

Efficacy of Enlicitide Across CKM Syndrome Stages in CORALreef Lipids and CORALreef HeFH

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Background

- CKM Syndrome Continuum:** The multi-society AHA/ACC/ADA/ASN consensus defines Cardiovascular-Kidney-Metabolic (CKM) syndrome as a progressive continuum linking metabolic risk factors, CKD, and ASCVD across Stages 0 to 4¹
- Atherogenic Burden:** Cumulative exposure to LDL-C, apoB, non-HDL-C, and Lp(a) drives ASCVD risk across all CKM stages, yet guideline-recommended lipid goals are commonly not attained in clinical practice^{2,3}
- Enlicitide:** Enlicitide decanoate is a once-daily oral macrocyclic peptide PCSK9 inhibitor that has demonstrated ~60% LDL-C reductions in Phase 3 trials and is approved by the U.S. FDA for treatment of hypercholesterolemia^{4,5}

Purpose

- To evaluate the efficacy and safety of enlicitide across baseline CKM syndrome stages in pooled data from the CORALreef Lipids and CORALreef HeFH trials

Methods

Trial Design & Study Population

Trial Designs:

- CORALreef Lipids and CORALreef HeFH** - Phase 3, double-blind, randomized controlled trials of enlicitide 20 mg daily vs placebo in adults with hypercholesterolemia + a history of a major ASCVD event & LDL-C ≥55 mg/dL or at risk for 1st Major ASCVD event & LDL-C ≥70 mg/dL
- Participants were on optimized and stable background LLT with moderate- or high-intensity statin (or with documented statin intolerance in CORALreef Lipids) ± other LLTs; in CORALreef HeFH, all participants had heterozygous familial hypercholesterolemia (HeFH)
- Pooled Population:** Baseline characteristics based on the intention-to-treat population comprised of all randomized participants. Mean changes from baseline in efficacy based on participants with data (ie, all randomized participants who have data at the timepoint; no missing data imputed) from CORALreef Lipids and CORALreef HeFH
- Exclusion criteria:** Screening fasting triglycerides ≥400 mg/dL; HbA1c ≥9%; eGFR <30 mL/min/1.73 m²; ASCVD event in last 3 months from screening

Baseline CKM Stage Categorization

STAGE 0	STAGE 1	STAGE 2	STAGE 3	STAGE 4
No CKM risk	Excess/ dysfunctional adiposity	Metabolic risk factors/ moderate CKD	Subclinical CVD/risk equivalents	Clinical CVD
Normal BMI, normoglycemia, normotension, normal lipid panel, no CKD or subclinical/clinical CVD	BMI ≥25 kg/m ² (≥23 if Asian) Glycemia FPG 100–125 mg/dL or HbA1c 5.7%–6.4%	Hypertension history, BP ≥130/80 mm Hg, or treatment Triglycerides ≥150 mg/dL T2D history, FPG ≥126 mg/dL, or HbA1c ≥6.5% eGFR 30–<60 mL/min/1.73 m ²	Heart failure or atrial fibrillation CAC Agatston score ≥100 eGFR <30 mL/min/1.73 m ² PREVENT 10-year CVD risk ≥20%	Documented history of a major ASCVD event

Endpoints

- The following endpoints were evaluated at Week 24 and Week 52 in enlicitide and placebo participants:
 - Placebo-adjusted mean % reduction in LDL-C, ApoB, and non-HDL-C
 - Placebo-adjusted median % reduction in Lp(a)
 - Goal Attainment: Proportions of participants attaining guideline-recommended treatment goals of <55 mg/dL and <70 mg/dL for LDL-C and ApoB at Week 24

Results

Participants

- 3,212 total participants were evaluated (2,142 enlicitide; 1,070 placebo)
- Participant characteristics varied across CKM stages. More advanced stages generally included greater use of background statin therapy and lower baseline LDL-C levels

