ODYSSEY ALTERNATIVE: Efficacy and safety of alirocumab versus ezetimibe, in patients with statin intolerance defined by placebo run-in and statin rechallenge arm

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Statin Intolerance (SI): Limits Many Patients from Achieving LDL-C Goals

- SI: Inability to use statins for long-term reduction of lipids and/or CV risk because of significant symptoms and/or biomarker abnormalities that can be temporally attributed to the initiation or dose escalation of statins[1]
- ~10–25% patients in clinical practice report SI[2,3]
  - Cleveland Clinic
    - Myalgia was most common complaint
    - However, 63.2% patients with previous SI were able to tolerate daily statin therapy[4]

Large, well-controlled randomized trials of cholesterol-lowering drugs in statin intolerant patients are lacking[5]

1. Mancini GBJ et al. *Can J Cardiol*. 2013;29:1553–1568; 2. Bruckert E et al. *Cardiovasc Drugs Ther*. 2005;19:403–414.
3. Cohen JD et al. *J Clin Lipidol*. 2012;6:208–215. 4. Mampuya WM et al. *Am Heart J*. 2013;166:597–603.
5. Guyton JR et al. *J Clin Lipidol*. 2014;8:S72–S81.

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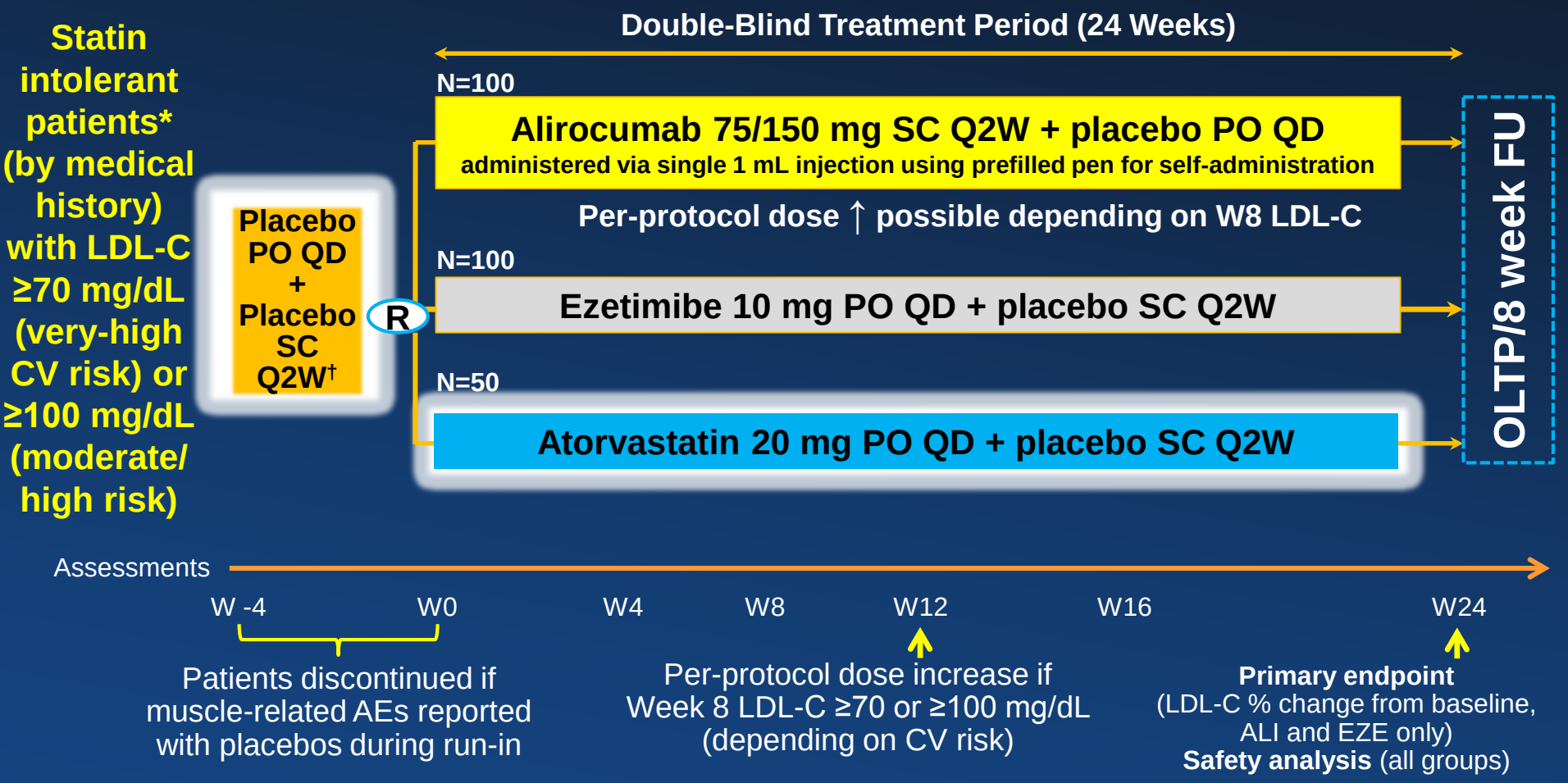
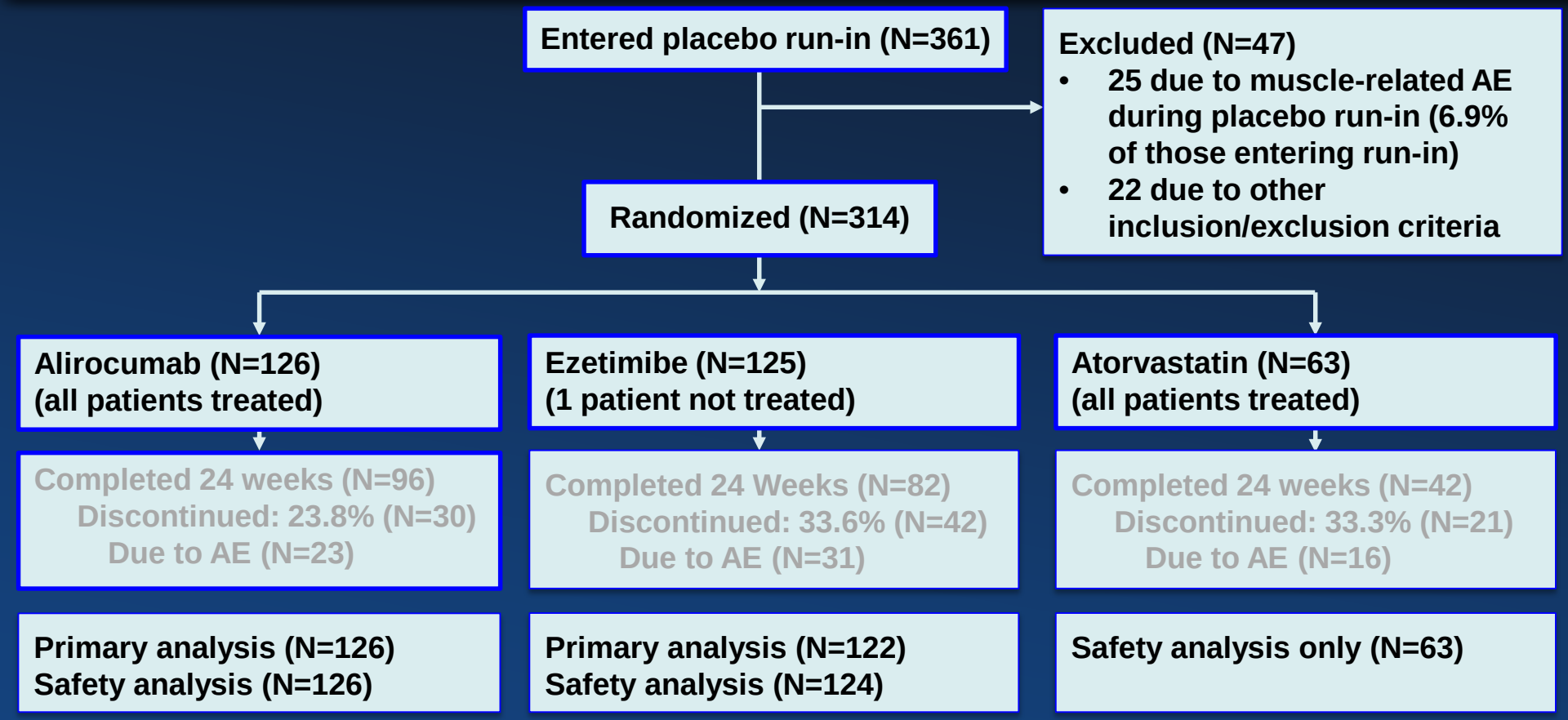
ODYSSEY ALTERNATIVE Study Design



