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Randomized, Open-Label, Cross-Over, Phase 3 Study to Evaluate the Efficacy and Safety of LIB003 (Lerodalcibep) Compared with Evolocumab in Homozygous Familial Hypercholesterolemia Patients on Stable Lipid-Lowering Therapy (LIBerate-HoFH)

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Background

- HoFH is a rare but serious genetic disorder characterized by reduced hepatic clearance of LDL with resultant markedly elevated LDL-C levels resulting in early onset of atherosclerosis and accelerated ASCVD
- High-intensity statins together with ezetimibe form the foundation of lipid-lowering therapy for patients with HoFH and should be initiated at the time of diagnosis, but achieving LDL-C goals remains difficult
- LDL-C response to treatment with PCSK9 inhibitor mAbs in this population is effective but highly variable
- Recent studies in HoFH patients from India and other countries with novel pathogenic variants have shown substantially less response to PCSK9 inhibitor mAbs than prior studies[1] and a placebo-controlled trial with a siRNA showed minimal response[2]
- In addition, a post hoc analysis of paediatric HoFH subjects, has also shown less response than in adults with similar variants[3]

1. Bansal S et al, *J Clin Lipidol*. 2021;15:814-821.
2. https://clinicaltrials.gov/ct2/show/results/NCT03851705?term=inclisiran&draw=1&rank=19
3. Bruckert E et al. *Arterioscler Throm Vasc Biol* 2022 ;42 :1447-1457.

ASCVD, atherosclerotic cardiovascular disease; HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipid cholesterol; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9.

Objectives

- LIB-003 (Lerodalcibep), a small recombinant fusion protein of a PCSK9-binding domain (adnectin) and albumin, demonstrated highly effective PCSK9 and LDL-C suppression in Phase 2 studies.[1,2]
- The **LIBerate-HoFH** global Phase 3 trial, including India, Turkey and 32% paediatric participants, evaluated safety and efficacy of lerodacibep 300 mg SC QM compared to evolocumab (EVO) 420 mg SC QM in patients with genetically confirmed HoFH on stable lipid lowering therapy not receiving lipoprotein apheresis.

1 Stein, E. et al. *Atherosclerosis* 2019;287;e7.
2. Stein, E. A. et al. *Circulation* 2019;140 (Suppl. 1), A17222.

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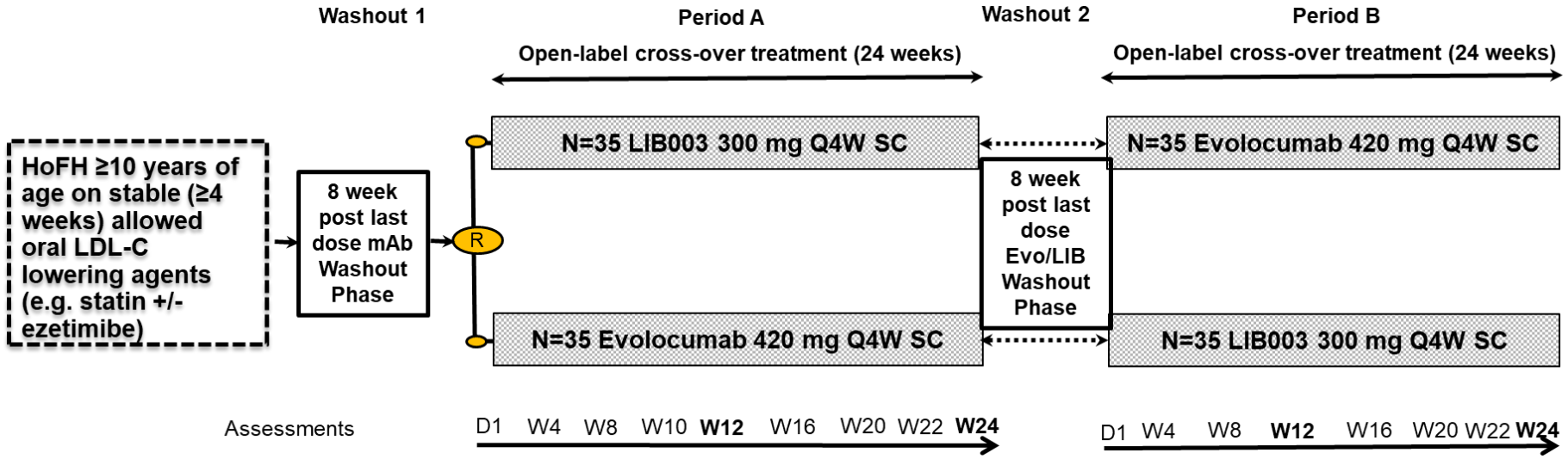
Methods

- Eligible patients (age ≥10 years) were randomized to either Lerodalcibep or Evolocumab for 24 weeks (Period A) followed by an 8-week washout and crossed over to the alternate therapy for the next 24 weeks (Period B).