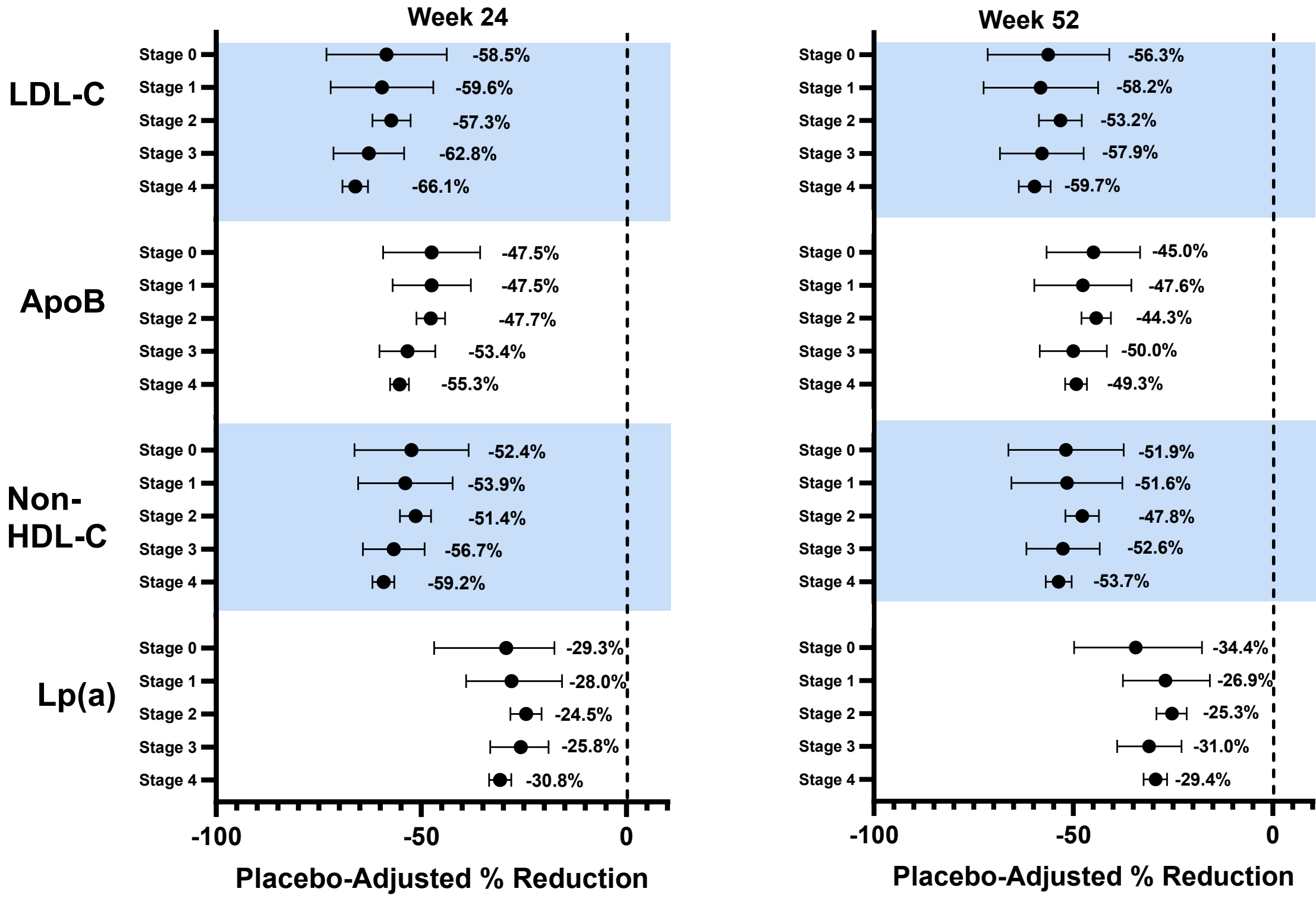
Table 1 - Baseline Participant Characteristics

	Stage 0 N=64	Stage 1 N=115	Stage 2 N=990	Stage 3 N=265	Stage 4 N=1,778
Age (years), Mean (SD)	43.3 (14.3)	50.5 (13.9)	59.3 (11.2)	69.5 (7.7)	63.4 (10.0)
Male, (%)	29.7	42.6	40.6	53.6	73.3
Race: White/Asian/Black (%)	65.6/34.4/0.0	60.9/31.3/0.0	63.6/17.9/8.3	61.1/20.8/10.6	49.2/29.5/8.5
BMI (kg/m ²), Mean (SD)	22.0 (2.0)	26.8 (4.6)	30.5 (6.7)	29.5 (5.7)	28.8 (5.6)
Type 2 Diabetes Mellitus, (%)	0.0	0.0	57.1	71.7	40.1
eGFR (mL/min/1.73 m ²), Mean (SD)	104.0 (13.6)	97.4 (14.8)	91.3 (16.2)	77.6 (17.8)	85.1 (18.3)
Baseline Statin Use, (%)	98.4	98.3	95.6	95.1	97.8
Baseline LDL-C (mg/dL), Mean (SD)	131.6 (52.6)	117.2 (37.1)	111.8 (40.2)	101.8 (33.0)	87.8 (36.4)
Baseline ApoB (mg/dL), Mean (SD)	105.9 (30.6)	100.4 (23.8)	101.1 (28.5)	95.4 (22.6)	86.1 (25.5)
Baseline Non-HDL-C (mg/dL), Mean (SD)	148.8 (55.6)	137.8 (38.5)	139.7 (45.3)	131.0 (35.4)	113.5 (39.9)
Baseline Lp(a) (nmol/L), Median [Q1, Q3]	30.9 [18.1, 96.1]	61.9 [16.8, 181.9]	33.2 [11.1, 118.3]	34.1 [14.0, 133.2]	45.7 [14.5, 161.8]

