#AHA24

LONG-TERM EFFICACY OF LERODALCIBEP IN 1,468 PATIENTS WITH, OR AT VERY HIGH AND HIGH RISK FOR, CVD IN THE 72 WEEK OPEN-LABEL EXTENSION TRIAL

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American Heart Association.

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DISCLOSURES

Dean J Kereiakes reports grants to his institution from LIB Therapeutics during the conduct of the study; and has received research grants, honoraria, or consulting fees for professional input and/or delivered lectures from Edwards Life Sciences, Elixer Medical, Orchestra Biomed Inc., Shockwave, J.C. Medical, Inc.

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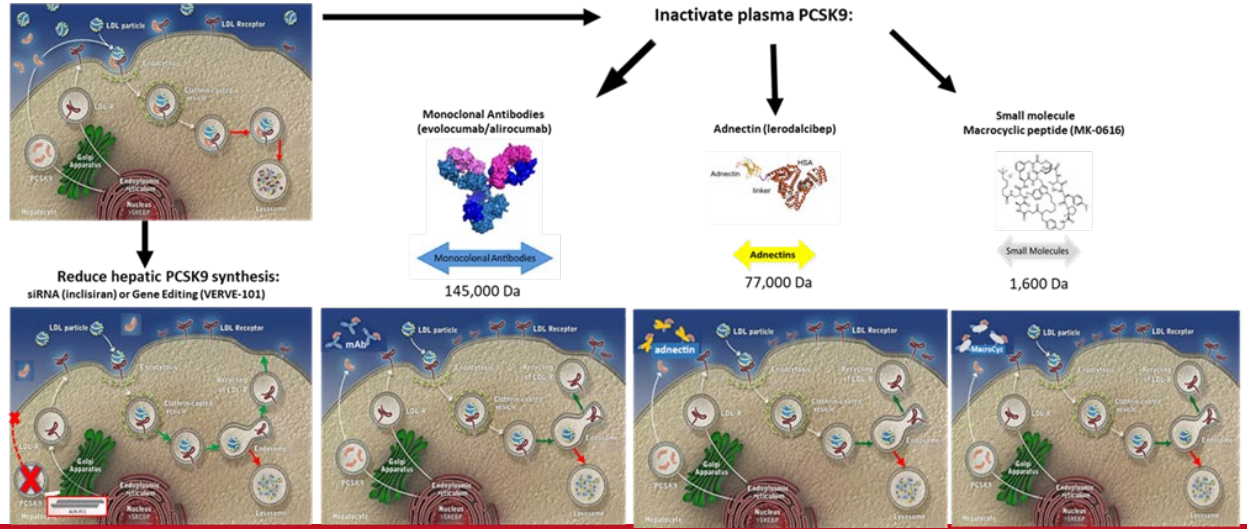
LERODALCIBEP: MECHANISM OF ACTION

- Lerodalcibep consists of a highly potent 11kDa PCSK9-binding domain (Adnectin), derived from human fibronectin, fused with human serum albumin (HSA) extending plasma half-life to 12-15 days with prolonged stability at ambient temperature. The small size (77kDa) reduces *monthly* injection volume for 300 mg to 1.2 mL while maintaining similar LDL-C lowering efficacy to mAbs.

- Similar to mAbs, lerodalcibep binds PCSK9 in the circulation, inactivates PCSK9 binding to LDLRs, preventing LDLR degradation, increasing LDLR recycling, enhancing LDL-C clearance, and lowering LDL-C levels.