*Unable to tolerate at least two different statins, including one at the lowest dose, due to muscle-related symptoms

†4-week single-blind placebo run-in follows 2-week washout of statins, ezetimibe and red yeast rice.
OLTP: Alirocumab open-label treatment period; W, Week.

Patient Disposition



Baseline Characteristics

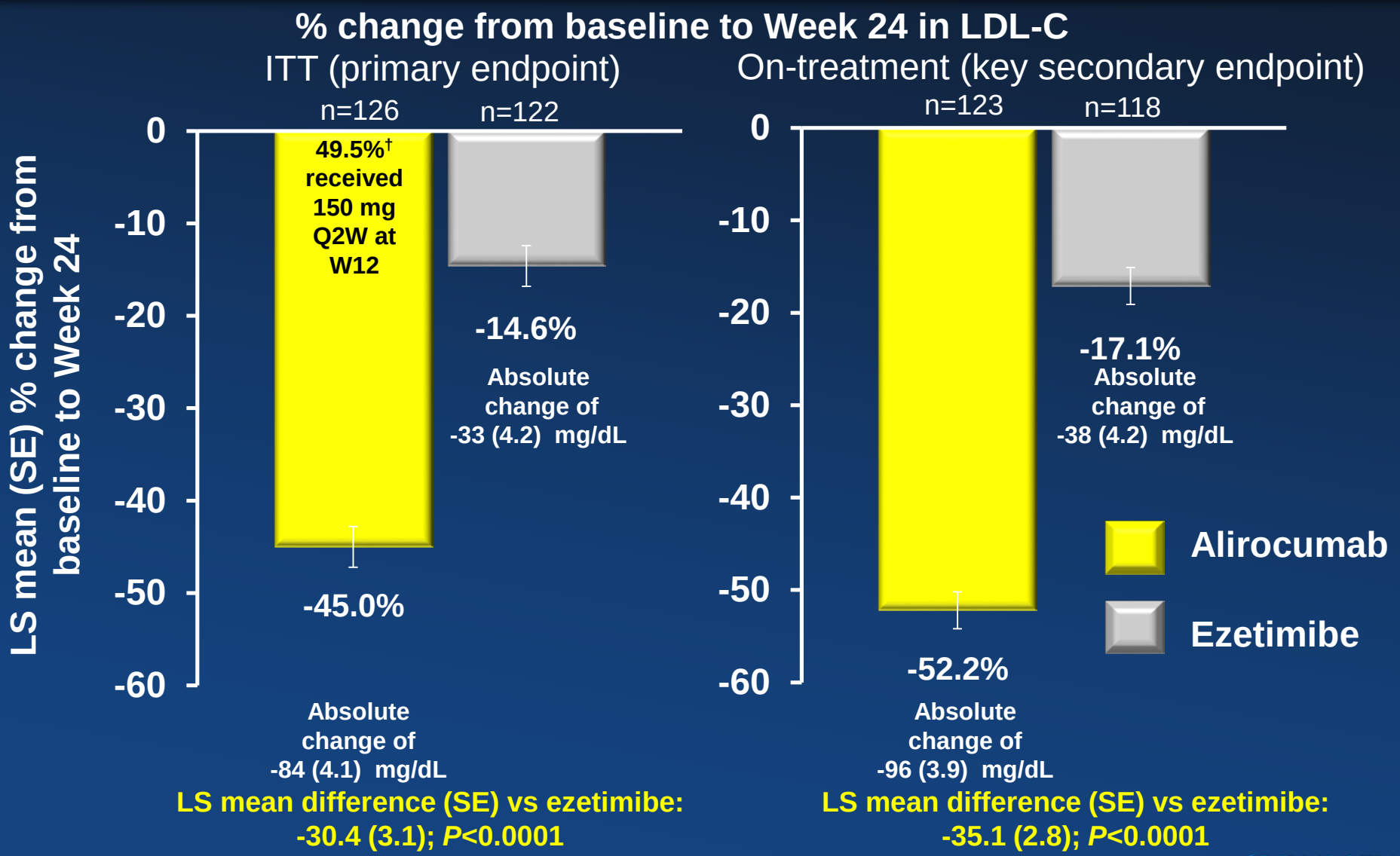
	Alirocumab (N=126)	Ezetimibe (N=125)	Atorvastatin (N=63)
Age, years, mean (SD)	**64.1** (9.0)	**62.8** (10.1)	**63.4** (8.9)
Male, %	**55.6%**	**53.6%**	**55.6%**
Race, white, %	**92.9%**	**92.8%**	**98.4%**
BMI, kg/m^2, mean (SD)	**29.6** (6.6)	**28.4** (4.9)	**29.7** (5.4)
HeFH, %	**11.1%**	**20.0%**	**12.7%**
Hypertension, %	**67.5%**	**61.6%**	**55.6%**
Type 2 diabetes, %	**28.6%**	**19.2%**	**23.8%**
CHD history, %	**50.8%**	**43.2%**	**44.4%**
