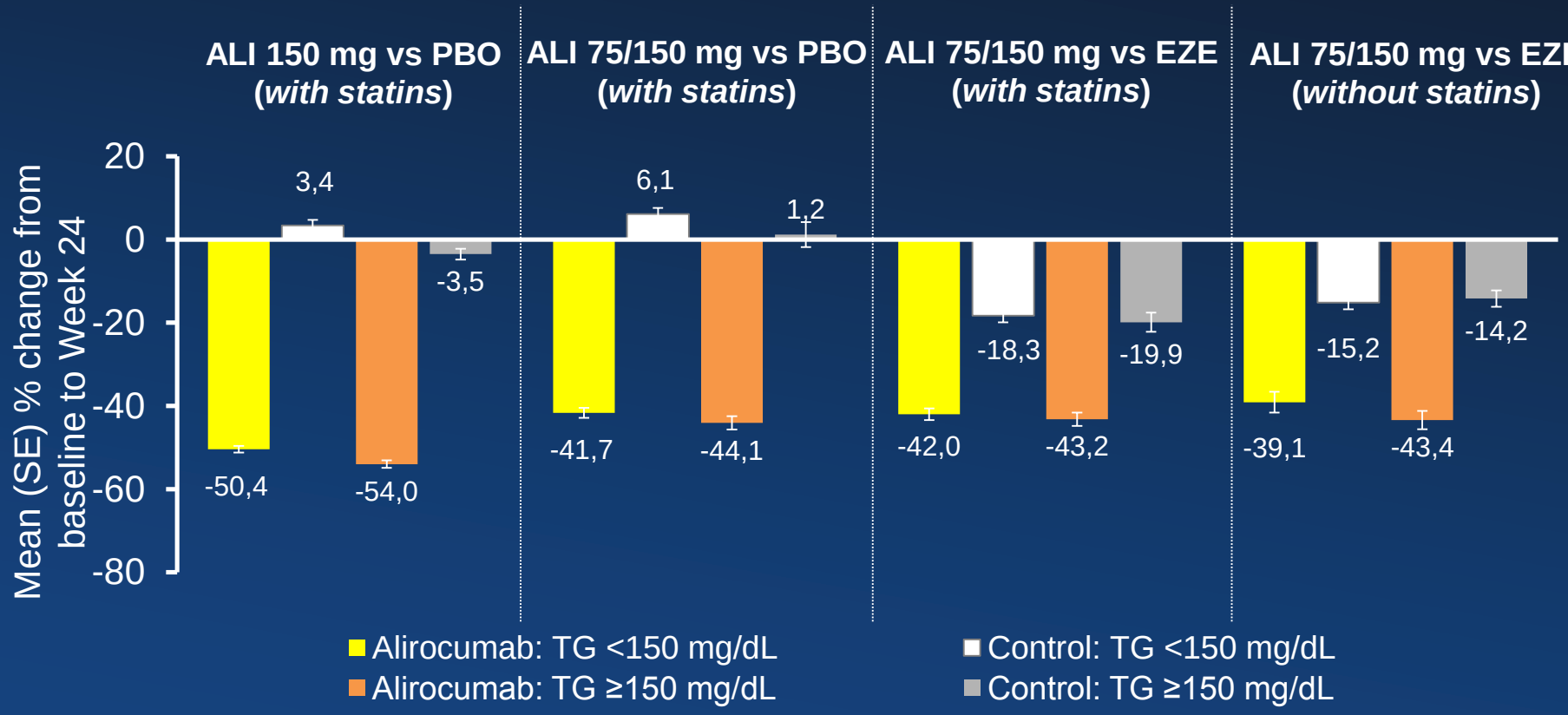
All *P*<0.0001 versus placebo

Percentage Change from Baseline in ApoB Level at Week 24 Subgroup Analysis According to TG baseline



All *P*<0.0001 versus placebo

Percentage Change from Baseline in Non-HDL-C Level at Week 24 Subgroup Analysis According to TG baseline