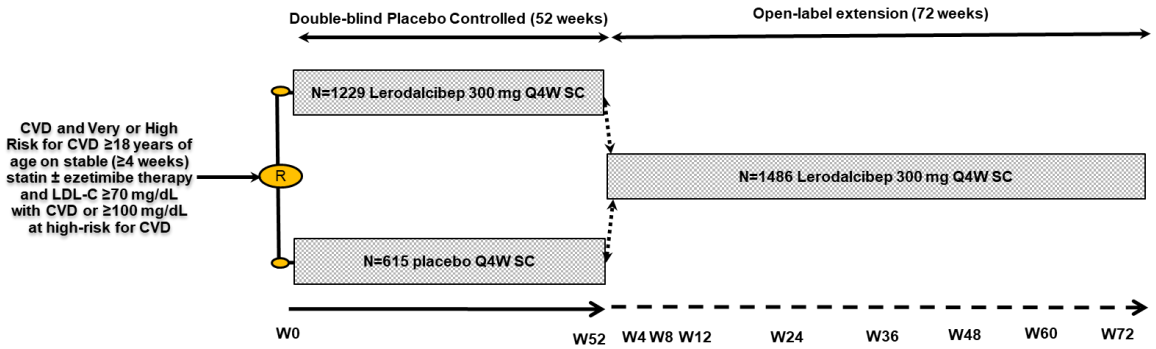
BACKGROUND AND RATIONALE

- Recently revised guidelines for LDL-C in patients with cardiovascular disease (CVD) or at very-high or high risk for CVD, recommend further large reductions plus lower targets if not attained with statins[1].
  - For patients with, or at very-high risk for, CVD the target is an absolute LDL-C of <55mg/dL (1.4 mmol/L), *plus* ≥50% reduction in LDL-C from current baseline.
  - For patients at high-risk for CVD the target is an absolute LDL-C of <70mg/dL (1.8 mmol/L), *plus* ≥50% reduction in LDL-C from current baseline
- Lerodalcibep, dosed SC 300 mg (1.2 mL) QM, reduced placebo-adjusted LDL-C by a mean of 59.1% in the 52-week Phase 3 LIBerate CVD and HR base trials[2] with good tolerability, safety and no in-vivo neutralizing antibody (NAb) activity.
- However, as lerodalcibep is a novel biologic designed for long-term LDL-C reduction, and based on substantial attenuation of LDL-C efficacy with a prior mAb due to NAbs, even longer assessment of exposure is deemed important.
- The open label extension (OLE) trial[3] assessed LDL-C efficacy for a further 72 weeks, in CVD & HR subjects from 2 base trials who either switched from placebo to, or continued on, lerodalcibep and provides >2-years of continuous treatment in ~1,000 patients.

1. Mach F, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41(1):111-88.
2. Protocols: base trials (NCT04806893, NCT04797247) 3. OLE trial (NCT04798430)

METHODS

- **Study Design**



- The study was conducted in **11 countries and 76 clinical sites**
- **Eligible and consented (OLE) subjects received lerodalcibep 300mg SC immediately on completing, or <28 days of, the final base study visit**, then monthly in clinic for 3 months and every 3 months thereafter and were able to self-dose between visits.
- **Of 1655** (89.8%) **patients**, 1096 on lerodalcibep, 559 on placebo, **who completed week 52 of the base trials, 1486 (90%) continued in the ongoing OLE** with **1397 (94%) and 880 (60%) now at W48 and W72 respectively**
- The **primary efficacy endpoints were percent and absolute LDL-C reduction after 48 and 72 weeks of OLE treatment.**
- **Secondary endpoints included changes in LDL-C at all clinic visits, Apo B, Lp(a), achievement of current LDL-C targets for high or very-high risk for CVD, and safety measures.**

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	All Subjects (N=1486)
Age (yrs) mean (range) **Sex**; female (%)/**male** (%)	**63.9** (25-89) 550(37%)/936 (**63%**)
Race: **White**	1158 (**79.5%**)
Black/African-American/Multiracial	275 (18.5%)
S. Asian	51 (3.4%)
Ethnicity: Hispanic	110 (7.4%)
Body mass index (kg/m^2) mean (range)	30.1 (17.9-42.2)
Diabetes mellitus	581 (**39.1%**)
CVD (secondary prevention)	**998 (67.2%)**
Very high risk for CVD (primary prevention)	**356 (24.0%)**
High risk for CVD (primary prevention)	132 (**9.4%**)
Any statin	**1271 (85.5%)**
High intensity statin	697 (46.9%)
Ezetimibe	**264(17.8%)**

