#AHA24

EFFICACY AND SAFETY OF LERODALCIBEP, A THIRD GENERATION PCSK9 INHIBITOR, IN 703 HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA SUBJECTS FROM THE OPEN LABEL EXTENSION TRIAL

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American Heart Association.

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DISCLOSURES

Professor Frederick J. Raal reports grants 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 Amgen, MSD, Novartis, Sanofi, Regeneron, Ultragenyx, Chiesi and LIB Therapeutics.

This study was funded by LIB Therapeutics.

BACKGROUND AND RATIONALE

- **FH is a genetic disorder affecting ~1 in 300 or over 30 million people worldwide**
  - Life-long elevated LDL-C, starting at birth, drives early onset, accelerated atherosclerotic cardiovascular disease (ASCVD) in FH.[1]
  - Untreated, or under treated, FH is frequently associated with the onset of ASCVD in the 4th or 5th decade, thus it is imperative to initiate effective LDL-C reduction to achieve guideline directed targets as early as possible.[2]
  - For FH patients with ASCVD, or an additional ASCVD risk factor, the target is an absolute LDL-C of < 55mg/dL (1.4 mmol/L), plus at least a 50% reduction in LDL-C from current baseline.[3]
  - For FH patients without ASCVD, or an additional risk factor, the target is a LDL-C of <70 mg/dL (1.8 mmol/L) together with a reduction of ≥50% from current baseline.[3]

1. Ference BA et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. *Eur Heart J* 2017;38(32):2459-72.
2. Vallejo-Vaz AJ et al . Global perspective of familial hypercholesterolaemia. *Lancet* 2021;398:1713-1725.
3.. 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.

BACKGROUND AND RATIONALE

Management is prevention of ASCVD through LDL-C lowering with high intensity statins, ezetimibe and/or other oral lipid lowering agents.

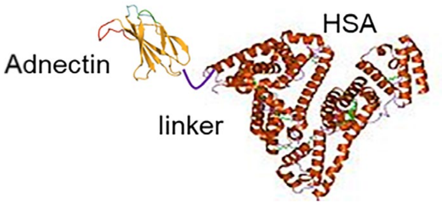
- Despite oral therapy, the majority of FH patients fail to achieve sufficient LDL-C reduction and additional therapies are required.
- PCSK9 directed therapies provide the best opportunity to achieve these targets.
- Lerodalcibep is a novel small binding protein PCSK9 inhibitor administered SC 300mg monthly (QM) in a small volume of 1.2mL.
- In the 24 week placebo-controlled LIBerate-HeFH trial in 478 subjects, lerodalcibep lowered placebo adjusted LDL-C by 58% and 51% from baseline.[1]
- In an ongoing open label extension trial, LIBERATE-OLE, 800 subjects identified as having HeFH* in five Phase 3 trials of 12 to 52 week duration, were evaluated for an additional 72 weeks to assess longer-term efficacy and safety of lerodalcibep.

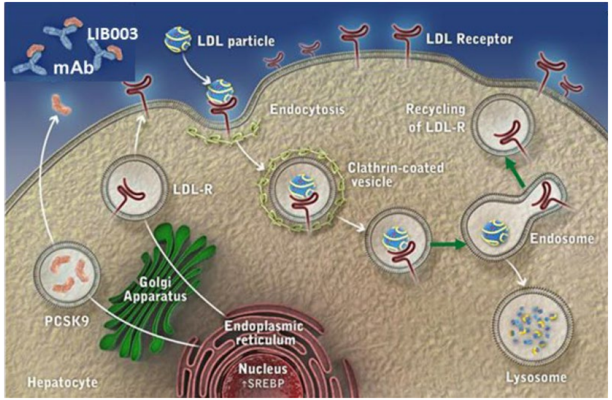
*By clinical phenotype (DLC or SB criteria) or genotype

[1]Raal F, et al. Long-term efficacy and safety of lerodalcibep in heterozygous familial hypercholesterolemia; the LIBerate-HeFH trial. *Eur Heart J* 2023;44:4272-4280

LERODALCIBEP (LIB-003)

- **Lerodalcibep** is a small binding protein (SBP) alternative to monoclonal antibodies, consisting of an 11kDa PCSK9-binding domain (Adnectin), derived from human fibronectin, fused with human serum albumin (HSA) to extend plasma half-life to 12 to 15 days.