Current smoker, %	**8.7%**	**4.0%**	**7.9%**
LLT other than statin/ezetimibe	**37.3%**	**44.0%**	**54.0%**

LLT, lipid-lowering therapy

Baseline Lipids

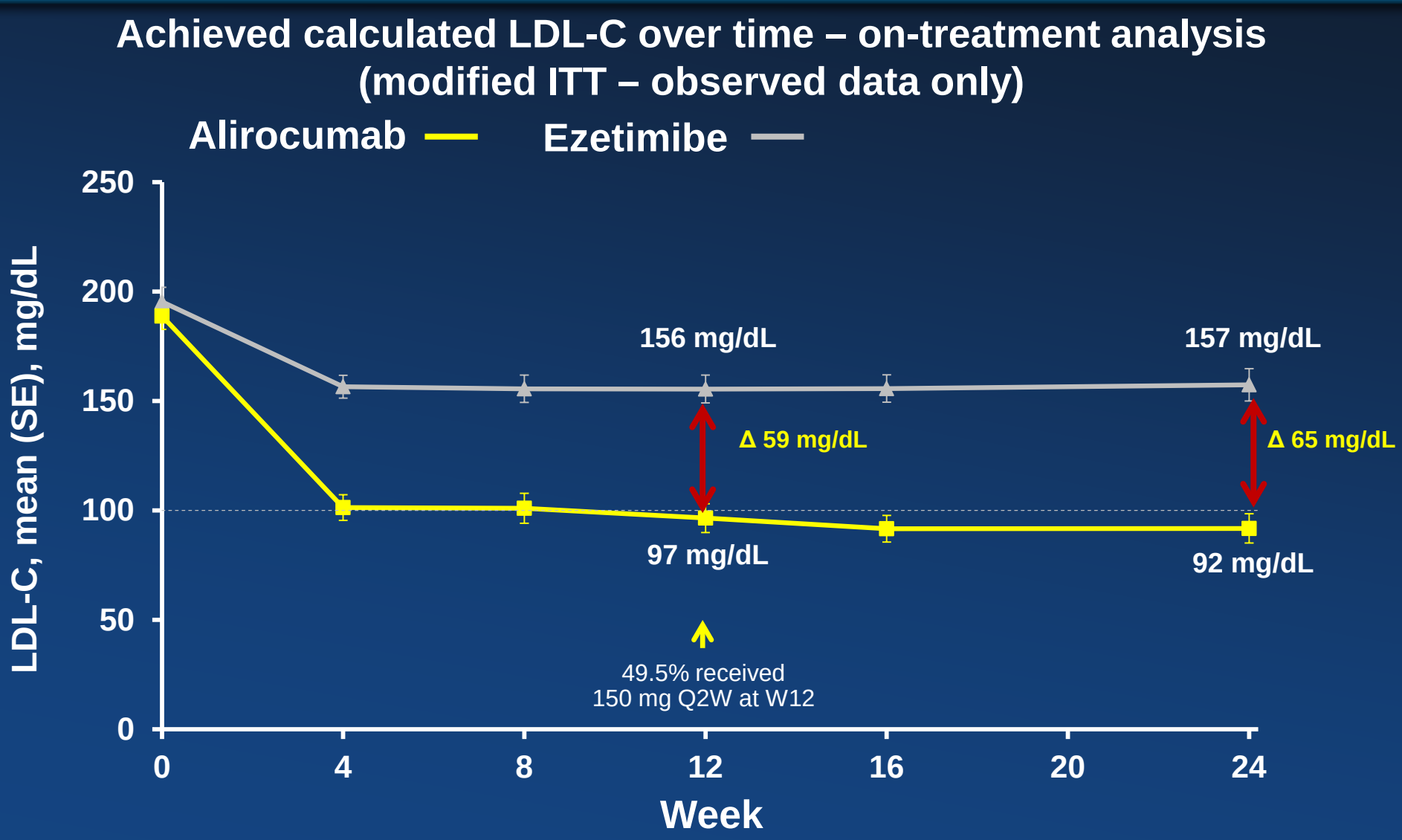
	Alirocumab (N=126)	Ezetimibe (N=125)	Atorvastatin (N=63)
LDL-C (calculated), mg/dL, mean (SD)	**191.1** (72.7)	**193.5** (70.9)	**187.3** (59.5)
Non-HDL-C, mg/dL, mean (SD)	**230.0** (80.4)	**229.8** (82.7)	**223.8** (64.8)
Apo B, mg/dL, mean (SD)	**141.7** (39.5)	**138.2** (37.4)	**139.1** (34.7)
Lp(a), mg/dL, median (IQR)	**18** (8:47)	**14** (7:43)	**12** (6:50)
Triglycerides, mg/dL, median (IQR)	**164** (114:233)	**140** (95:218)	**158** (119:246)
HDL-C, mg/dL, mean (SD)	**48.9** (15.3)	**50.7** (14.1)	**51.1** (12.5)
Apo A1, mg/dL, mean (SD)	**149.4** (25.0)	**150.0** (24.2)	**154.2** (24.8)

Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Ezetimibe



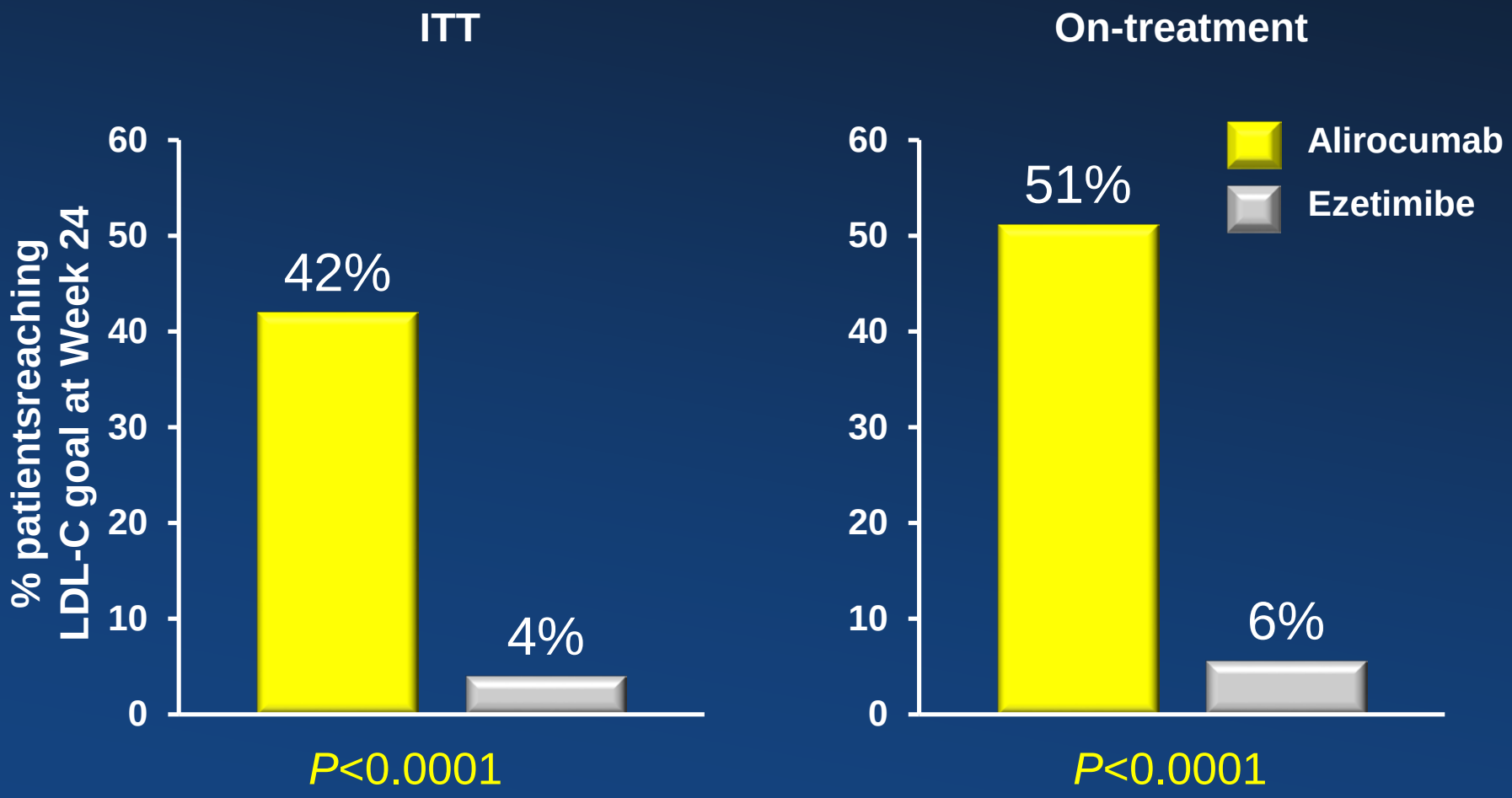
†49.5% of 109 patients who received at least one injection after Week 12 had dose increase.