BASELINE LIPID AND LIPOPROTEINS

Baseline lipids; mean(SD)*	
Total-cholesterol mg/dL	186.8 (46.4)
Triglycerides mg/dL	149.4 (74.2)
LDL-C (Friedewald) mg/dL	**108.8 (40.8)**
LDL-C (ultracentrifugation) mg/dL	108.7 (38.9)
LDL-C (Hopkins) mg/dL	112.7 (40.3)
HDL-C mg/dL	48.2 (14.5)
Non HDL-C mg/dL	138.6 (45.4)
Apolipoprotein B mg/dL	**99.6 (27.3)**
Lipoprotein(a) nmol/L (mean/median)	**106.1/49**

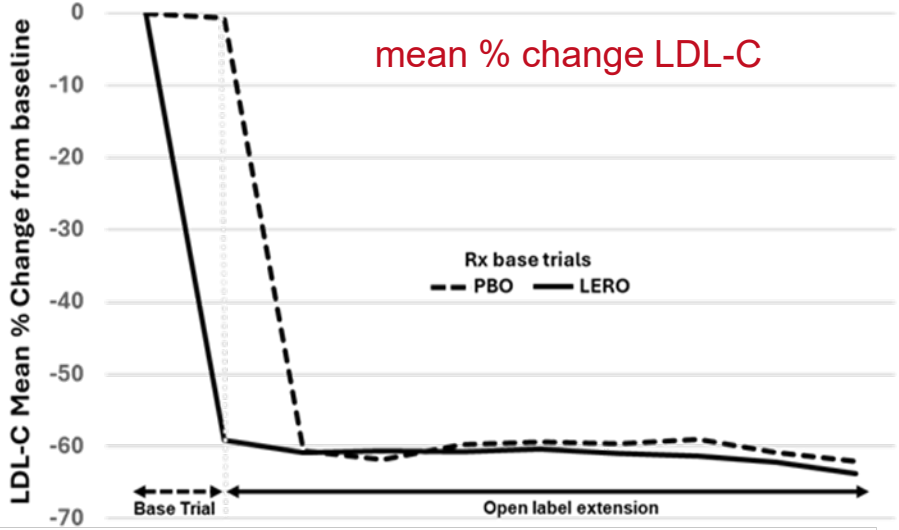
* Baseline is defined as Day 1 of the base trials

