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Randomized, Double-blind, Placebo-controlled, Phase 3, Study Evaluating Lerodalcibep 52 Week Efficacy And Safety In Patients With CVD On Stable Lipid-lowering Therapy: (LIBerate-CVD)

Disclosure

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COI statement: Chief Scientific Officer, LIB Therapeutics USA
Co-founder, Employee and share-holder LIB Therapeutics

Dean Kereiakes, Nyda Fourie, Johannes Engelbrecht, Lesley Burgess, Jane Kerr, Zafir Yalim, Jeffrey Vest, David Kallend, ***for the LIBerate-CVD Investigators***

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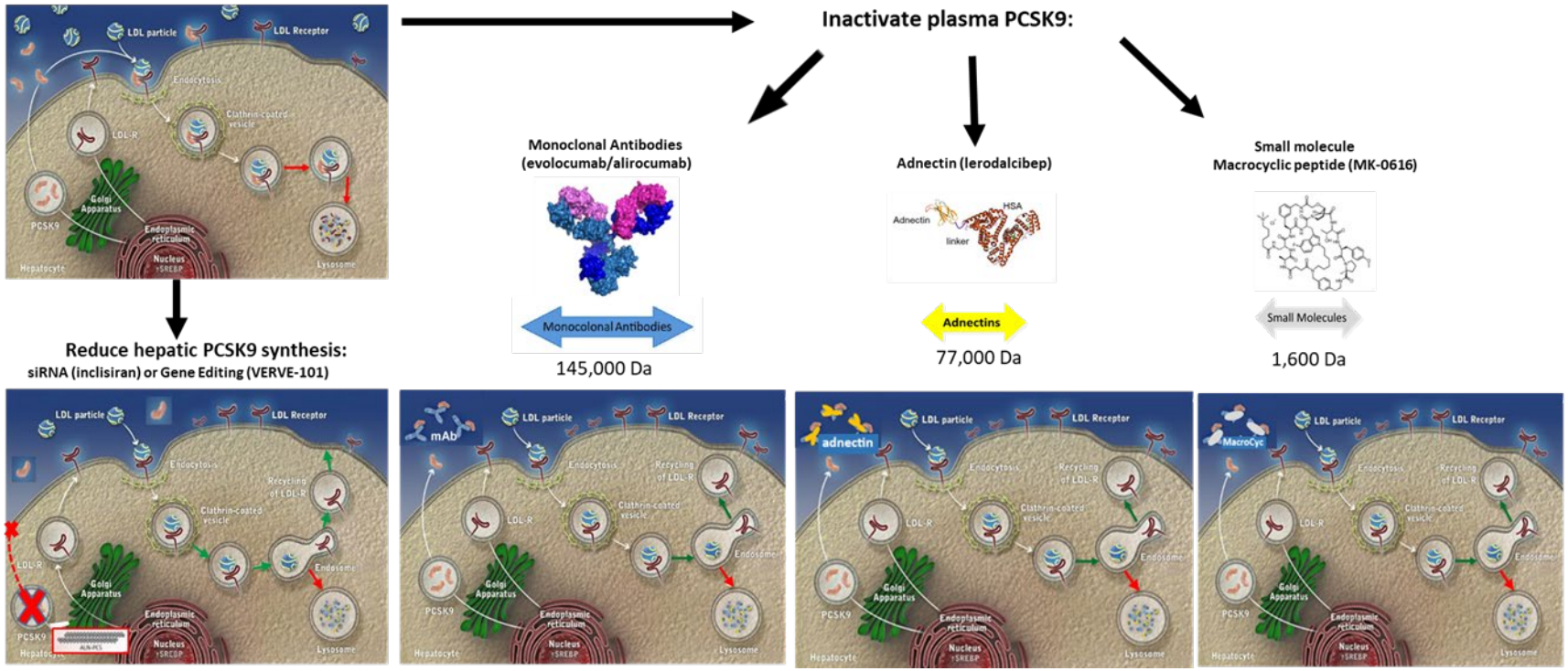
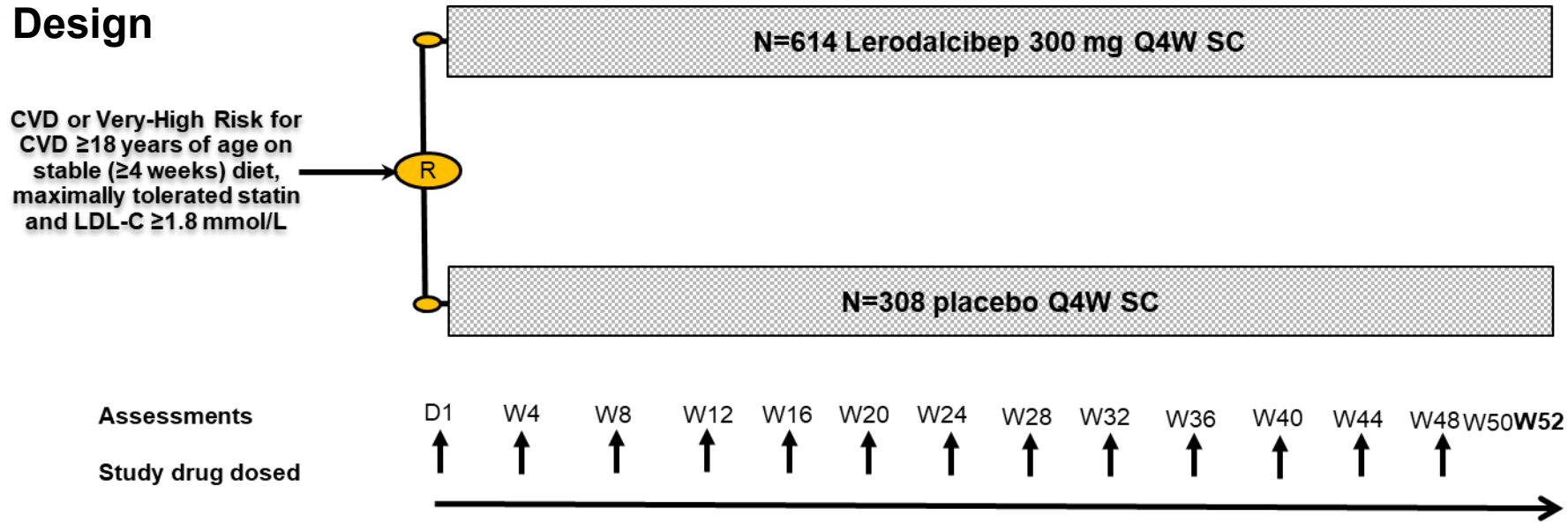
Lerodalcibep (LIB-003): Third Generation PCSK9 Inhibitor