Study Design



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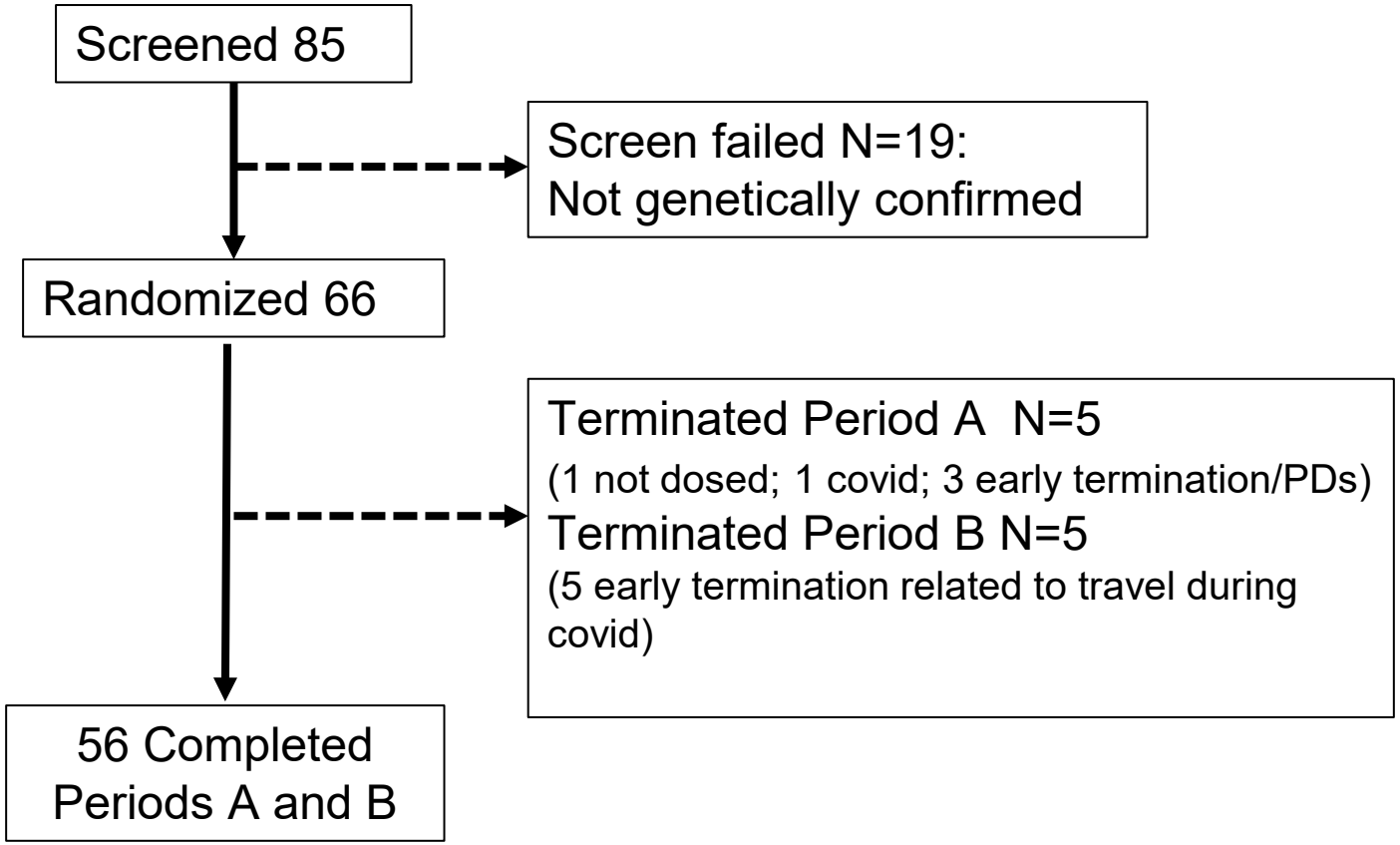
Consort Diagram: Participant Disposition