Alirocumab Maintained LDL-C Reductions Week 4–24



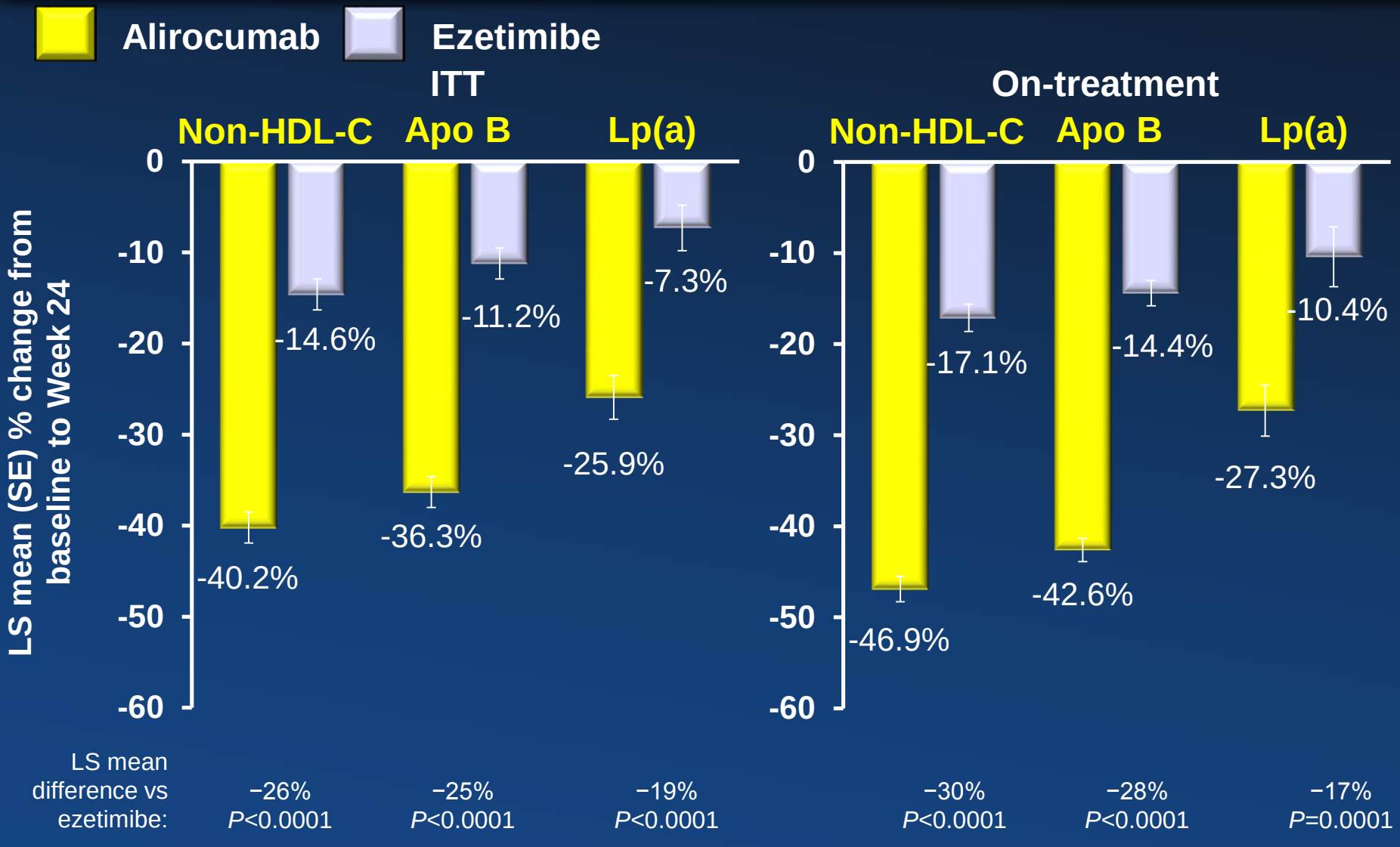
Significantly More SI Patients Achieved Target LDL-C <70 or <100 mg/dL (depending on CV risk) with Alirocumab vs Ezetimibe

Goals: Very high-risk: LDL-C <70 mg/dL, High/moderate-risk: <100 mg/dL



Baseline LDL-C levels (ITT): 191.1 and 194.2 mg/dL in alirocumab and ezetimibe arms.
Baseline LDL-C levels (on-treatment): 188.8 and 195.3 mg/dL in alirocumab and ezetimibe arms.

Significant Reductions in Secondary Lipid Parameters at Week 24



For Lp(a): Adjusted mean (SE) from robust regression with multiple imputation procedure.