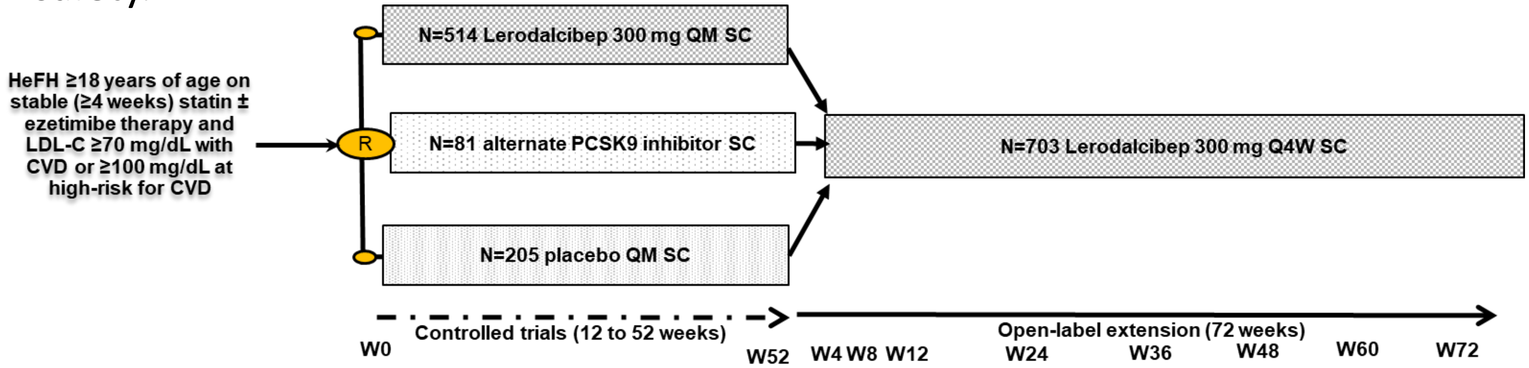




- Similar to mAbs, Lerodalcibep binds to PCSK9, blocks the interaction between PCSK9 and LDLR, preventing LDLR degradation, increasing LDLR recycling, enhancing LDL-C clearance, and lowers LDL-C levels.
- Prolonged stability at ambient temperature, small size (77kDa) and high solubility allows for a smaller injection volume than mAbs to achieve stable and prolonged LDL-C reductions between injections.

LIBERATE-OLE FH STUDY: METHODS

- Of 800 FH subjects randomized to five phase 3 studies of 12 to 52 weeks duration, 703 (88%) completed the final visit of each base trial and continued in a 72 week open-label extension (OLE) study in order to assess longer-term LDL-C efficacy and safety.



- Subjects signed IC immediately on, or within 28 days of, completing the final base study visit, and received lerodalcibep 300 mg SC monthly in clinic for 3 months and 3 monthly thereafter and were able to self-dose between the 3 monthly clinic visits.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	All HeFH Subjects (N=703)
Age (yrs); mean (range) Sex; female (%)/male (%)	53.8 (18-80) 331(47.1%)/372 (52.9%)
Race: White Asian/multiracial/Black	617 (87.8%) 86 (12.2%)
Body mass index (kg/m^2); mean (range)	29.0 (17.6-42.9)
Diabetes mellitus	97 (13.8%)
CVD Risk: Established ASCVD	291 (41.4%)
Very high risk for ASCVD	217 (30.9%)
High risk for ASCVD	195 (27.7%)
Background Treatment: Any statin	636 (90.5%)
High intensity statin	500 (71.1%)
Ezetimibe	362 (51.5%)