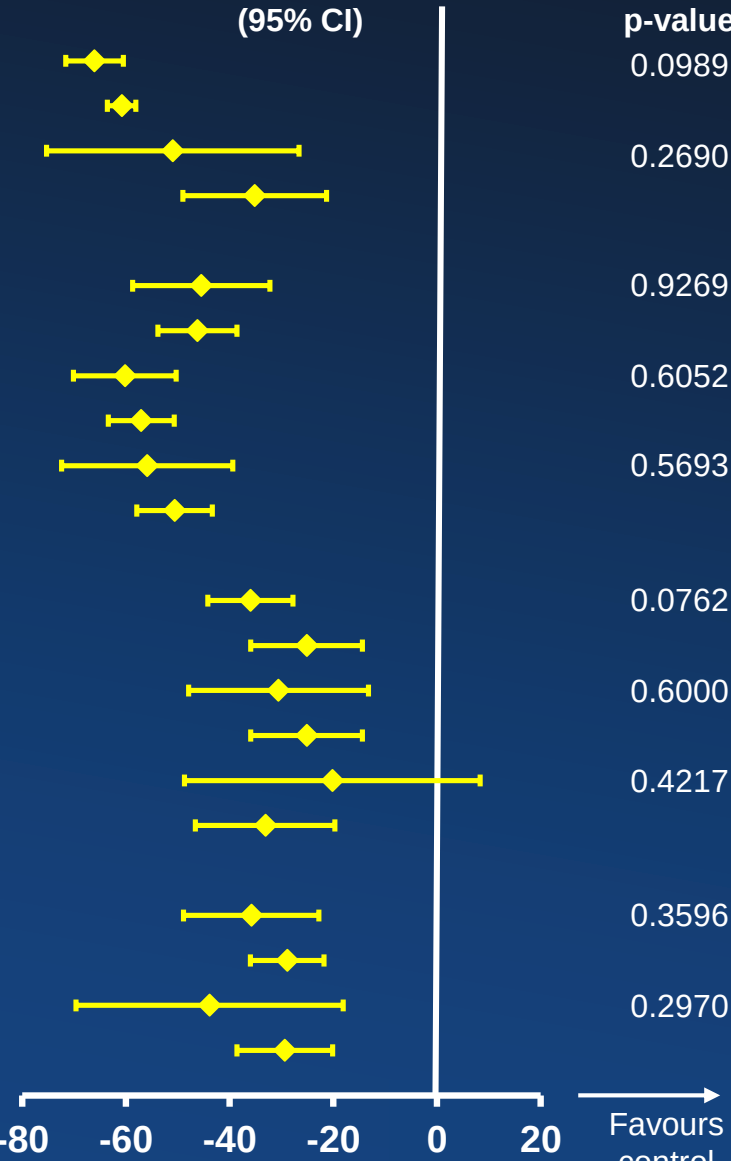
All *P*<0.0001 versus placebo

Baseline Characteristics, by Baseline HDL-C (Pooled Randomized Population)

	Baseline HDL-C <40 mg/dL (1.03 mmol/L)		Baseline HDL-C ≥40 mg/dL (1.03 mmol/L)	
	Alirocumab n=753	Control n=393	Alirocumab n=2435	Control n=1402
Age, years, mean (SD)	**57.5** (12.0)	**57.6** (11.9)	**60.2** (10.8)	**60.6** (10.5)
Males, % (n)	**82.2** (619)	**77.9** (306)	**56.6** (1377)	**56.6** (794)
Race, white, % (n)	**88.8** (669)	**88.5** (348)	**91.0** (2215)	**90.7** (1272)
BMI, kg/m^2, mean (SD)	**31.4** (5.4)	**31.5** (5.3)	**29.7** (5.8)	**29.9** (5.7)
Calculated LDL-C, mmol/L [mg/dL], mean (SD)	**3.17** (1.2) [122.5 (47.9)]	**3.20** (1.2) [123.6 (46.4)]	**3.28** (1.3) [126.9 (47.7)]	**3.29** (1.3) [127.1 (50.0)]
Apo B, mg/dL, mean (SD)	**107.2** (31.2)	**107.8** (30.1)	**102.5** (28.9)	**102.3** (29.7)
Non HDL-C, [mg/dL], mean (SD)	**4.13** (1.4) 159.7 (54.3)	**4.15** (1.3) 160.6 (52.1)	**3.99** (1.3) 153.9 (50.9)	**4.00** (1.4) 154.6 (54.9)
HDL-C, mmol/L [mg/dL], mean (SD)	**0.90** (0.1) [34.8 (3.9)]	**0.89** (0.1) [34.3 (4.1)]	**1.40** (0.3) [54.2 (11.9)]	**1.40** (0.3) [54.1 (11.9)]
Fasting TGs, mmol/L [mg/dL], median (Q1:Q3)	**1.82** (0.4:2.7) 161.1 (120:235)	**1.9** (1.3:2.6) 169.0 (119:230)	**1.35** (1.0:1.9) 119.5 (87.6:167.0)	**1.37** (1.0:1.9) 121.2 (89.0:166)
Lp(a), mg/dL, median (Q1:Q3)	**23.0** (8.0:62.7)	**19.3** (7.0:52.0)	**25.0** (8.0:71.0)	**24.0** (7.4:68.1)