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Safety Analysis

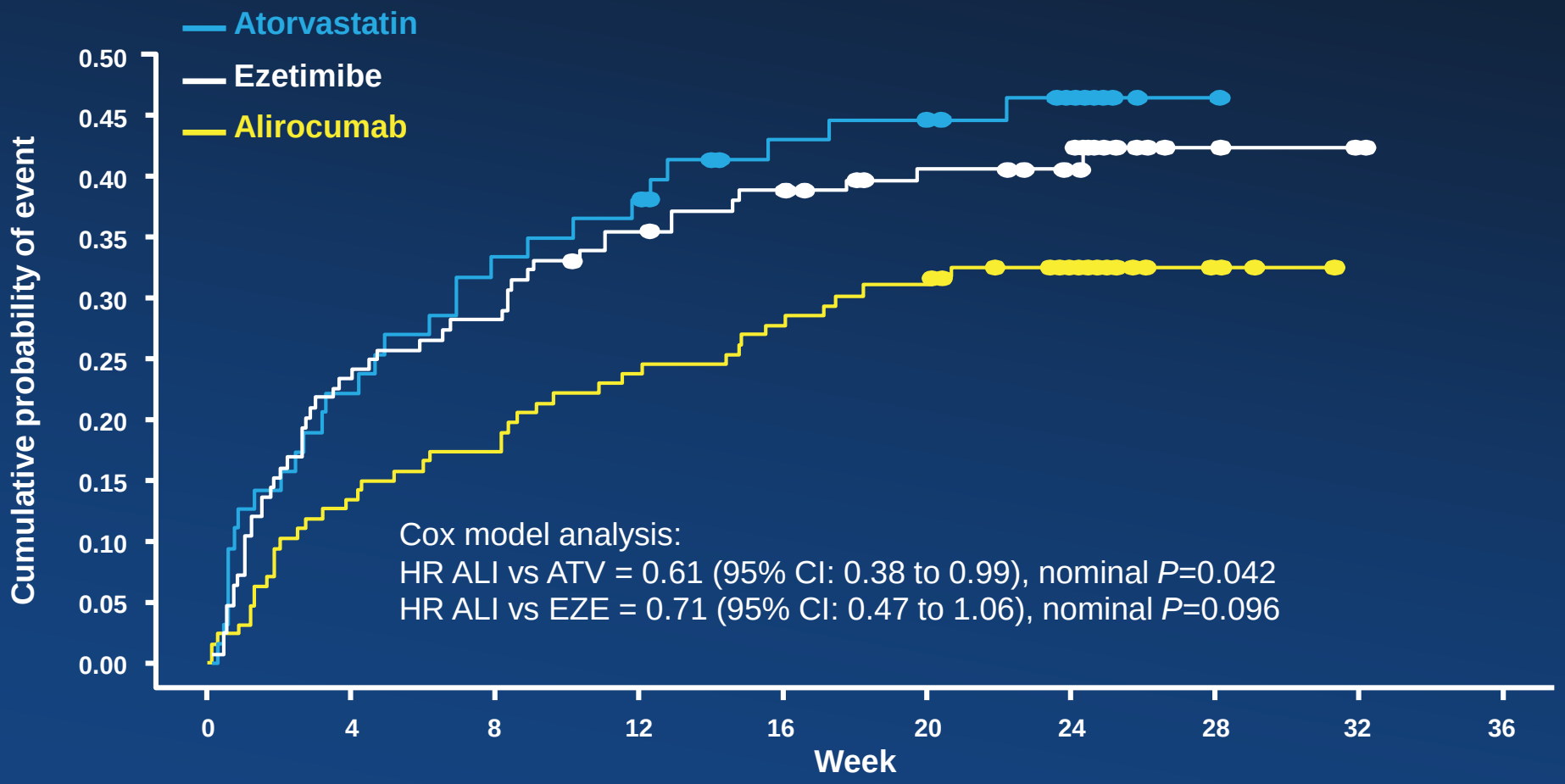
Safety analysis from double-blind treatment period

% of patients	Alirocumab (N=126)	Ezetimibe (N=124)	Atorvastatin (N=63)
TEAEs[†]	82.5%	80.6%	85.7%
Treatment-emergent SAEs	9.5%	8.1%	11.1%
TEAEs leading to death	0	0	0
TEAEs leading to discontinuation	18.3%	25.0%	25.4%
Any skeletal-muscle related TEAE[‡]	32.5%	41.1%	46.0%
HR (95% CI) alirocumab vs comparator	-	0.71 (95% CI: 0.47 to 1.06)	0.61 (95% CI: 0.38 to 0.99)
P-value vs alirocumab[§]	-	0.096	0.042
Skeletal-muscle related TEAE leading to discontinuation	15.9%	20.2%	22.2%
HR (95% CI) alirocumab vs comparator	-	0.78 (95% CI: 0.43 to 1.41)	0.67 (95% CI: 0.34 to 1.32)
P-value vs alirocumab[§]	-	0.409	0.240

[†]TEAE (treatment emergent adverse event) period = time from first to last injection of study treatment + 70 days.
SAE = serious adverse event.
[‡]Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
[§] Although not pre-planned analysis, the *P*-value is shown for descriptive purposes.

Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event†



†Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.
ALI, alirocumab; ATV, atorvastatin, EZE, ezetimibe.