BASELINE LIPIDS: MEAN (SD) OR MEDIAN

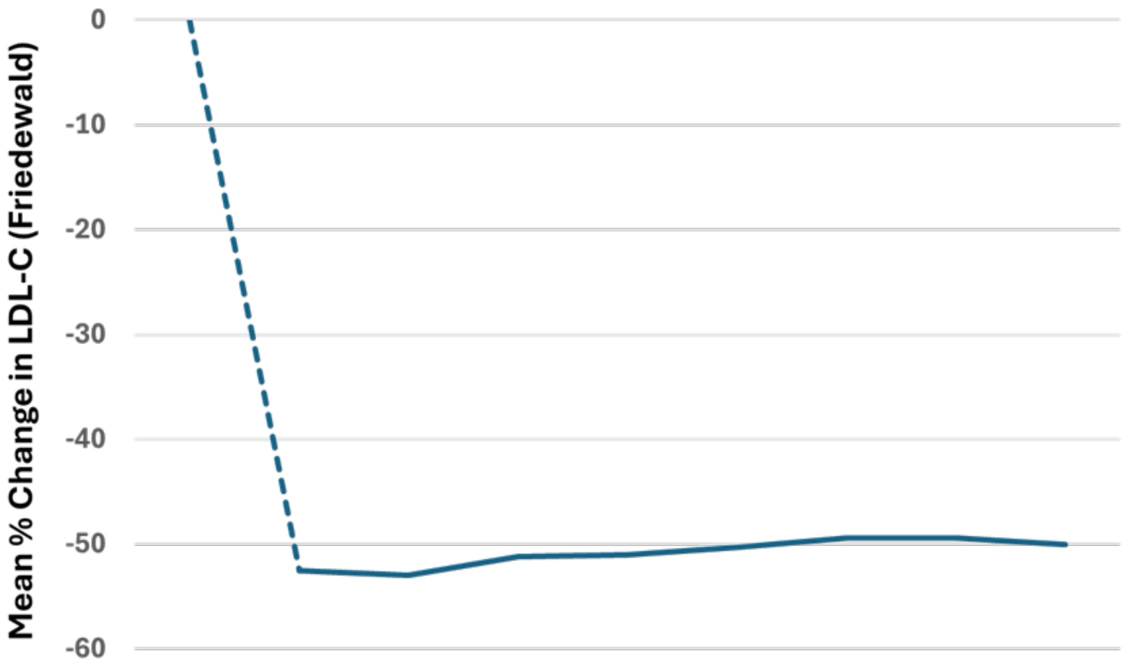
Total-cholesterol mg/dL	222.9 (66.2)
Triglycerides mg/dL	138.3 (84.5)
LDL-C (Friedewald) mg/dL	**144.9 (61.9)**
LDL-C (ultracentrifugation) mg/dL	142.8 (58.7)
LDL-C (Hopkins) mg/dL	146.7 (61.9)
HDL-C mg/dL	50.4 (16.0)
Non HDL-C mg/dL	172.5 (67.4)
Apolipoprotein B mg/dL	**119.9 (39.3)**
Lipoprotein(a) nmol/L (mean/median)	115.6/55.0

RESULTS: CHANGES IN KEY LIPID PARAMETERS THROUGH 72 WEEKS

	Baseline	W4	W8	W12	W24	W36	W48	W60	W72
	703	696	697	690	683	675	651	606	572
LDL-C (Friedewald) mean; mg/dL	144.9	69.2	68.6	70.7	69.8	70.3	71.7	71.7	72.8
absolute change; mg/dL		-75.2*	-75.8*	-73.8*	-73.9*	-73.5*	-72.3*	-72.1*	-71.9*
mean % change		-52.5*	-53.0*	-51.2*	-51.1*	-50.8*	-49.8*	-49.8*	-49.5*
LDL-C (Hopkins) mean; mg/dL	146.7	72.2	71.5	73.6	72.9	73.2	74.6	74.9	75.9
absolute change; mg/dL		-74.3*	-74.8*	-72.7*	-72.8*	-72.4*	-71.4*	-70.6*	-70.7*
mean % change		-51.1*	-51.5*	-49.7*	-49.6*	-49.3*	-48.5*	-48.2*	-48.0*
Apo B mean; mg/dL	119.9						74.2		74.9
absolute change; mg/dL							-44.9*		-44.0*
mean % change							-36.6*		-36.1*
Non-HDL-C mean % change	172.5	-45.6*	-45.9*	-44.2*	-44.0*	-43.8*	-43.2*	-43.2*	-42.6*
Triglyceride median % change	114.0	-11.0	-13.2	-10.3	-8.8	-11.9	-8.3	-7.1	-7.6
HDL-C mean % change; mg/dL	50.4	10.1*	11.5*	12.2*	12.2*	12.0*	11.6*	12.5*	13.1*
Lp(a) median % change; nmol/L	55.0						-24.4*		-26.8*