RESULTS: CHANGES IN KEY LIPID PARAMETERS THROUGH 72 WEEKS

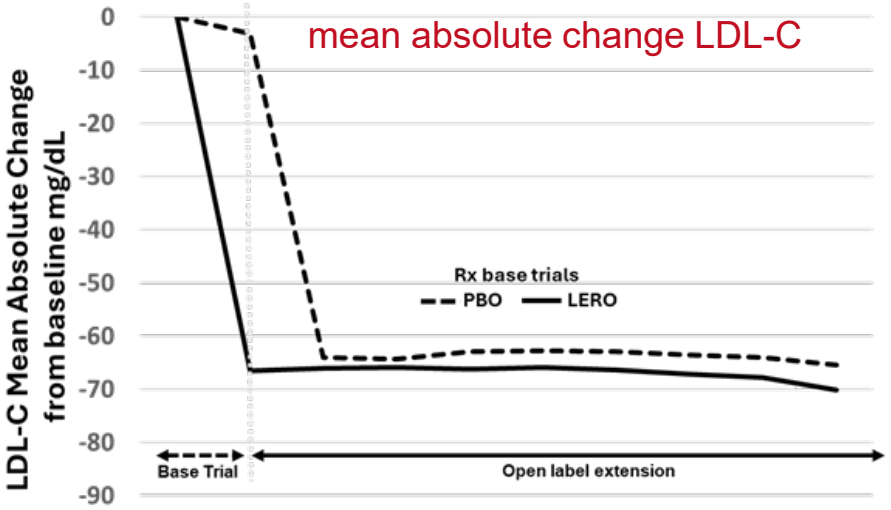
	Baseline	W4	W8	W12	W24	W36	W48	W60	W72
Number per visit	1486	1471	1467	1455	1440	1422	1397	1151	880
LDL-C$^{\Phi}$ mean; mg/dL	108.8	42.4	42.4	42.7	42.8	42.8	42.4	41.6	41.0
absolute change; mg/dL		-66.3*	-66.5*	-66.2*	-65.8*	-66.3*	-67.0*	-67.7*	-68.3*
mean % change		-61.3*	-61.6*	-61.1*	-60.7*	-61.2*	-61.4*	-62.5*	-62.8*
Apo B mean; mg/dL	99.4						54.6		53.2
absolute change; mg/dL							-45.4*		-45.7*
mean % change							-45.0*		-45.8*
Non-HDL-C mean % change	137.6	-50.4*	-50.3*	-49.9*	-49.5*	-49.9*	-50.7*	-51.6*	-52.1*
Triglyceride median % change	149.9	-19.0	-6.5	-7.4	-6.0	-6.5	-6.4	-6.5	-6.7
HDL-C mean % change; mg/dL	48.7	9.6*	9.7*	10.2*	11.4*	11.4*	13.6*	13.6*	14.3*
Lp(a) median % change; nmol/L	49.0						-30.0*		-32.4*

$^{\Phi}$Friedewald formula *P<0.0001

PERCENT AND ABSOLUTE LDL-C CHANGE (FRIEDEWALD) FROM BASELINE IN BASE TRIAL AT EACH OLE VISIT: BY TREATMENT IN BASE TRIALS (ITT POPULATION)



# pts	Base W0	Base W52	OLE W4	OLE W8	OLE W12	OLE W24	OLE W36	OLE W48	OLE W60	OLE W72
PBO	490	490	482	481	478	473	468	460	386	299
LIB	996	996	989	986	977	967	954	937	765	581
Total	1486	1486	1471	1467	1455	1440	1422	1397	1151	880