- **Lerodalcibep** a small binding protein, consists of an 11kDa anti-PCSK9 domain (Adnectin), derived from human fibronectin, fused with human serum albumin with plasma half-life 12 to 15 days.
- Lerodalcibep binds to plasma PCSK9, blocks PCSK9 binding to LDLR, preventing LDLR degradation, increasing LDLR recycling, enhancing LDL-C clearance, and lowers LDL-C levels.
- The small size (77kDa) and high solubility allows for a much smaller monthly injection volume of 1.2 mL to achieve stable and prolonged LDL-C reductions between injections.



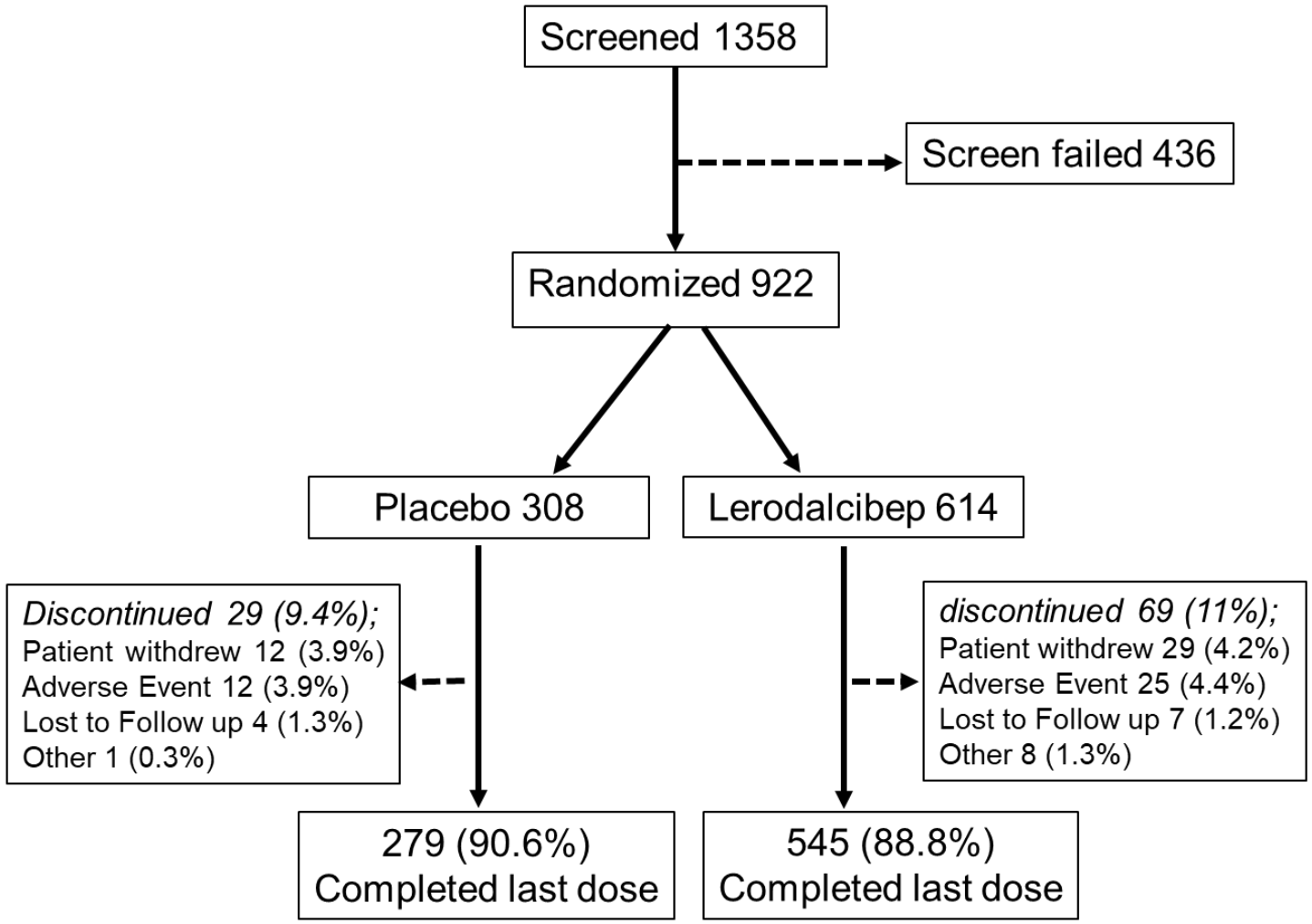
Study Design and Methodology

Study Design



- **Intervention:** Randomized 2:1 to monthly 1.2 mL sub-cutaneous (SC) lerodalcibep 300mg or placebo for 52 weeks.
- **Setting:** 65 clinical centers in 11 countries
- **Co-primary efficacy endpoints**: LDL-C % change from baseline at Week 52 and the mean of Weeks 50 and 52.
- **Secondary outcomes:** achievement of EAS/ESC LDL-C targets, other lipid and apolipoproteins changes.