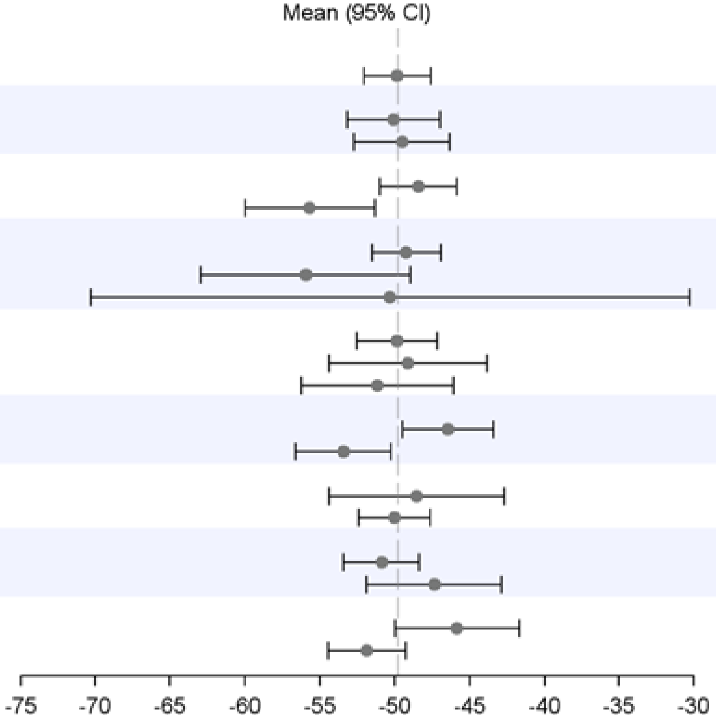
* P<0.0001

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



Baseline	W4	W8	W12	W24	W36	W48	W60	W72
703	696	697	690	683	675	651	606	572

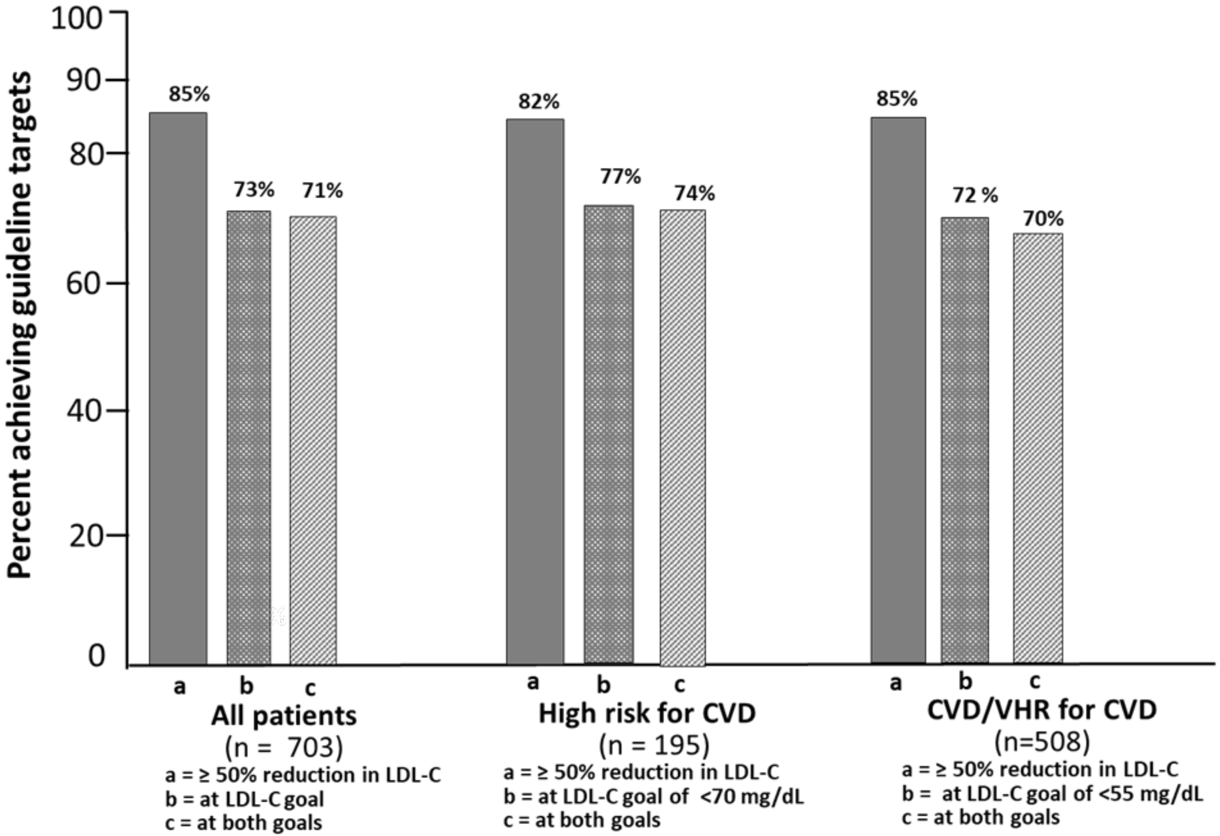
FOREST PLOT SHOWING PERCENT (%) LDL-C REDUCTION WITH LERODALCIBEP IN DIFFERENT SUBGROUPS*