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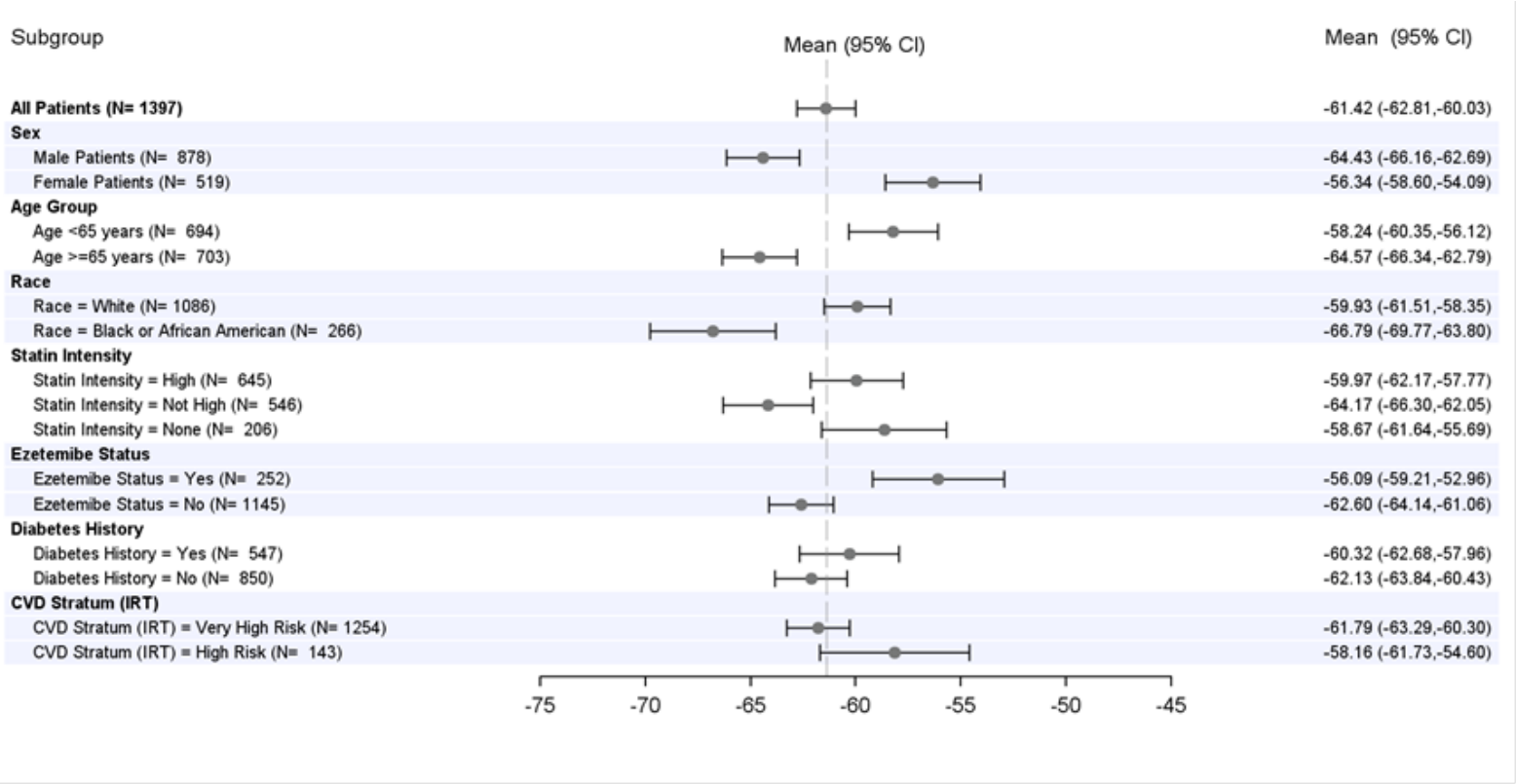
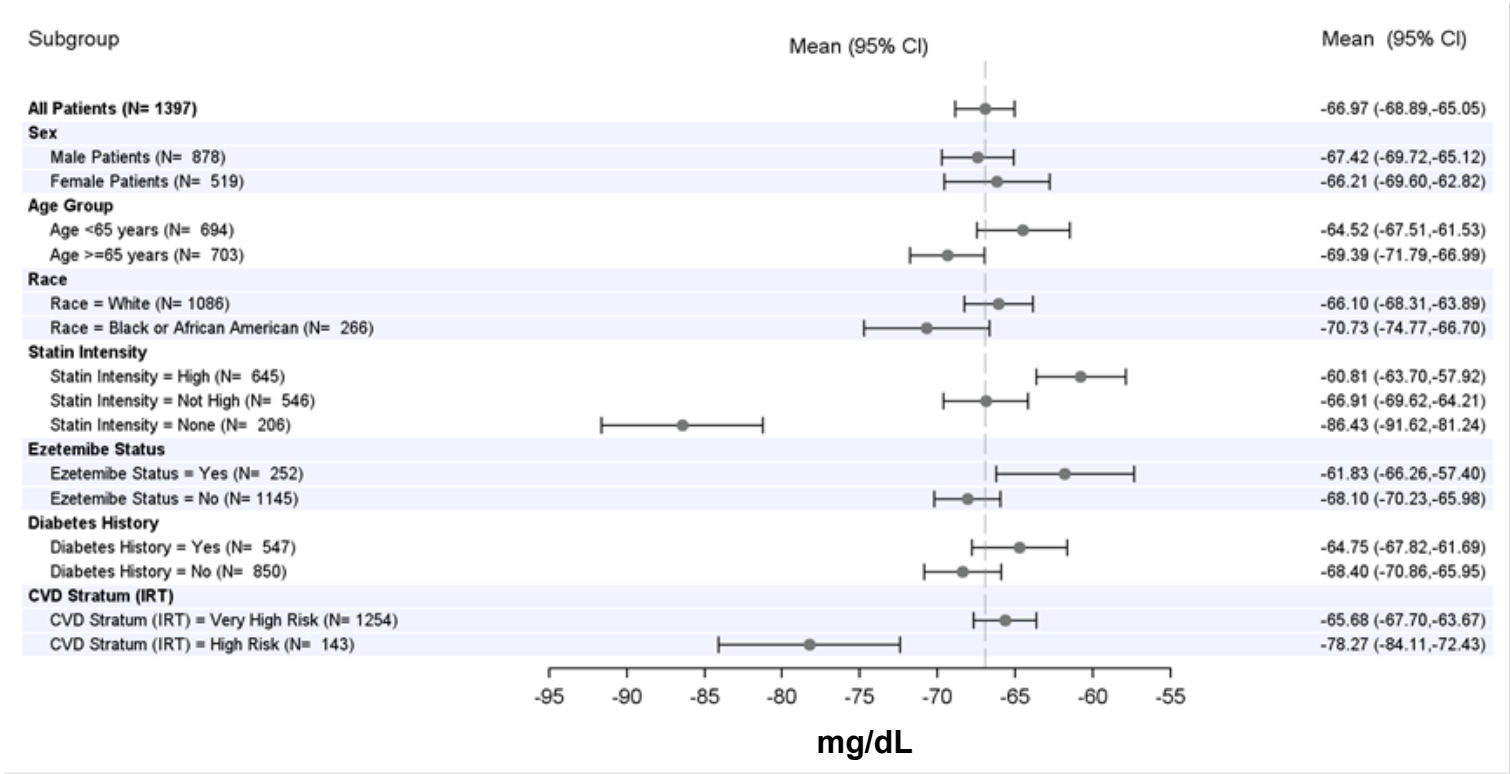
FOREST PLOT SHOWING PERCENT (%) LDL-C REDUCTION WITH LERODALCIBEP IN DIFFERENT SUBGROUPS: WEEK 48*