- **Safety analysis:** included all patients randomized and receiving a dose of study drug.
- **Trial Registrations:** EudraCT: 2020-004392-40 Clinicaltrials.gov NCT04797247

Patient Disposition (Consort Diagram) and Analysis Populations



Co-primary Efficacy Endpoint Analysis Populations

Population	Placebo N (%)	Lerodalcibep N (%)
Modified ITT (mITT)	285 (92.5%)	550 (89.6%)
Per-Protocol (PP)	216 (70.1%)	436 (71.0%)
ITT with imputation (ITT)*	308 (100%)	614 (100%)

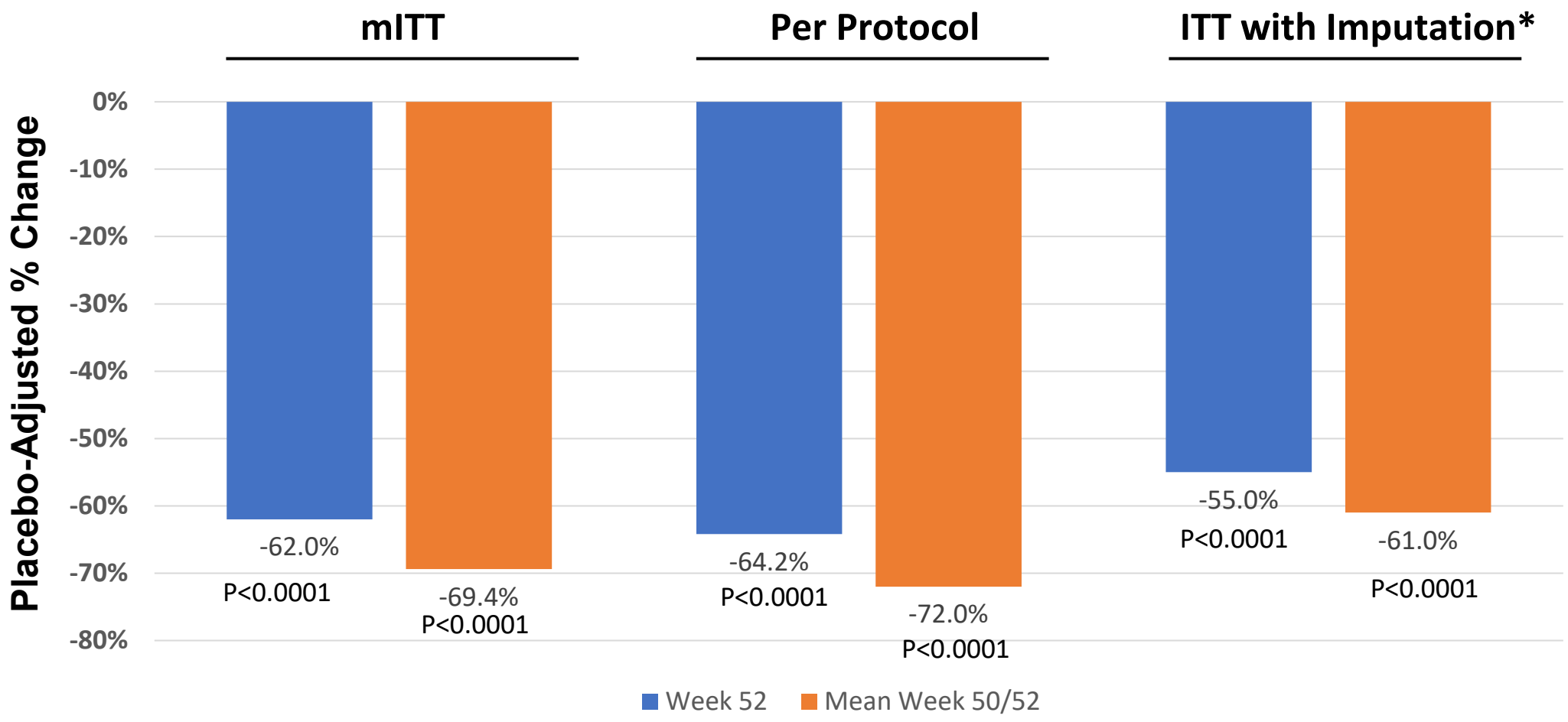
- mITT: all pts with W52 visit
- PP: all pts with ALL visits per-protocol
- ITT with imputation washout model assumes lerodalcibep subjects discontinued to have an outcome similar to those in the placebo group as per new FDA guidance 2021

*FDA. E9(R1) statistical principles for clinical trials: Estimands and sensitivity analysis in clinical trials. 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical