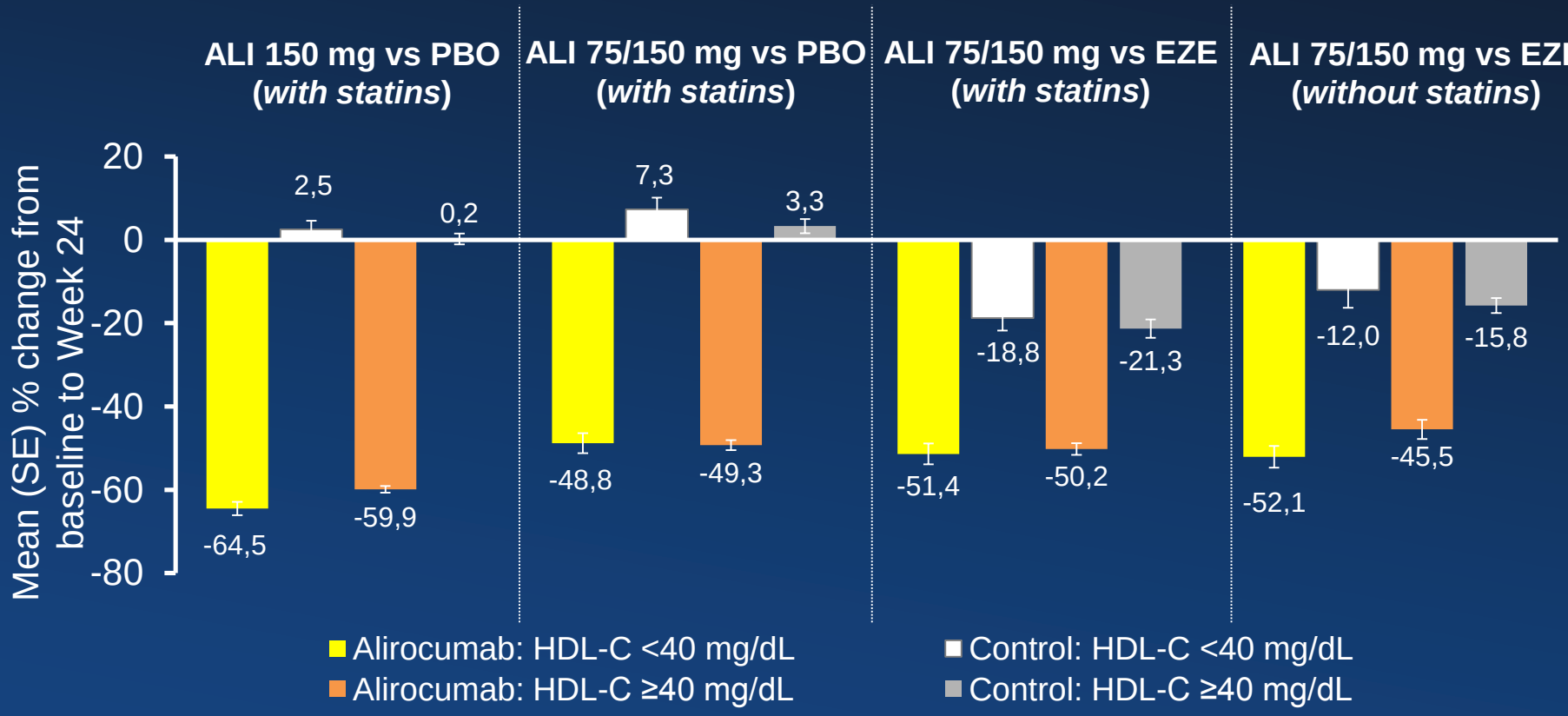
LDL-C Reduction with Alirocumab vs Control was Generally Consistent Across Phase 3 Trials Regardless of Baseline HDL-C