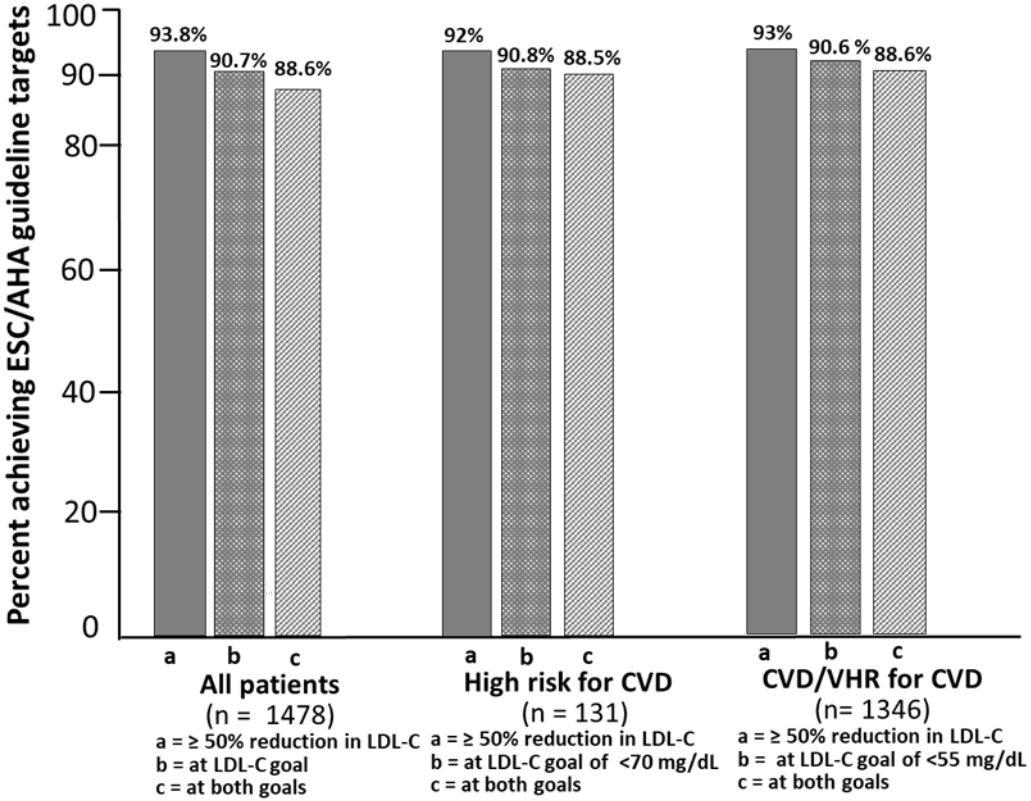
relative to mean LDL-C % reduction for all patients