Efficacy by CKM Stage

- Placebo-adjusted reductions in atherogenic lipids at Week 24 with enlicitide were robust and significant ($P<0.001$) and consistent across all CKM stages; efficacy was maintained through Week 52 (Figure 1)

Figure 1. Placebo-adjusted Lipid Reductions



$P<0.001$ for all comparisons vs placebo; P -values are nominal (i.e., provided as a descriptive measure without adjustment for multiplicity and, therefore, not intended for statistical inference). For LDL-C, ApoB, and Non-HDL-C, the overall estimate of difference in LS means between treatment groups (Enlicitide - Placebo) was estimated based on participants with data through the ANCOVA model with treatment and study ID as fixed effects and baseline value as a covariate. For Lp(a), difference in medians and 95% CI were obtained via the Hodges-Lehmann estimation, stratified by study; P -value was obtained via the aligned rank Wilcoxon test.

Goal Attainment

- High proportions of participants achieved guideline-recommended goals for LDL-C as well as for ApoB across all CKM stages (Figures 2 and 3); $P<0.001$ for all comparisons vs placebo

Figure 2. % LDL-C Goal Attainment by CKM Stage at Week 24

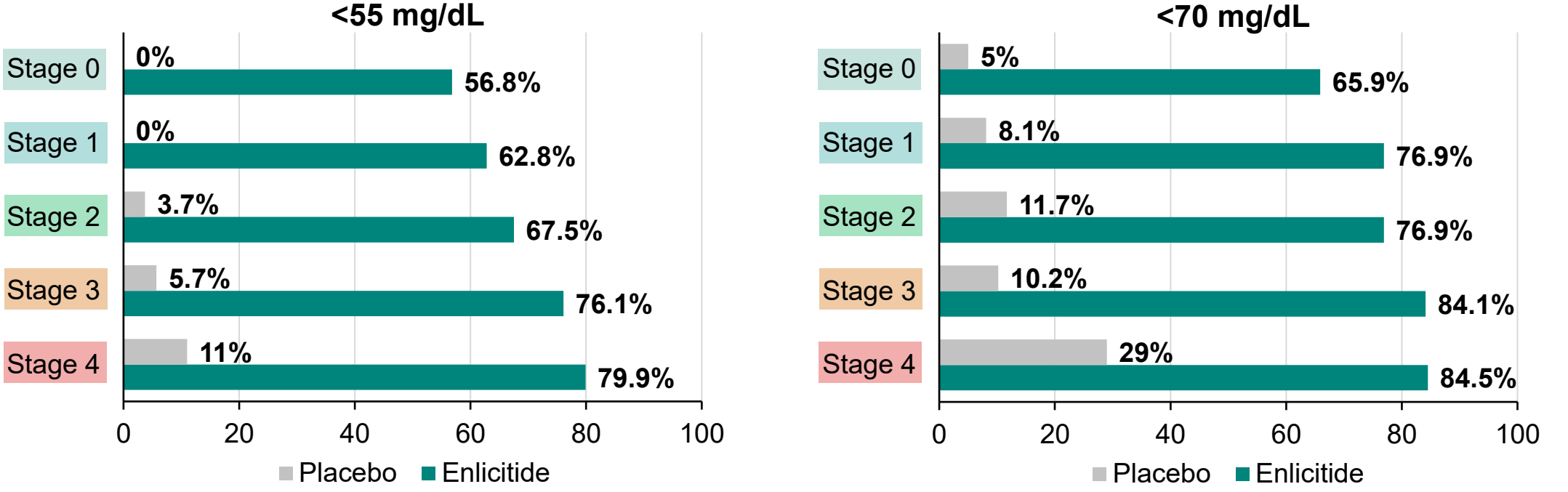
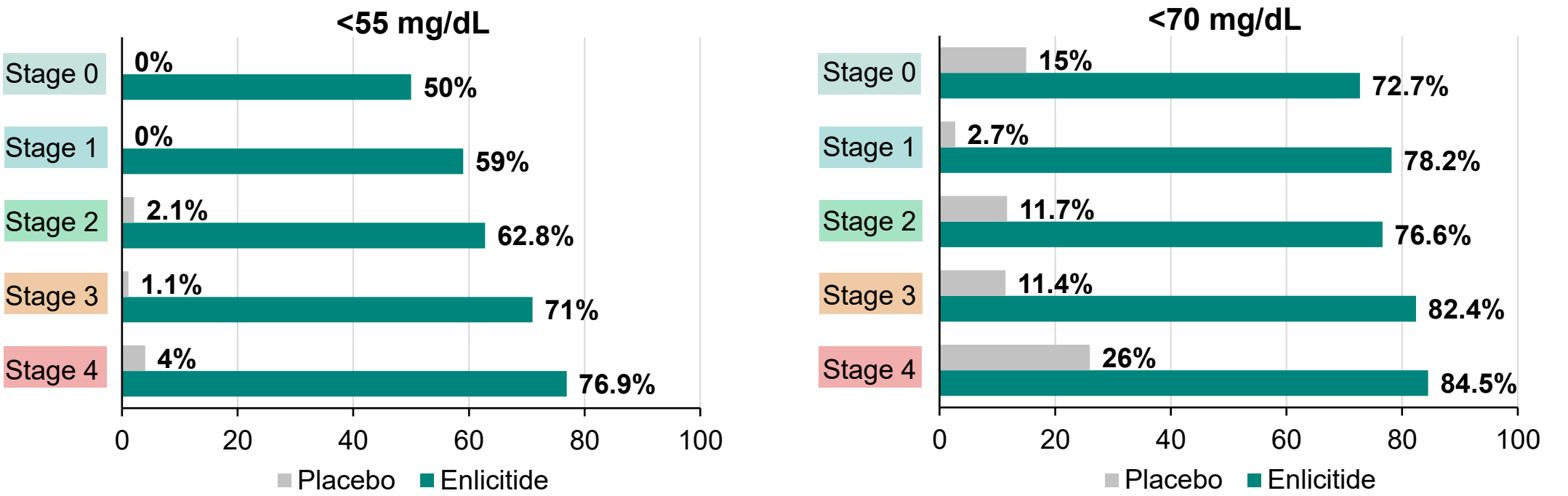