Baseline Demographics and Clinical Characteristics

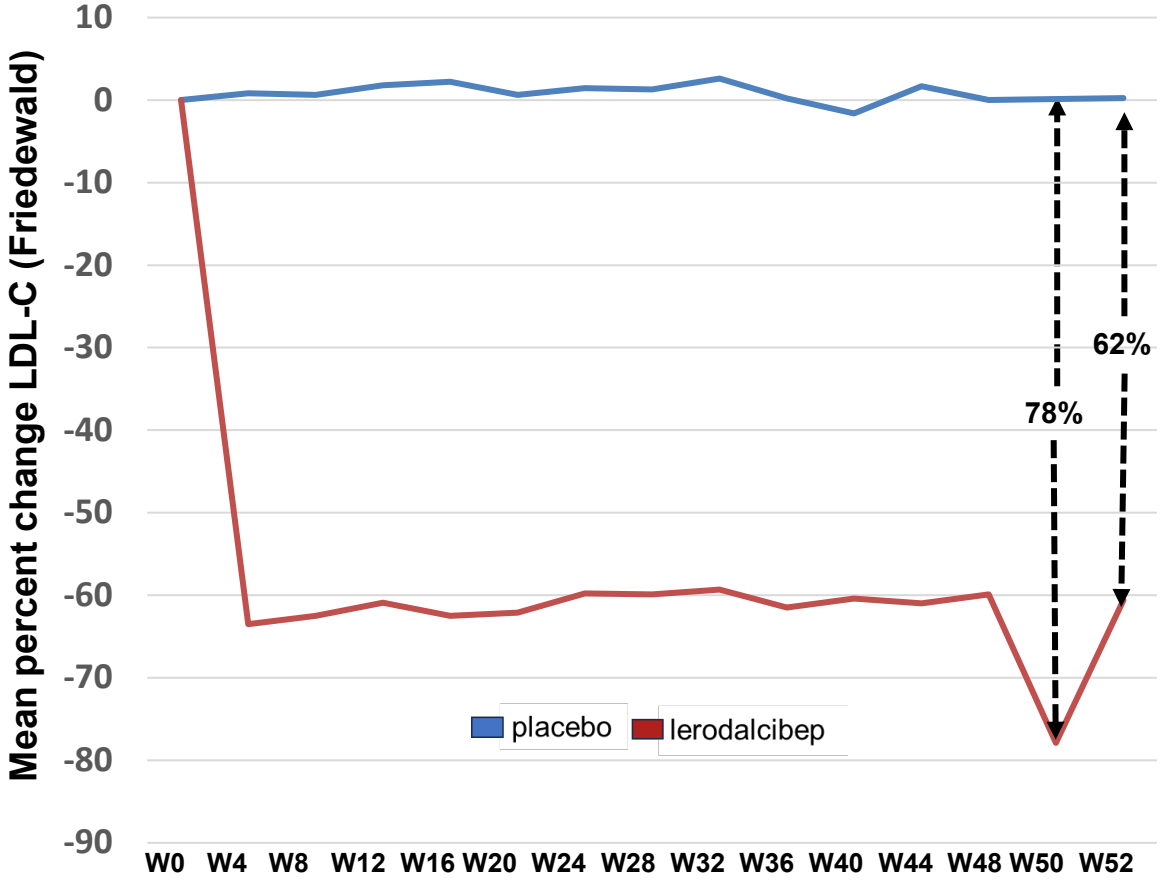
Characteristic	Placebo (N=308)	Lerodalcibep (N=614)
Age – yr (range)	64.5 (25-89)	63.3 (26-90)
Sex – male/female (%)	70/30	70/30
Race: White (%)	79	80
Black/Multiracial (%)	18	17
South Asian (%)	3	3
Body mass Index – kg/m^2 mean(SD)	29.9 (4.95)	29.9 (5.02)
CVD Risk: Secondary Prevention - Documented CVD no. (%)	266 (86.4%)	524 (85.3%)
Primary prevention – Very-High risk for CVD no. (%)	42 (13.6%)	90 (14.7%)
Diabetes Mellitus no. (%)	102 (33.1%)	210 (34.2%)
Heterozygous Familial Hypercholesterolaemia no. (%)	19 (6.2%)	66 (10.7%)
Lipid modifying therapy		
Statin; any dose	82%	87%
High intensity statin	50.6%	54.9%
Ezetimibe	15.1%	15.3%
Lipid measures at baseline –mmol/L; mean(SD)		
LDL-cholesterol (Friedewald calculated)	2.66 (0.91)	2.63 (0.97)
LDL-cholesterol (UltraCentrifugation)	2.69 (0.88)	2.63 (1.09)
Non HDL-cholesterol	3.43 (1.01)	3.37 (42.3)
HDL-Cholesterol	1.22 (0.38)	1.22 (0.36)
Triglycerides	1.69 (0.92)	1.64 (0.84)
Apolipoprotein B (g/L)	0.967 (0.025)	0.953 (0.026)
Lipoprotein (a) mean/median nmol/L	115.3/57	105.6/48