	Study	Baseline HDL-C	N	% change from baseline* Control	% change from baseline* Alirocumab	Interaction p-value
ALI 150 vs PBO (+ statin)	Long Term	<40 mg/dL	457	0.5 (2.3)	-65.5 (1.6)	0.0989
		≥40 mg/dL	1853	0.9 (1.1)	-59.9 (0.8)	
	High FH	<40 mg/dL	26	4.6 (9.8)	-46.3 (7.2)	0.2690
		≥40 mg/dL	80	-10.4 (5.7)	-45.5 (4.0)	
ALI 75/150 vs PBO (+ statin)	COMBO I	<40 mg/dL	85	-1.7 (5.6)	-47.2 (3.7)	0.9269
		≥40 mg/dL	226	-2.4 (3.1)	-48.6 (2.3)	
	FH I	<40 mg/dL	138	10.7 (4.0)	-49.4 (3.1)	0.6052
		≥40 mg/dL	347	8.5 (2.7)	-48.6 (1.9)	
	FH II	<40 mg/dL	44	8.6 (7.0)	-47.2 (4.6)	0.5693
		≥40 mg/dL	203	1.7 (3.0)	-49.0 (2.2)	
ALI 75/150 vs EZE (+ statin)	COMBO II	<40 mg/dL	218	-16.1 (3.4)	-52.1 (2.4)	0.0762
		≥40 mg/dL	489	-22.8 (2.3)	-49.9 (1.6)	
	OPTIONS I	<40 mg/dL	57	-22.3 (6.8)	-52.9 (5.6)	0.6000
		≥40 mg/dL	143	-21.1 (3.7)	-46.2 (3.9)	
	OPTIONS II	<40 mg/dL	37	-18.6 (11.0)	-38.8 (9.4)	0.4217
		≥40 mg/dL	161	-10.5 (4.8)	-43.6 (4.9)	
ALI 75/150 vs EZE (no statin)	ALTERNATIVE	<40 mg/dL	59	-10.5 (5.2)	-46.3 (4.2)	0.3596
		≥40 mg/dL	189	-15.5 (2.5)	-44.4 (2.6)	
	MONO	<40 mg/dL	13	-11.6 (10.7)-	55.4 (7.2)	0.2970
		≥40 mg/dL	90	-16.0 (3.2)	-45.4 (3.3)	