Figure 3. % ApoB Goal Attainment by CKM Stage at Week 24

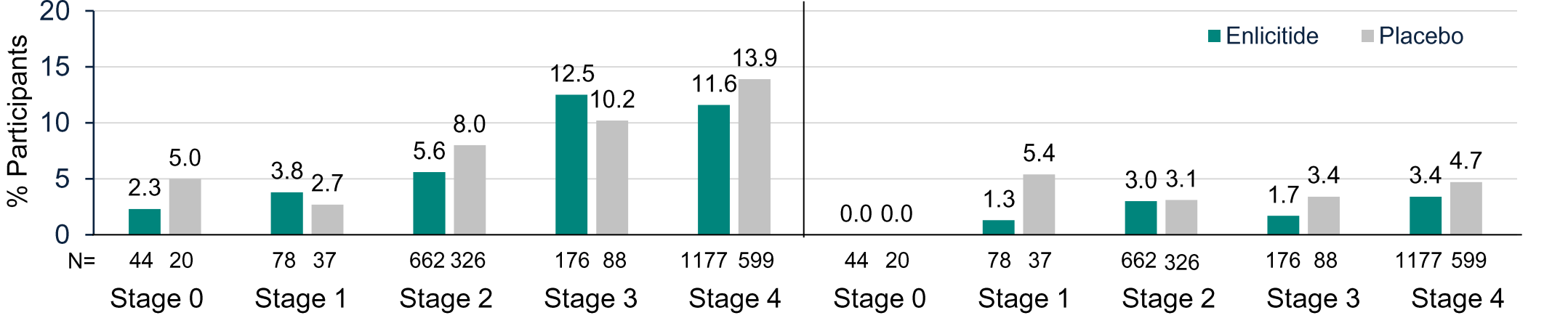


$P<0.001$ for all comparisons vs placebo. P -values based on the Miettinen & Nurminen method (with sample size weighting). Pooled results are stratified by study.

Safety and Tolerability

- The proportions of participants with ≥1 AE were generally similar between enlicitide and placebo across CKM stages, ranging from 63% to 75% and from 61% to 80%, respectively

Figure 4. % Participants with Serious AEs and Discontinuations due to AEs



Conclusions

- Enlicitide 20 mg once daily demonstrated potent, durable reductions across all atherogenic lipoproteins and led to higher achievement of lipid guideline goals vs. placebo regardless of baseline CKM syndrome stage.
- Safety and tolerability were comparable to placebo across all CKM syndrome stages
- These findings demonstrate that oral enlicitide is an effective intervention to address atherogenic risk across the entire CKM continuum, suggesting that enlicitide may be a valuable tool in the effort to combat the ongoing cardiovascular epidemic

References

- Ndumele CE, et al. *Circulation*. 2026;154(4):e50–e158.
- Grundt SM, et al. *Circulation*. 2019;139(25):e1082–e1143.
- Pearson GJ, et al. *J Am Coll Cardiol*. 2021;78(3):260–298.
- Navar AM, et al. *N Engl J Med*. 2026;394(6):529–539.
- Ballantyne CM, et al. *JAMA*. 2026;335(2):129–139.

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