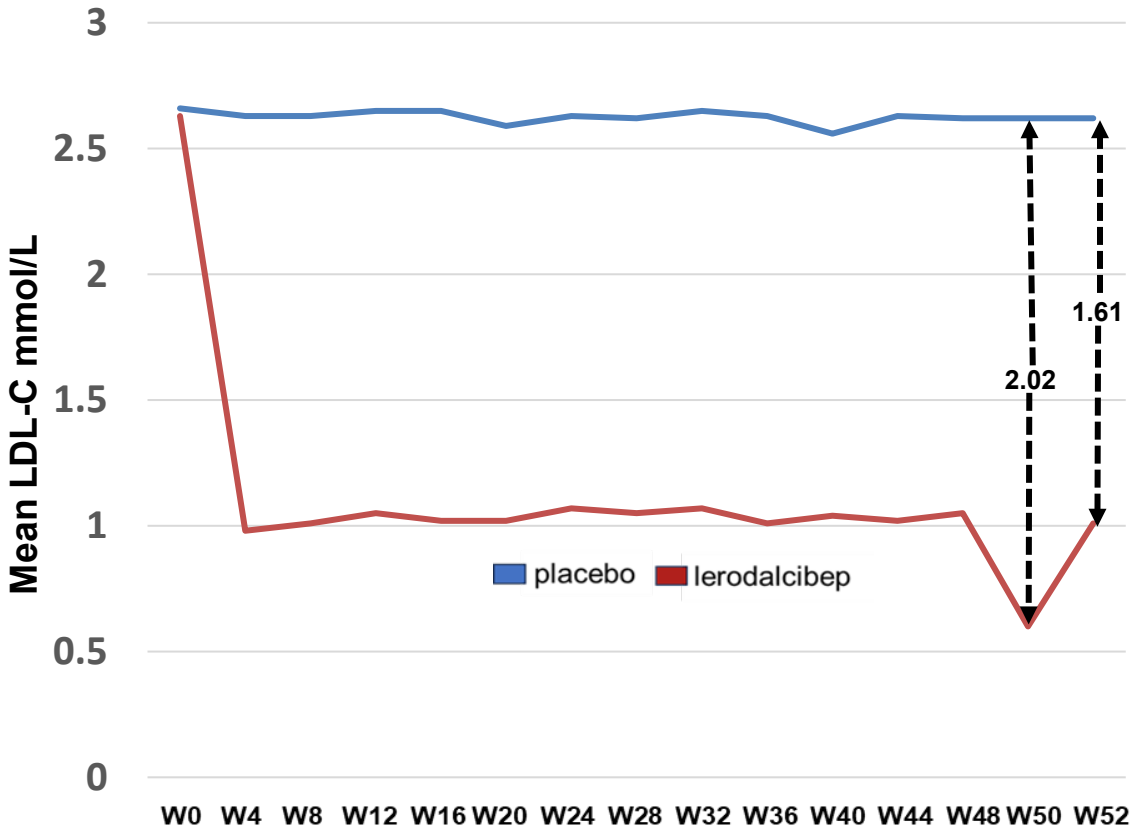
LS mean Change in LDL-C from Baseline: Co-Primary Endpoints by mITT, PP and ITT



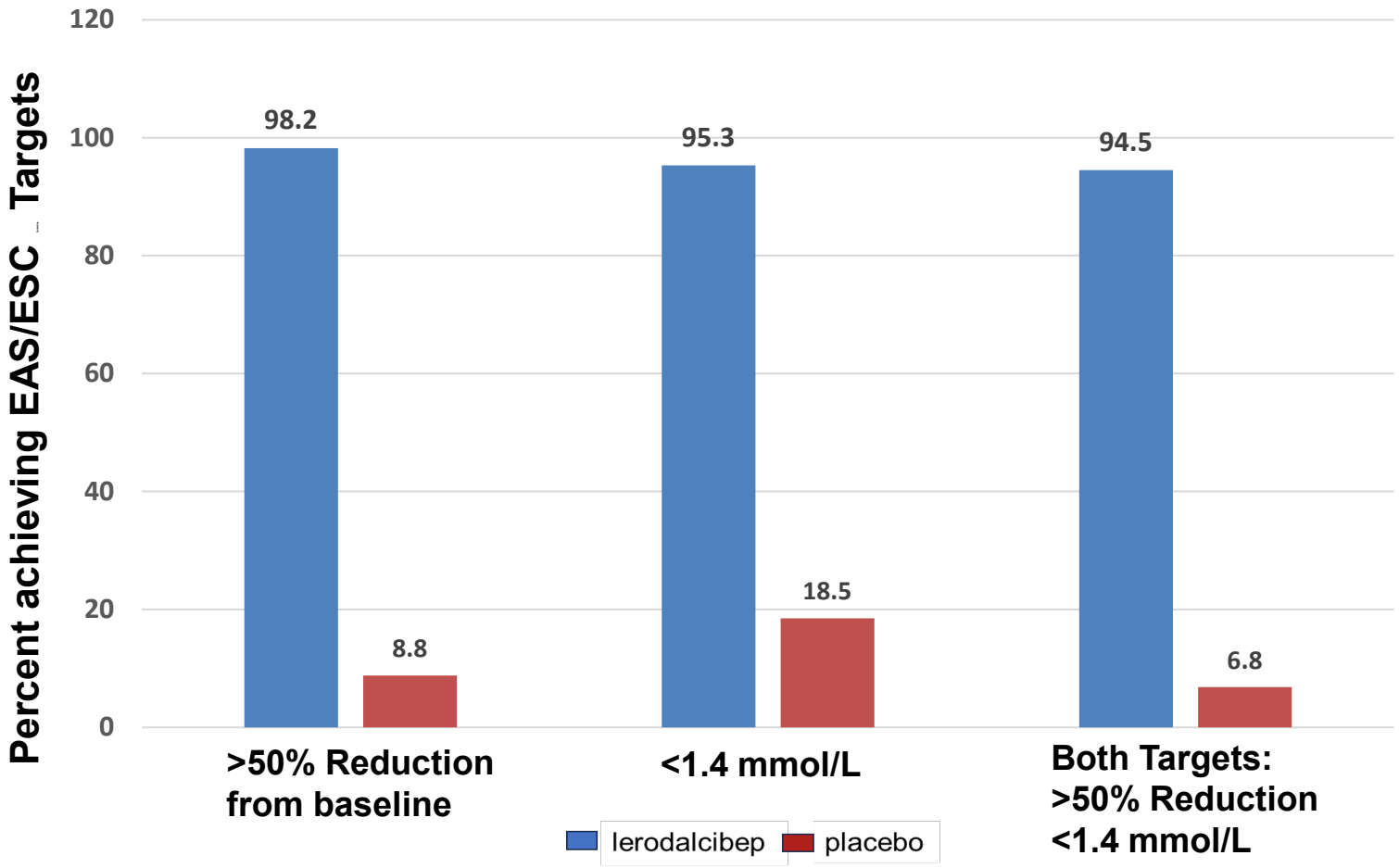
*multiple imputation washout model assumes lerodalcibep subjects who discontinued to have an outcome similar to the placebo group, as per new FDA 2021 guidance