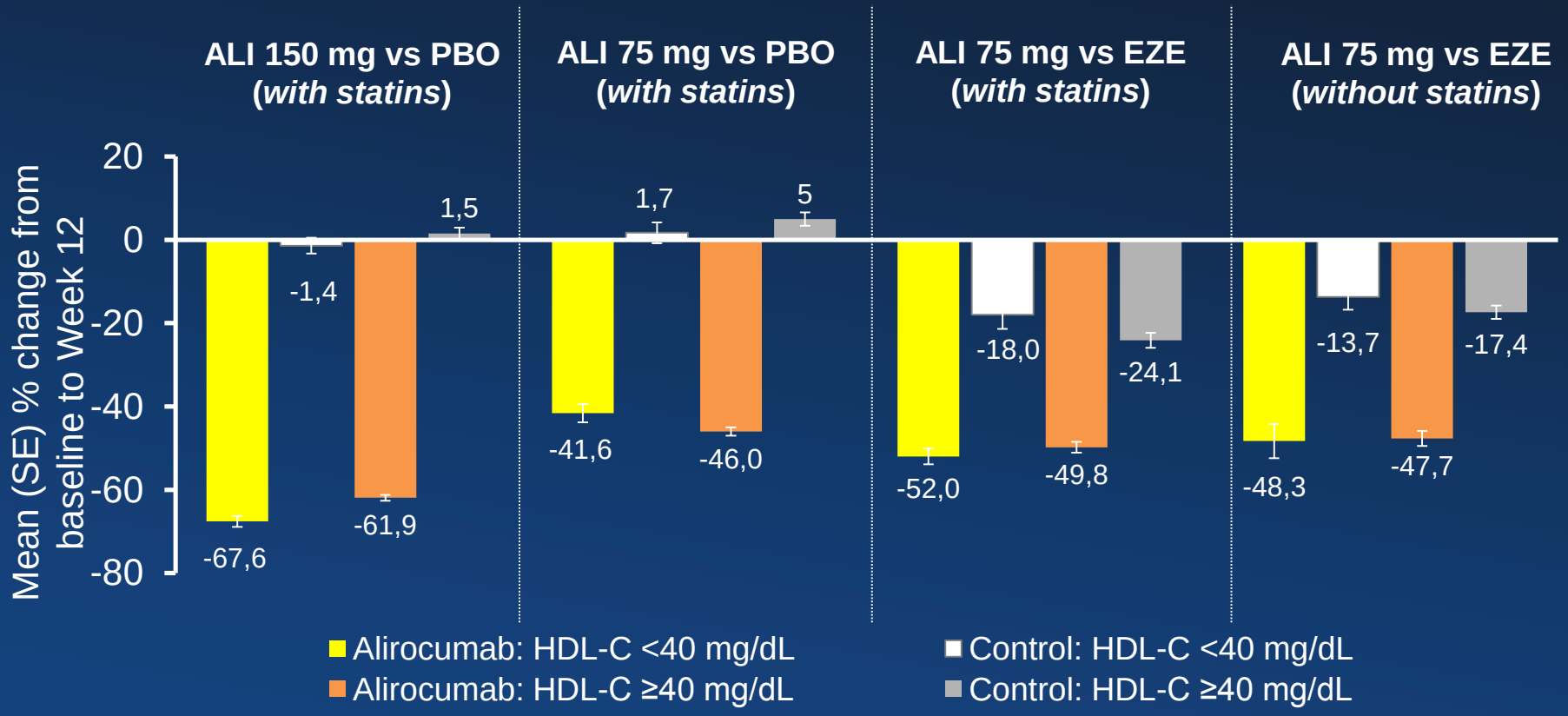
*Least square mean (SE). ITT analysis.
ALI, alirocumab, EZE, ezetimibe, PBO, placebo.

Percentage Change from Baseline in Calculated LDL-C Level at Week 24 Subgroup Analysis According to HDL-C baseline