FOREST PLOT SHOWING ABSOLUTE (mg/dL) LDL-C REDUCTION WITH LERODALCIBEP IN DIFFERENT SUBGROUPS: WEEK 48*



*relative to mean absolute LDL-C reduction for all patients

PERCENT ACHIEVING A ≥50% REDUCTION IN LDL-C AND CURRENTLY RECOMMENDED LDL-C TARGETS



ADVERSE EVENTS AND KEY SAFETY LABORATORY FINDINGS

Adverse events- n (%)	**All Patients (N=1486)**
Patients with at least one adverse event	1116 (75.1)
Patients with at least one event leading to withdrawal of study drug	**19 (1.3)**
Serious adverse events	
Patients with at least one serious adverse event	255 (17.2)
Death	15 (1.0)
Cardiovascular deaths	5 (0.3)
Cancer deaths	1 (0.1)
Other cardiovascular adverse events	
Prespecified exploratory cardiovascular events Ω	55 (3.7)
Fatal and non-fatal myocardial infarction	20 (1.3)
Fatal and non-fatal stroke	5 (0.3)
Frequent adverse events ¥	
Urinary tract infections	146 (9.8)
Upper respiratory tract infection	145 (9.8)
COVID-19	122 (8.2)
Nasopharyngitis	112 (7.5)
Arthralgia	92 (6.2)
Injection Site Reactions: number patients (%)	**66/1478 (4.4%)**
number events as % total doses	**134/24,749 (0.6%)**
Laboratory results – n (%)	
Liver Function ALT >3x ULN	4 (0.3)
AST > 3x ULN	3 (0.2)
Muscle CK>5xULN	19 (1.3)
Haematology Platelet count < $75x10^9$ /L	2 (0.1)

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.**

*Safety population includes all patients in the OLE study and adverse events over 72 weeks. Ω MedDRA-defined CV basket of non-adjudicated terms including those classified within cardiac death, and any signs or symptoms of cardiac arrest, non-fatal MI and/or stroke ¥ Defined as occurring with a frequency of 5% or more

SUMMARY

- Lerodalcibep 300mg SC monthly, added to maximally tolerated oral lipid-lowering therapy, maintained 60+% reductions in LDL-C through 72 weeks with no signals of attenuation even with treatment for >2 years
- Lerodalcibep resulted in ~90% of patients achieving both a reduction in LDL-C of ≥50% and the recommended LDL-C targets for those with CVD or high-risk for CVD during the 72 weeks.
- Lerodalcibep reduced mean Apo B by 45% and median Lp(a) by 30-32%.
- Lerodalcibep was equally effective in all subgroups, including females and minorities, when adjusted for baseline LDL-C
- Lerodalcibep was well tolerated over 72 weeks with <1% of doses associated with mild or moderate ISRs and <2% of subjects terminating the trial due to side effects and with no new safety concerns.
- These results support the long-term use of monthly lerodalcibep for the management of subjects with CVD, or at very-high or high risk of CVD, unable to achieve LDL-C target with standard oral lipid-lowering therapy.
- Lerodalcibep offers the potential for improved long-term adherence with only 12 doses per year, home dosing without the need for refrigeration by patients, maximal LDL-C reductions, good tolerability and safety