LS mean Percent and Absolute Change in LDL-C from Baseline at each visit: ITT analysis

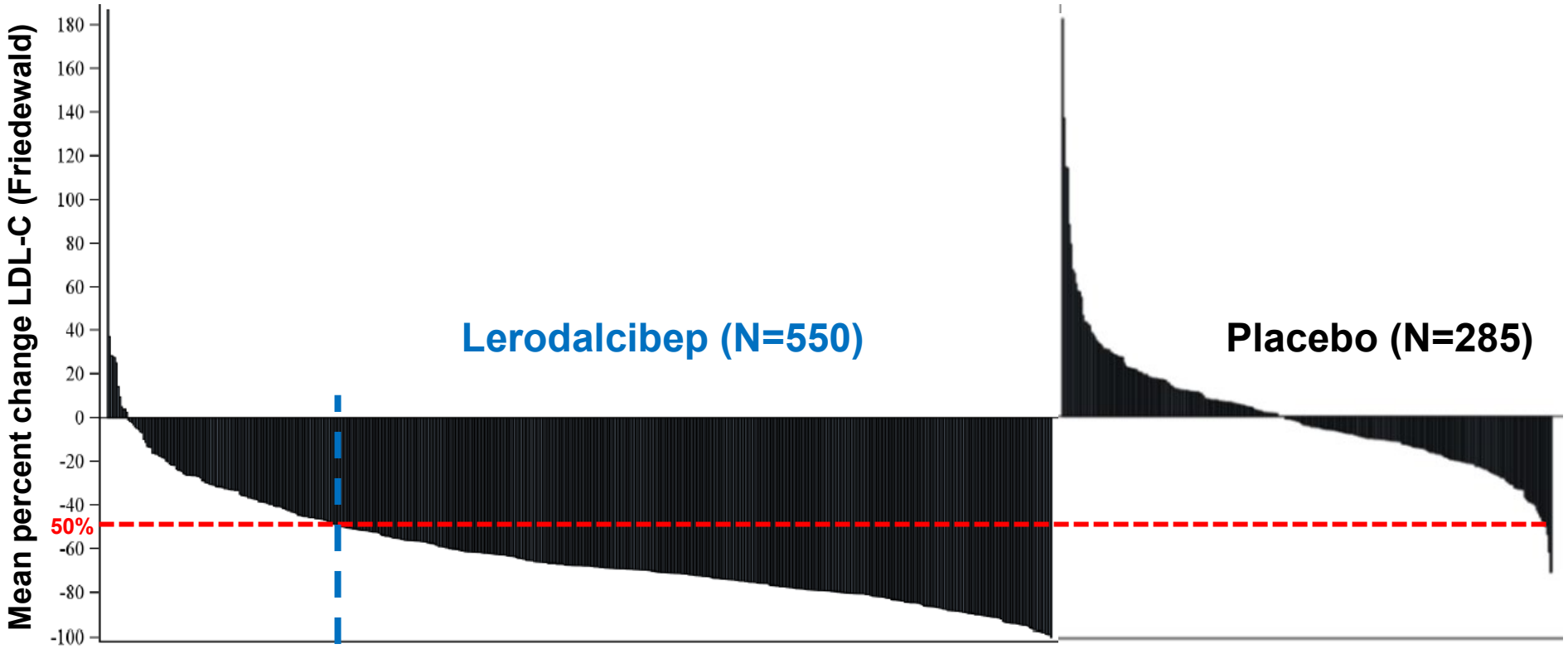




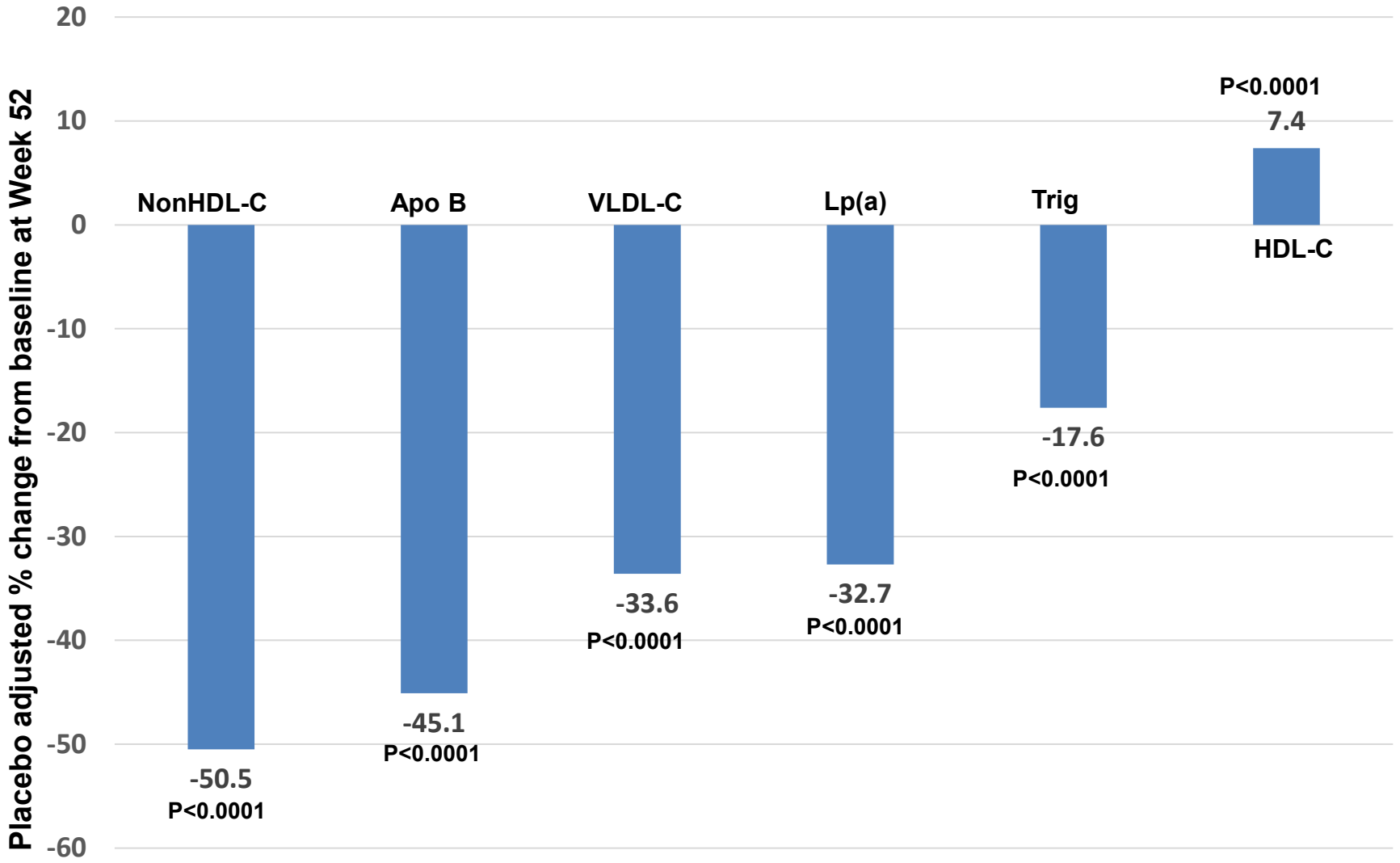
Percent achieving EAS/ESC recommended ≥50% reduction in LDL-C *and* LDL-C Targets with Lerodalcibep Compared to Placebo During the Study: ITT analysis



Waterfall plot of LDL-C Change from baseline at Week 52: mITT population



Additional Lipid and Apolipoproteins Placebo Adjusted LS mean change from Baseline: Week 52 - ITT Analysis



Adverse events and key safety laboratory findings: Safety Population

	Placebo (N=305)	Lerodalcibep (N=616)	Risk Difference (95% CI)
Adverse events- n (%)			
Patients with at least one adverse event	252 (82.6)	479 (77.8)	-4.9 (-10.2, 0.5)
Adverse event leading to withdrawal of study drug	11 (3.6)	26 (4.2)	
Serious adverse events			
Patients with at least one serious adverse event	45 (14.8)	98 (15.9)	
Death	3 (1.0)	3 (0.5)	
Cardiovascular deaths	1 (0.3)	2 (0.3)	
Cancer deaths	1 (0.3)	0	
Other cardiovascular adverse events			