Subgroup	Mean (95% CI)
All HeFH Patients (N= 651)	-49.84 (-52.07,-47.62)
Sex	
Male Patients (N= 345)	-50.12 (-53.24,-47.01)
Female Patients (N= 306)	-49.53 (-52.71,-46.34)
Age Group	
Age <65 years (N= 525)	-48.44 (-50.98,-45.89)
Age >=65 years (N= 126)	-55.70 (-60.02,-51.38)
Race	
Race = White (N= 571)	-49.25 (-51.52,-46.97)
Race = Black or African American (N= 51)	-55.98 (-62.97,-48.99)
Race = Asian (N= 27)	-50.32 (-70.35,-30.30)
Statin Intensity	
Statin Intensity = High (N= 462)	-49.86 (-52.56,-47.17)
Statin Intensity = Not High (N= 128)	-49.14 (-54.42,-43.86)
Statin Intensity = None (N= 61)	-51.18 (-56.26,-46.09)
Ezetemibe Status	
Ezetemibe Status = Yes (N= 337)	-46.46 (-49.51,-43.41)
Ezetemibe Status = No (N= 314)	-53.47 (-56.68,-50.26)
Diabetes History	
Diabetes History = Yes (N= 92)	-48.57 (-54.42,-42.72)
Diabetes History = No (N= 559)	-50.05 (-52.46,-47.65)
CVD Stratum (IRT)	
CVD Stratum (IRT) = Very High Risk (N= 454)	-50.91 (-53.43,-48.39)
CVD Stratum (IRT) = High Risk (N= 197)	-47.38 (-51.88,-42.88)
HeFH Genotype Confirmation	
HeFH Genotype Confirmed = Yes (N= 221)	-45.86 (-50.00,-41.71)
HeFH Genotype Confirmed = No (N= 430)	-51.89 (-54.49,-49.30)

* Week 48

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



ADVERSE EVENTS AND KEY SAFETY LABORATORY FINDINGS

Adverse events	Number (%) Total Patients 705
Patients with at least one adverse event	577 (81.4)
Patients with at least one event leading to withdrawal of drug	13 (1.8)
Total deaths, CV deaths, cancer deaths	8 (1.1); 6(0.9); 0(0)
Frequent adverse events (5% or more)	
Upper respiratory tract infection	134 (19.1)
COVID-19	77 (11.0)
Nasopharyngitis	81 (11.5)
Urinary tract infection	59 (8.4)
Arthralgia	42 (6.0)
ISRs number patients (%)	79/703 (11.2%)
number events/doses (%)	273/11,939 (2.3%)
Laboratory results	
Liver Function ALT or AST >3x ULN	3 (0.4)
AST or ALT > 5x ULN	2 (0.3)
Muscle CK> 5x ULN	15 (2.1)
Haematology Platelet count < $75x10^9$ /L	4 (0.6)