THANK YOU

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BACK-UP SLIDES

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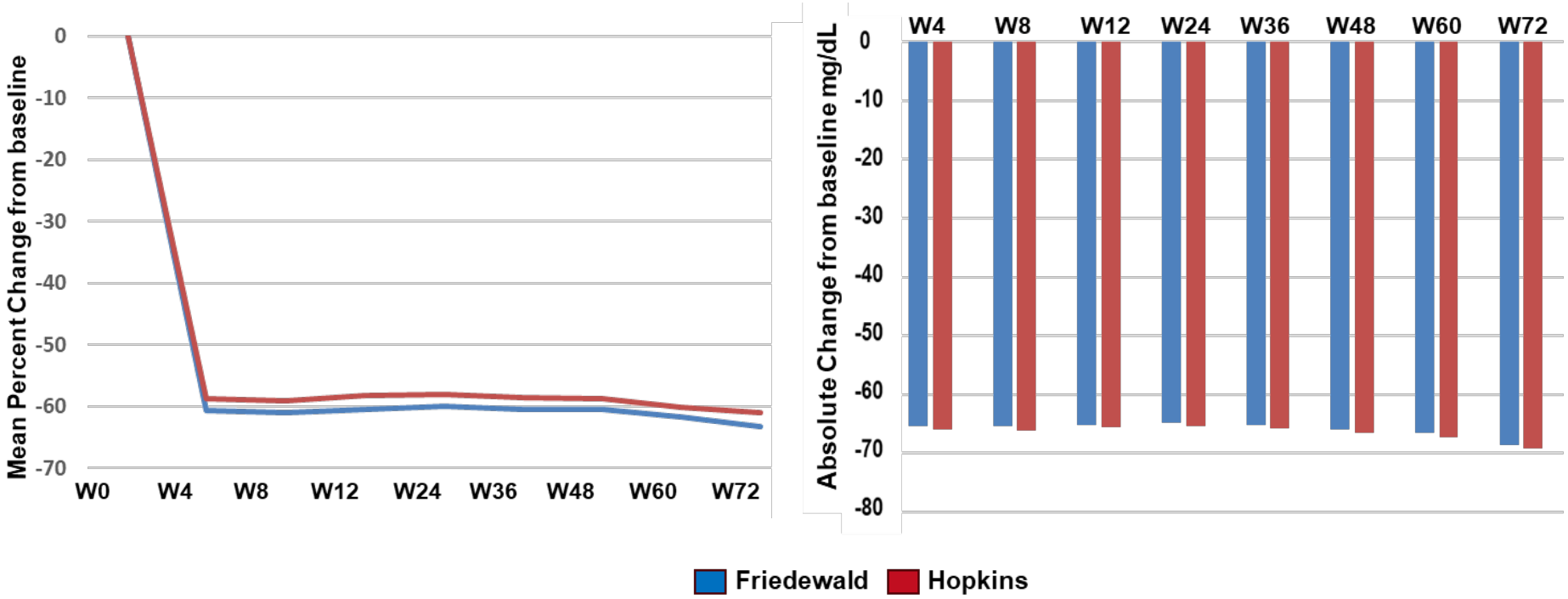
ABSOLUTE LDL-C CHANGE FRIEDEWALD VERSUS HOPKINS FROM BASELINE IN BASE TRIAL AT EACH VISIT DURING THE OPEN LABEL EXTENSION (OLE) – ITT POPULATION



PERCENT OF PATIENTS ACHIEVING ≥50% REDUCTION IN LDL-C AND LDL-C TARGETS: BY FRIEDEWALD AND HOPKINS