Prespecified exploratory cardiovascular events	14 (4.6)	23 (3.7)	
Fatal and non-fatal myocardial infarction	3 (1.0)	3 (0.5)	
Fatal and non-fatal stroke	2 (0.7)	3 (0.5)	
Frequent adverse events			
COVID-19	34 (11.1)	72 (11.7)	0.54 (-3.8, 4.9)
Upper respiratory tract infection	26 (8.5)	49 (8.0)	-0.57 (-4.4, 3.2)
Hypertension	22 (7.2)	43 (7.0)	-0.23 (-3.8, 3.3)
Nasopharyngitis	16 (5.2)	43 (7.0)	1.73 (-1.5, 5.0)
Urinary tract infection	17 (5.6)	36 (5.8)	0.27 (-2.9, 3.4)
Diarrhoea	20 (6.6)	29 (4.7)	-1.85 (-5.1, 1.4)
Injection site reaction (ISR) N(%) of subjects*	6 (2.0)	33 (5.4)	4.2 (-1.7, 6.7)
Total ISR events (% of doses)	0.2%	1.2%	
Study discontinuations due to ISR (%)	0	1 (0.2)	
Laboratory results – n (%)			
Liver Function ALT or AST >3x ULN	1 (0.3)	1 (0.2)	
AST or ALT > 5x ULN	2 (0.7)	1 (0.2)	
Muscle CK>5xULN	6 (2.0)	12 (2.0)	

Immunogenicity:

- Low levels transient and sporadic ADAs
- In-vitro NAbs in 0.9% ***not associated*** with;
  - ISRs
  - Any attenuation in PCSK9 or LDL-C lowering efficacy.