Immunogenicity

- Low levels of transient and sporadic ADAs
- In-vitro NAbs in <2% ***not associated*** with:
  - ISRs
  - Any attenuation in free PCSK9 or LDL-C lowering efficacy

ADAs = anti-drug antibodies
NAbs = neutralizing antibodies
ISR = injection site reactions

SUMMARY

- In HeFH patients, lerodalcibep 300mg SC QM, added to maximally tolerated oral lipid-lowering therapy, maintained a further consistent 50% reduction in LDL-C through an additional 72 weeks with no signals of attenuation even in those on treatment for >2 years.
- Lerodalcibep resulted in >80% of FH patients achieving ≥50% LDL-C reduction and ~70% achieving the recommended LDL-C targets for those with ASCVD or high-risk for ASCVD during the 72 weeks.
- Lerodalcibep reduced mean Apo B by 36% and median Lp(a) by 25%.
- Lerodalcibep was equally effective in all subgroups, including females, minorities and was independent of background oral lipid lowering treatment.
- Lerodalcibep was well tolerated over 72 weeks with only 2.3% of doses associated with mild or moderate ISRs and with no new safety concerns.
- These results support the long-term use of monthly lerodalcibep for the management of HeFH subjects unable to achieve LDL-C target with standard oral lipid-lowering therapy.
- Lerodalcibep requiring only 12 doses per year, home dosing without the need for refrigeration by patients, combined with robust LDL-C reductions, good tolerability and safety offers the potential for improved long-term adherence for life-long therapy needed in HeFH.