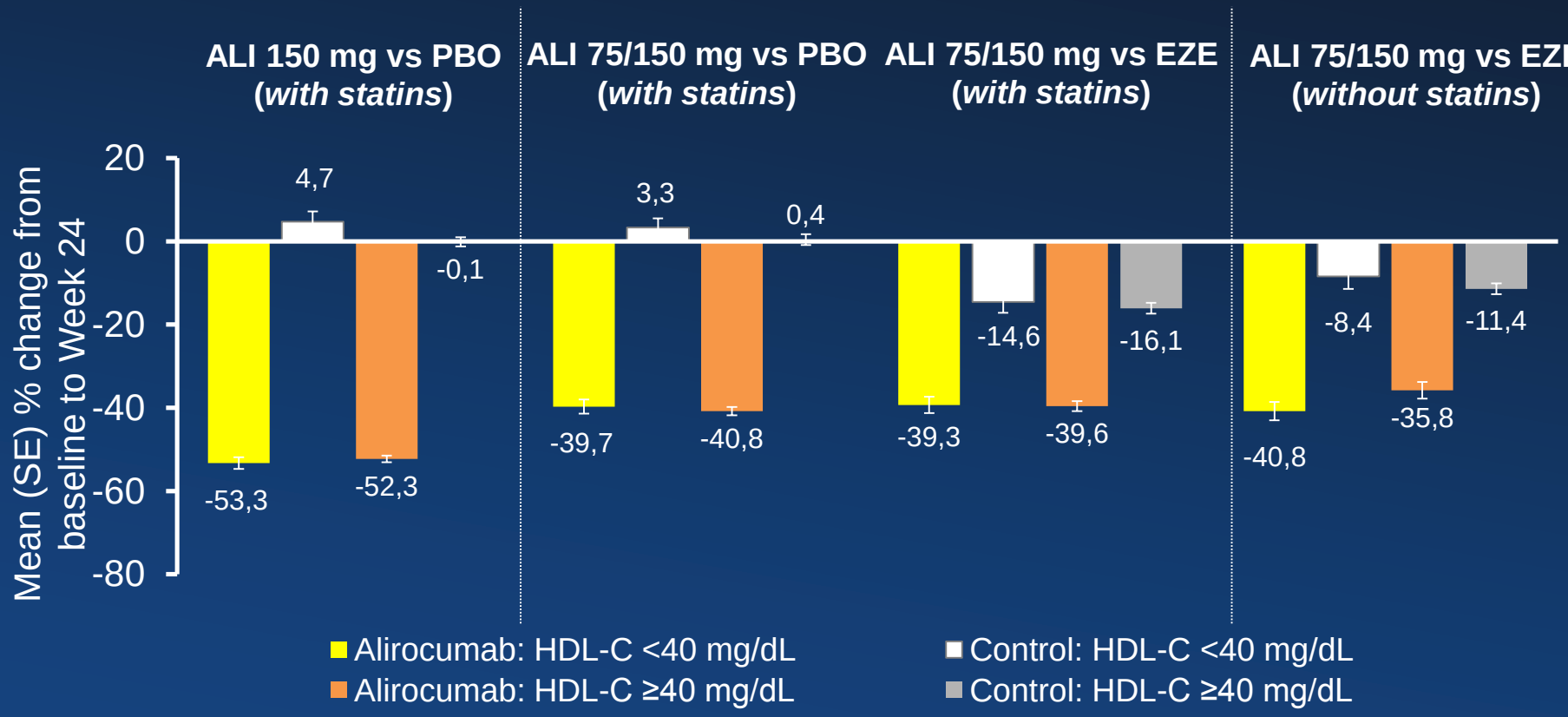
All *P*<0.0001 versus placebo

Percentage Change from Baseline in Calculated LDL-C Level at Week 12 Subgroup Analysis According to HDL-C baseline