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Safety Analysis: Additional AEs of Interest

Safety analysis from double-blind treatment period

% (n) of patients	Alirocumab (N=126)	Ezetimibe (N=124)	Atorvastatin (N=63)
Adjudicated CV events†	**2.4%** (n=3)	**0.8%** (n=1)	**1.6%** (n=1)
Ischemia-driven coronary revascularization procedure	**2.4%** (n=3)	**0.8%** (n=1)	**1.6%** (n=1)
Non-fatal MI	**0.8%** (n=1)	0	0
Injection-site reactions	**4.8%** (n=6)	**4.8%** (n=6)	**1.6%** (n=1)
Neurocognitive disorders	**2.4%** (n=3)	**1.6%** (n=2)	0
Creatine kinase >3x ULN, % (n/N)	**2.4%** (3/126)	**1.6%** (2/123)	**4.8%** (3/62)
Myositis*	0	0	1.6% (n=1)
ALT >3x ULN, % (n/N)	0	0	0

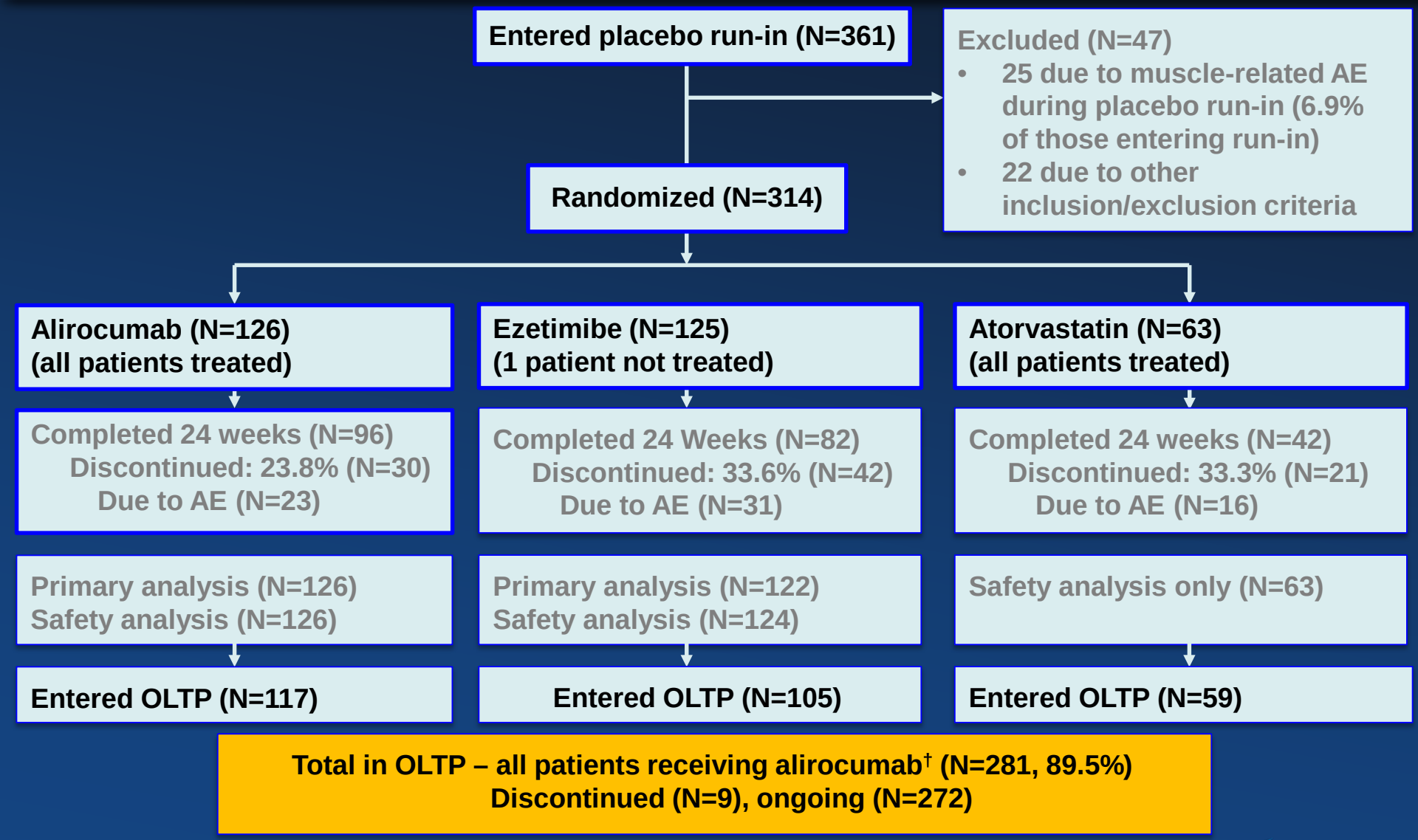
†Adjudicated CV events categories: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, ischemia-driven revascularization procedure (PCI, CABG).
*Muscle symptoms with CK ≥3 x ULN and <10 x ULN.
Patients can be reported as having more than one CV event.
ALT, alanine transaminase; ULN, upper limit of normal.

Safety Analysis: TEAEs Occurring in ≥5% of Patients in Any Group

Safety analysis from double-blind treatment period

% (n) of patients	Alirocumab (N=126)	Ezetimibe (N=124)	Atorvastatin (N=63)
Myalgia	**24.6** (31)	**23.4** (29)	**27.0** (17)
Nasopharyngitis	**6.3** (8)	**8.1** (10)	**3.2** (2)
Arthralgia	**5.6** (7)	**7.3** (9)	**7.9** (5)
Upper respiratory tract infection	**5.6** (7)	**4.0** (5)	**3.2** (2)
Headache	**4.8** (6)	**4.8** (6)	**6.3** (4)
Fatigue	**4.8** (6)	**3.2** (4)	**7.9** (5)
Muscle spasms	**4.0** (5)	**7.3** (9)	**11.1** (7)
Back pain	**4.0** (5)	**5.6** (7)	**7.9** (5)
Paraesthesia	**3.2** (4)	**0**	**6.3** (4)
Vomiting	**2.4** (3)	**0.8** (1)	**6.3** (4)
Muscular weakness	**0.8** (1)	**1.6** (2)	**6.3** (4)

Patient Disposition – Open Label Treatment Period (OLTP)



†Dose ↑ from 75 mg to 150 mg Q2W at W36 based on the LDL-C level at W32 and the judgment of the investigator

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Interim Safety Results from the Ongoing 3-Year OLTP

Safety analysis from start of OLTP up to 52 weeks

- 89.5% of randomized patients entered the OLTP (including 94% of those randomized to atorvastatin).
- All patients in OLTP receive alirocumab 75 mg Q2W (with dose increase possible to 150 mg Q2W after 12 weeks OLTP treatment).