THANK YOU

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BACK-UP SLIDES

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

Subgroup	Mean (95% CI)
All HeFH Patients (N= 651)	-72.34 (-76.26,-68.43)
Sex	
Male Patients (N= 345)	-70.62 (-75.99,-65.25)
Female Patients (N= 306)	-74.29 (-80.01,-68.57)
Age Group	
Age <65 years (N= 525)	-71.65 (-76.20,-67.11)
Age >=65 years (N= 126)	-75.22 (-82.32,-68.12)
Race	
Race = White (N= 571)	-70.82 (-74.93,-66.71)
Race = Black or African American (N= 51)	-78.86 (-90.69,-67.04)
Race = Asian (N= 27)	-92.44 (-121.1,-63.76)
Statin Intensity	
Statin Intensity = High (N= 462)	-70.34 (-75.03,-65.64)
Statin Intensity = Not High (N= 128)	-64.27 (-71.98,-56.57)
Statin Intensity = None (N= 61)	-104.5 (-116.6,-92.39)
Ezetemibe Status	
Ezetemibe Status = Yes (N= 337)	-65.50 (-70.77,-60.23)
Ezetemibe Status = No (N= 314)	-79.69 (-85.40,-73.98)
Diabetes History	
Diabetes History = Yes (N= 92)	-63.52 (-73.56,-53.48)
Diabetes History = No (N= 559)	-73.80 (-78.03,-69.56)
CVD Stratum (IRT)	
CVD Stratum (IRT) = Very High Risk (N= 454)	-71.59 (-76.32,-66.86)
CVD Stratum (IRT) = High Risk (N= 197)	-74.08 (-81.03,-67.13)
HeFH Genotype Confirmation	
HeFH Genotype Confirmed = Yes (N= 221)	-65.50 (-72.06,-58.94)
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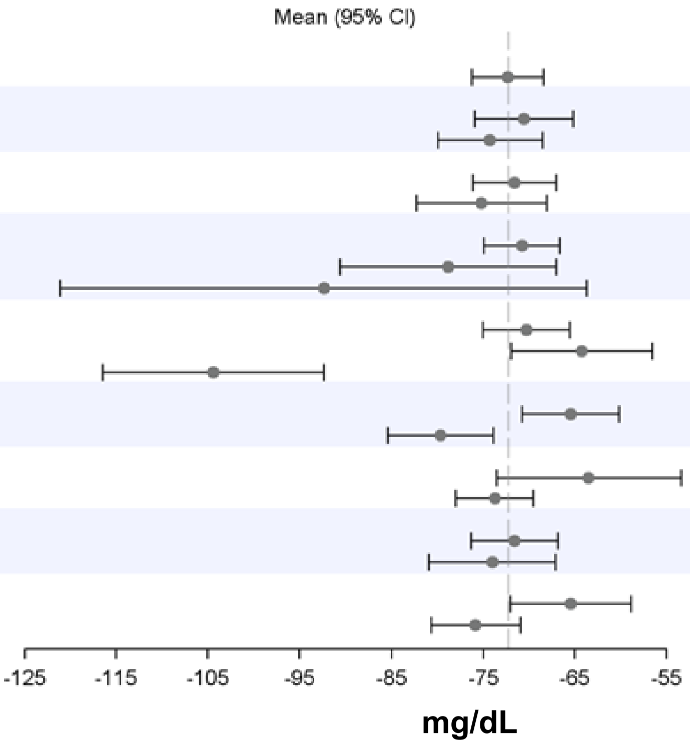
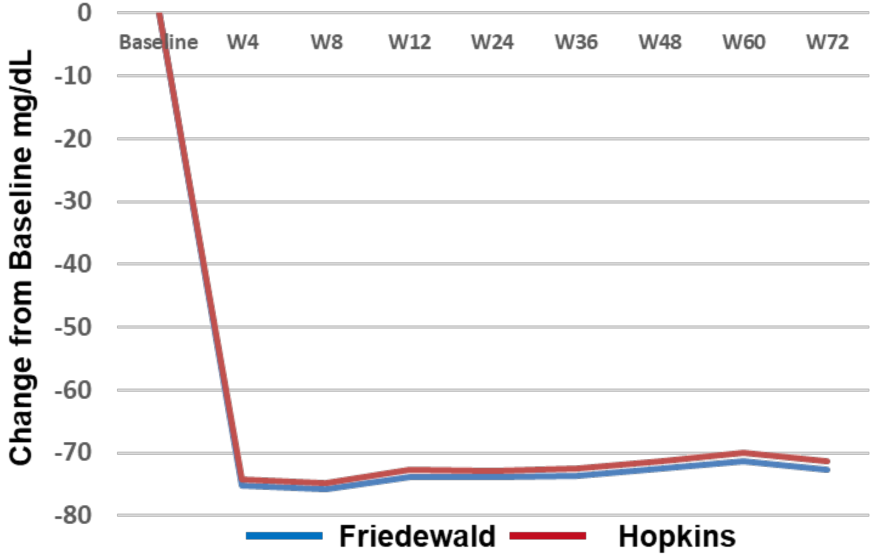
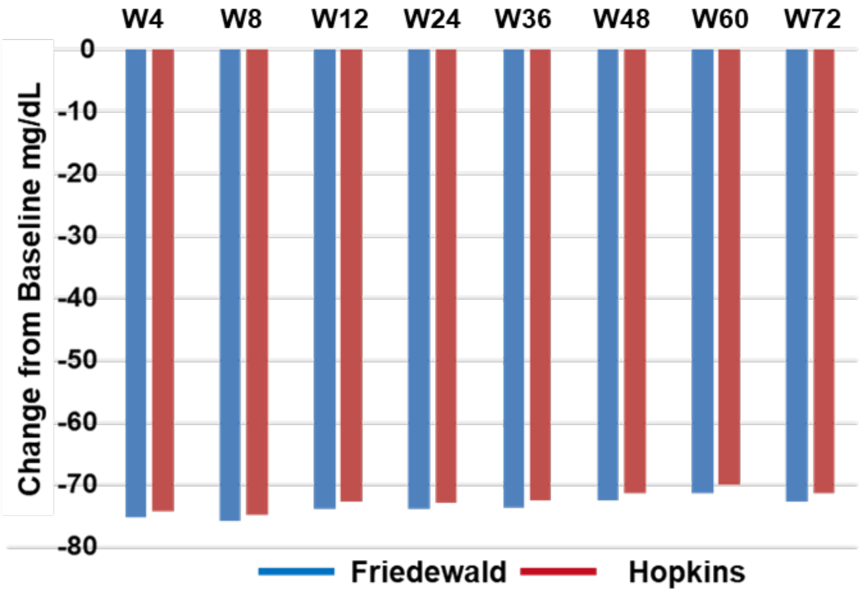