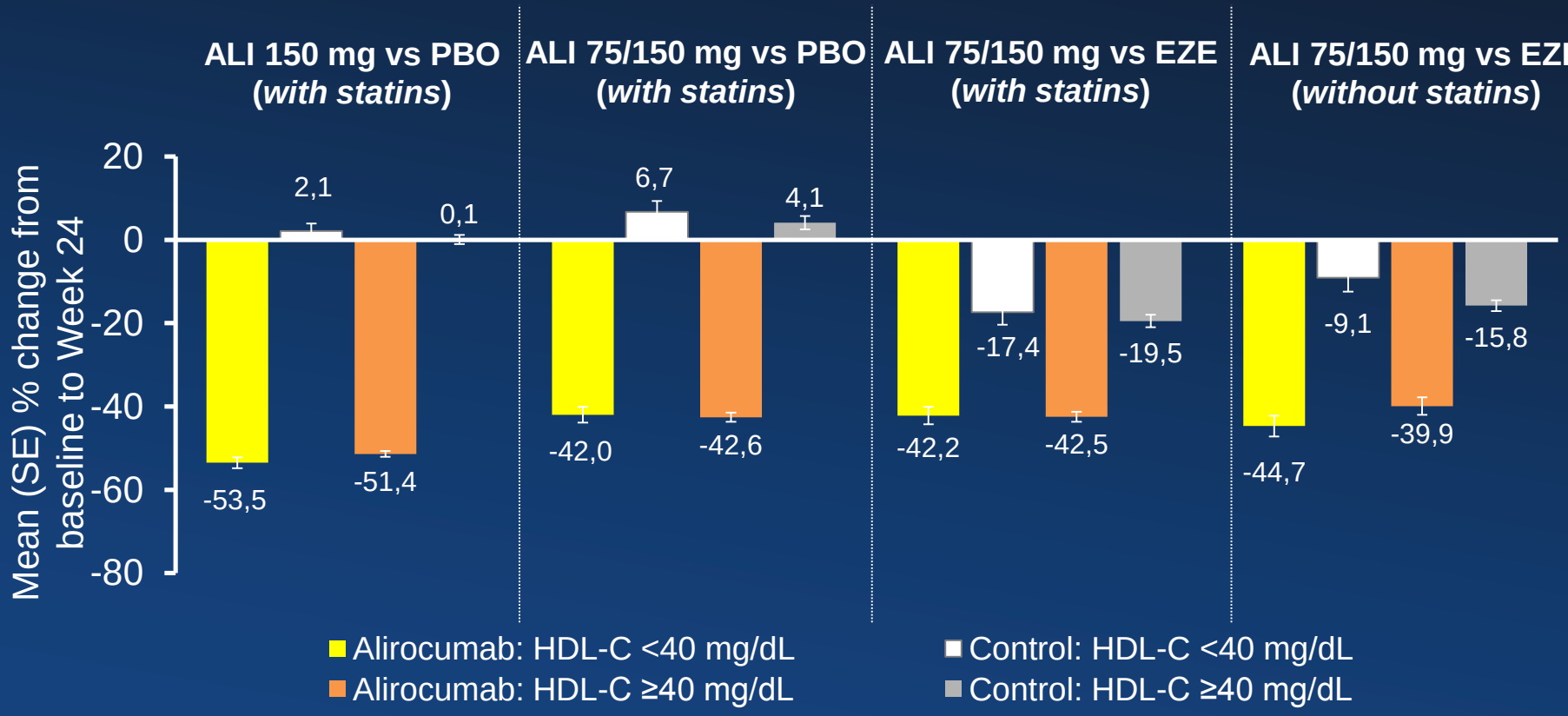
All *P*<0.0001 versus placebo

Percentage Change from Baseline in ApoB Level at Week 24 Subgroup Analysis According to HDL-C baseline



All *P*<0.0001 versus placebo

Percentage Change from Baseline in Non-HDL-C Level at Week 24 Subgroup Analysis According to HDL-C baseline



All *P*<0.0001 versus placebo

Safety Analysis (Pool of 4x Phase 2 + 10x Phase 3 trials*; safety population)

n (%) of patients	Ezetimibe-controlled pool (N=1482; 28%)		Placebo-controlled pool (N=3752; 72%)	
	ALI (n=864)†	EZE (n=618)	ALI (n=2476)†	PBO (n=1276)
TEAEs	607 (70.3)	421 (68.1)	1876 (75.8)	975 (76.4)
Treatment-emergent SAEs	113 (13.1)	69 (11.2)	340 (13.7)	182 (14.3)
TEAEs leading to death	2 (0.2)	7 (1.1)	13 (0.5)	11 (0.9)
TEAEs leading to discontinuation	76 (8.8)	60 (9.7)	131 (5.3)	65 (5.1)
Safety terms of interest				
Adjudicated CV events‡	27 (3.1)	12 (1.9)	83 (3.6)‖	41 (3.5)‖
Injection site reactions (HLT)	26 (3.0)	13 (2.1)	179 (7.2)	65 (5.1)
General allergic TEAE (CMQ)	59 (6.8)	33 (5.3)	213 (8.6)	99 (7.8)
Pruritus (PT)	7 (0.8)	3 (0.5)	28 (1.1)	5 (0.4)
General allergic serious TEAE (CMQ)	1 (0.1)	2 (0.3)	9 (0.4)	5 (0.4)
Neurocognitive disorders (CMQ)	8 (0.9)	6 (1.0)	21 (0.8)	9 (0.7)
ALT >3 x ULN (PCSA)	9/850 (1.1)	1/612 (0.2)	41/2455 (1.7)	18/1266 (1.4)

*Placebo-controlled studies: phase 3 (LTS11717, FH I, FH II, HIGH FH, COMBO I), phase 2 (DFI11565, DFI11566, CL-1003, DFI12361) Ezetimibe-controlled studies: phase 3 (COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE). Includes all data collected to last patient visit at 52 wks for COMBO, FH, HIGH FH and LONG TERM studies.