	Alirocumab (N=281)
Mean (SD) **exposure during OLTP (weeks)**	**13.9** (6.8)
Any TEAE	**55.9%** (n=157)
Myalgia	**4.3%** (n=12)
Muscle spasms	**1.8%** (n=5)
Musculoskeletal stiffness	**0.7%** (n=2)
TEAE leading to discontinuation	**2.8%** (n=8)
Myalgia (leading to discontinuation)	**0.7%** (n=2[†])

[†]The two patients who discontinued due to myalgia originally came from the alirocumab and ezetimibe arms, respectively.

Safety Summary

ODYSSEY ALTERNATIVE and alirocumab safety across placebo-controlled studies

	ODYSSEY ALTERNATIVE				Pooled alirocumab Phase 2/3 placebo-controlled studies	
	Double-blind Treatment Period			Open Label Treatment Period		
% of patients	Alirocumab (N=126)	Ezetimibe (N=124)	Atorvastatin (N=63)	Alirocumab (N=281)	Alirocumab (N=2476)	Placebo (N=1276)
Mean duration of treatment (weeks)	21.5	19.8	19.4	13.9	58.3	57.6
TEAEs†	82.5%	80.6%	85.7%	55.9%	75.8%	76.4%
TEAEs leading to discontinuation	18.3%	25.0%	25.4%	2.8%	5.3%	5.1%
Any skeletal-muscle related TEAE‡	32.5%	41.1%	46.0%	13.9%	15.1%	15.4%
Skeletal-muscle related TEAE leading to discontinuation	15.9%	20.2%	22.2%	1.4%	0.4%	0.5%

†TEAE period = time from first to last injection of study treatment + 70 days.
‡Pre-defined category including myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, muscle fatigue.

Conclusions: ODYSSEY ALTERNATIVE

- **In a population of statin intolerant patients with very high baseline LDL-C levels (~190 mg/dL):**
  - **Self-administered alirocumab produced significantly greater LDL-C reductions versus ezetimibe at Week 24 (LS mean difference of 30.4%)**
    - **Mean achieved LDL-C = 108.5 mg/dL at Week 24**
      - **92 mg/dL on-treatment analysis**
    - **~50% did not need dose increase to alirocumab 150 mg Q2W at Week 12**
    - **42% of alirocumab patients achieved their LDL-C goals at Week 24**
  - **In this study, alirocumab was better tolerated than atorvastatin (HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P=0.042)**
    - **Fewer patients with skeletal muscle-related TEAEs (myalgia, muscle spasms, muscular weakness, musculoskeletal stiffness, and muscle fatigue) with alirocumab than with atorvastatin and ezetimibe**
  - **Fewer skeletal muscle events observed to date in the alirocumab OLTP compared with the main study**
    - **Only two of 281 patients discontinued due to myalgia**

Overview of the ODYSSEY Phase 3 Program

Fourteen global Phase 3 trials including >23 500 patients across >2000 study centres

HeFH population

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

ODYSSEY FH I (NCT01623115; EFC12492)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=486; 18 months

ODYSSEY FH II (NCT01709500; CL1112)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=249; 18 months

ODYSSEY HIGH FH (NCT01617655; EFC12732)
LDL-C ≥160 mg/dL
n=107; 18 months

ODYSSEY OLE (NCT01954394; LTS 13463)
Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717
n≥1000; 30 months

ODYSSEY LONG TERM (NCT01507831; LTS11717)
LDL-C ≥70 mg/dL
n=2341; 18 months

HC in high CV-risk population

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

ODYSSEY COMBO I (NCT01644175; EFC11568)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=316; 12 months

[†]ODYSSEY COMBO II (NCT01644188; EFC11569)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=720; 24 months

ODYSSEY CHOICE I (NCT01926782; CL1308)
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=700; 12 months

ODYSSEY OUTCOMES (NCT01663402; EFC11570)
LDL-C ≥70 mg/dL
n=18 000; 64 months

Additional populations

ODYSSEY MONO (NCT01644474; EFC11716)
Patients on no background LLTs
LDL-C ≥100 mg/dL
n=103; 6 months

ODYSSEY ALTERNATIVE (NCT01709513; CL1119)
Patients with defined statin intolerance
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=314; 6 months

ODYSSEY CHOICE II (NCT02023879; EFC13786)
Patients not treated with a statin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=200; 6 months

ODYSSEY OPTIONS I (NCT01730040; CL1110)
Patients not at goal on moderate-dose atorvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=355; 6 months

ODYSSEY OPTIONS II (NCT01730053; CL1118)
Patients not at goal on moderate-dose rosuvastatin
LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL
n=305; 6 months

[†]For ODYSSEY COMBO II other LLT not allowed at entry.

Thank You to All Principal Investigators and National Coordinators!