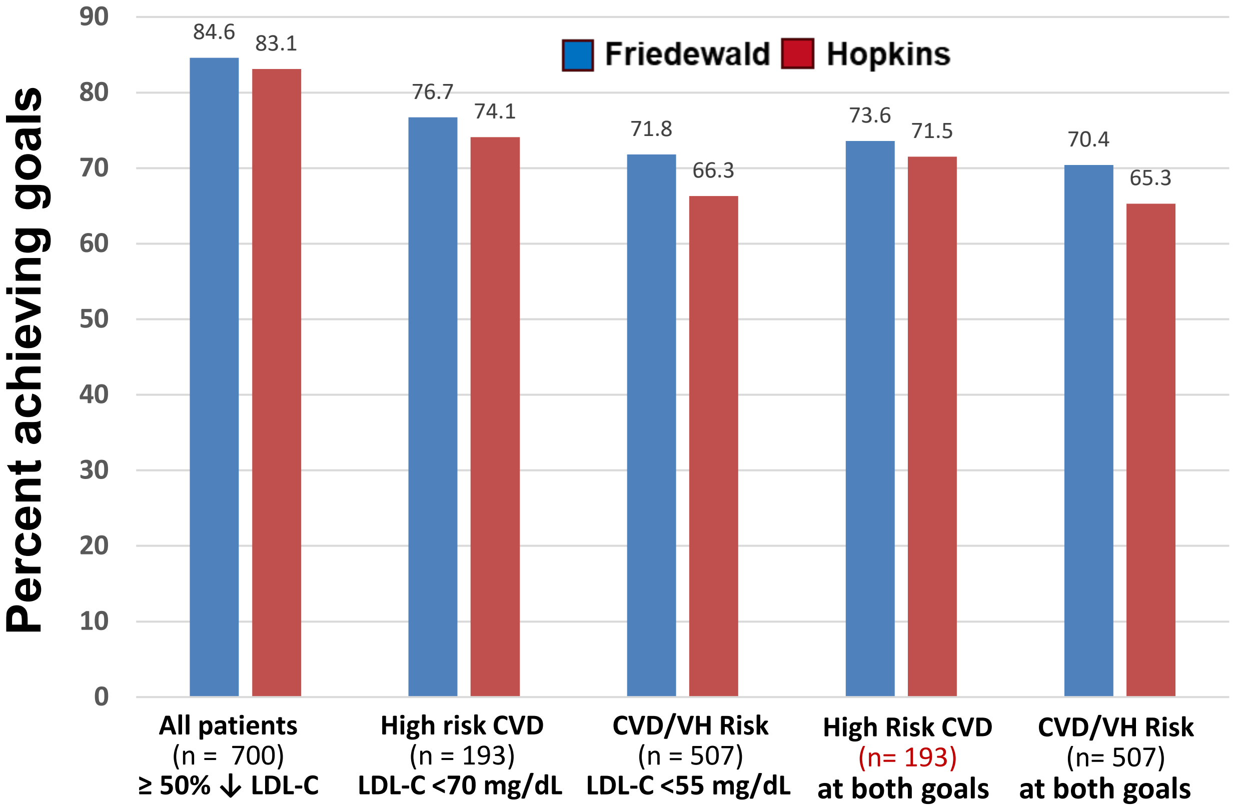
* Week 48

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



WATERFALL PLOT OF PERCENT CHANGE IN LDL-C (FRIEDEWALD) FROM BASELINE TO WEEK 72 WITH LERODALCIBEP IN INDIVIDUAL PATIENTS