†Safety data pool includes alirocumab 75 mg Q2W and alirocumab 150 mg Q2W doses only

‡Includes CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalization, Congestive heart failure requiring hospitalization, Ischemia driven coronary revascularization procedure.

‖ Calculated using N values of 2318 for alirocumab and 1174 for placebo (excludes phase 2).

CMQ, Custom MedDRA Query; HLT, High-Level Term, PCSA, Potentially Clinically Significant Abnormalities; PT, preferred term.

Pooled Safety Data by Baseline TG from Safety Population Included in the Current Analysis

N (%) of patients	TG <150 mg/dL ALI n=1984	TG ≥150 mg/dL ALI n=1198
TEAEs	1501 (75.7)	891 (74.4)
Treatment-emergent SAEs	285 (14.4)	166 (13.9)
TEAEs leading to death	12 (0.6)	3 (0.3)
TEAEs leading to discontinuation	112 (5.6)	91 (7.6)
Safety terms of interest		
Adjudicated CV events*	64 (3.2)	46 (3.8)
Injection site reactions (HLT)	132 (6.7)	57 (4.8)
General allergic TEAE (CMQ)	162 (8.2)	99 (8.3)
Pruritus (PT)	26 (1.3)	9 (0.8)
General allergic serious TEAE (CMQ)	7 (0.4)	3 (0.3)
Neurocognitive disorders (CMQ)	21 (1.1)	7 (0.6)
ALT >3 x ULN (PCSA)	23/1962 (1.2)	27/1186 (2.3)

*Includes CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization procedure.
Safety population: All randomized patients who received ≥1 full or partial dose of study drug.
ALT, alanine aminotransferase; CHD, coronary heart disease; CMQ, custom MedDRA query; HLT, high-level term; PCSA, potentially clinically significant abnormalities; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Pooled Safety Data by Baseline HDL-C from Safety Population Included in the Current Analysis

N (%) of patients	HDL-C <40 mg/dL ALI n=505	HDL-C ≥ mg/dL ALI n=2429
TEAEs	580 (77.0)	1812 (74.6)
Treatment-emergent SAEs	110 (14.6)	341 (14.0)
TEAEs leading to death	4 (0.5)	11 (0.5)
TEAEs leading to discontinuation	45 (6.0)	158 (6.5)
Safety terms of interest		
Adjudicated CV events*	30 (4.0)	80 (3.3)
Injection site reactions (HLT)	42 (5.6)	147 (6.1)
General allergic TEAE (CMQ)	52 (6.9)	209 (8.6)
Pruritus (PT)	6 (0.8)	29 (1.2)
General allergic serious TEAE (CMQ)	2 (0.3)	8 (0.3)
Neurocognitive disorders (CMQ)	3 (0.4)	25 (1.0)
ALT >3 x ULN (PCSA)	13/747 (1.7)	37/2401 (1.5)

*Includes CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia-driven coronary revascularization procedure.
Safety population: All randomized patients who received ≥1 full or partial dose of study drug.
ALT, alanine aminotransferase; CHD, coronary heart disease; CMQ, custom MedDRA query; HLT, high-level term; PCSA, potentially clinically significant abnormalities; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Summary

- In this large, pooled analysis of 4915 patients
  - Alirocumab consistently produced substantially lower LDL-C levels regardless of baseline TG or HDL-C
  - The rate of treatment-emergent adverse events was similar in alirocumab and control groups irrespective of baseline TG and HDL-C
- These findings hold potential for patients who are at high CVD risk due to high TG and/or low HDL-C levels

Q&A

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