*All ISRs graded as mild or moderate

Summary

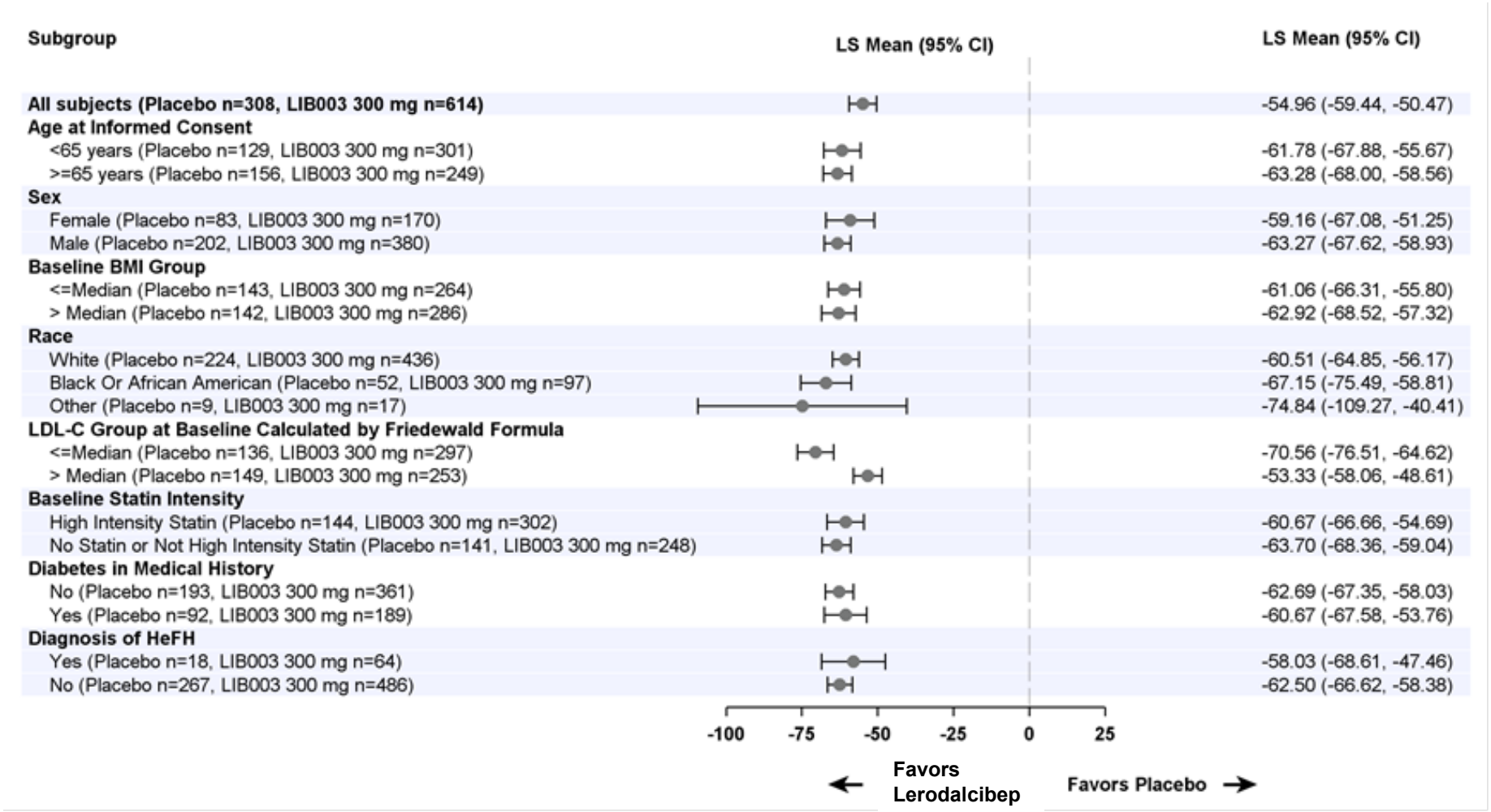
- Lerodalcibep decreased LDL-C; **62% at W52 (1.61 mmol/L),** and **69.4% at mean W50 and W52 (1.81 mmol/L);**
- On Lerodalcibep **≥90% CVD or, VHR for CVD patients** on maximally tolerated statins ***achieved both the new more stringent EAS/ESC targets.***
- Lerodalcibep reduced non-HDL-C 50%, Apo B 45%, Lp(a) 33%
- Lerodalcibep was well tolerated;
  - ✓ with adverse events similar to that with placebo:
  - ✓ ISRs, mild to moderate, no difference in overall discontinuations due to treatment adverse events [lerodalcibep (4.2%) - placebo (3.6%)]
- Lerodalcibep was not associated with in-vivo active ADAs or NAbs that attenuate either free PCSK9 suppression or LDL-C efficacy.

Conclusion

- **Lerodalcibep offers a novel, effective alternative to current PCSK9 inhibitors for patients with CVD or at very high risk for CVD:**
  - Substantial additional LDL-C reductions on top of existing oral agents
  - Ability for >90% of patients to achieve the new ESC guideline targets
  - Further robust reductions in all atherogenic lipids and lipoproteins
  - Tolerability and safety similar to placebo
  - A monthly, small (1.2 mL), SC dose and
  - Long ambient stability for patient home use

Thank You

Forest plot of LDL-cholesterol reduction in different subgroups : ITT analysis with imputation



Free (unbound) PCSK9:
Weeks 24 and 52 Change from Baseline Lerodalcibep Treated Group