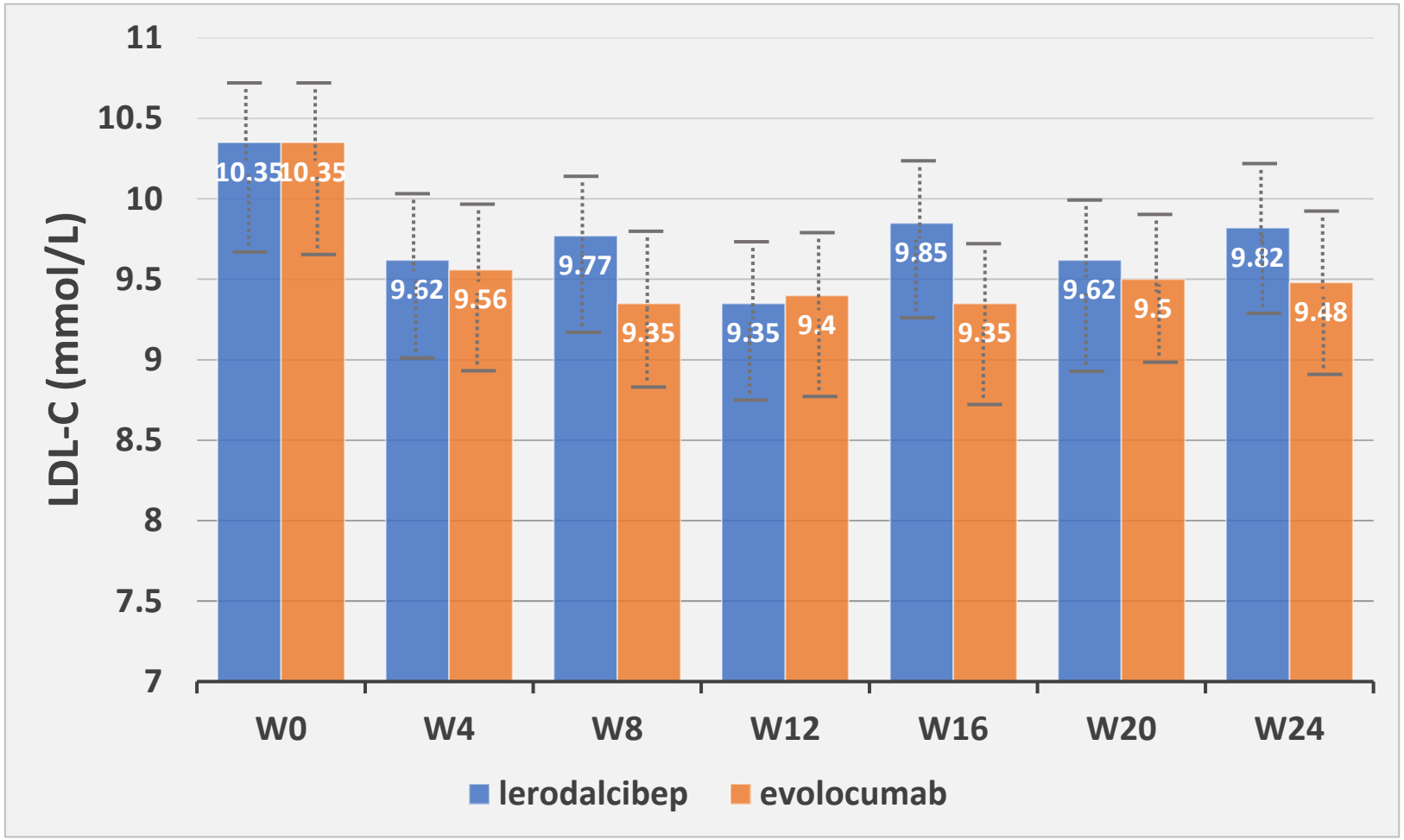
Baseline Characteristics (n=56)

Age (yrs) mean (range)	29.3 (10-58)
Age <18 years (n;%)	18 (32%)
Sex: M/F (n;%)	25 (45%)/31 (55%)
Race: (n;%)	
White	37 (66%)
South Asian	16 (29%)
Black (AA)	1 (2%)
Other	2 (4%)
Statin	100%
High intensity statin	95%
Ezetimibe	95%
Lomitapide	4%
Diabetes mellitus (n;%)	1 (2%)
BMI (kg/m^2); mean(SD)	24.8 (5.9)
Established ASCVD (n;%)	19 (34%)
Aortic Stenosis and/or valve replacement (n;%)	11 (19.6%)

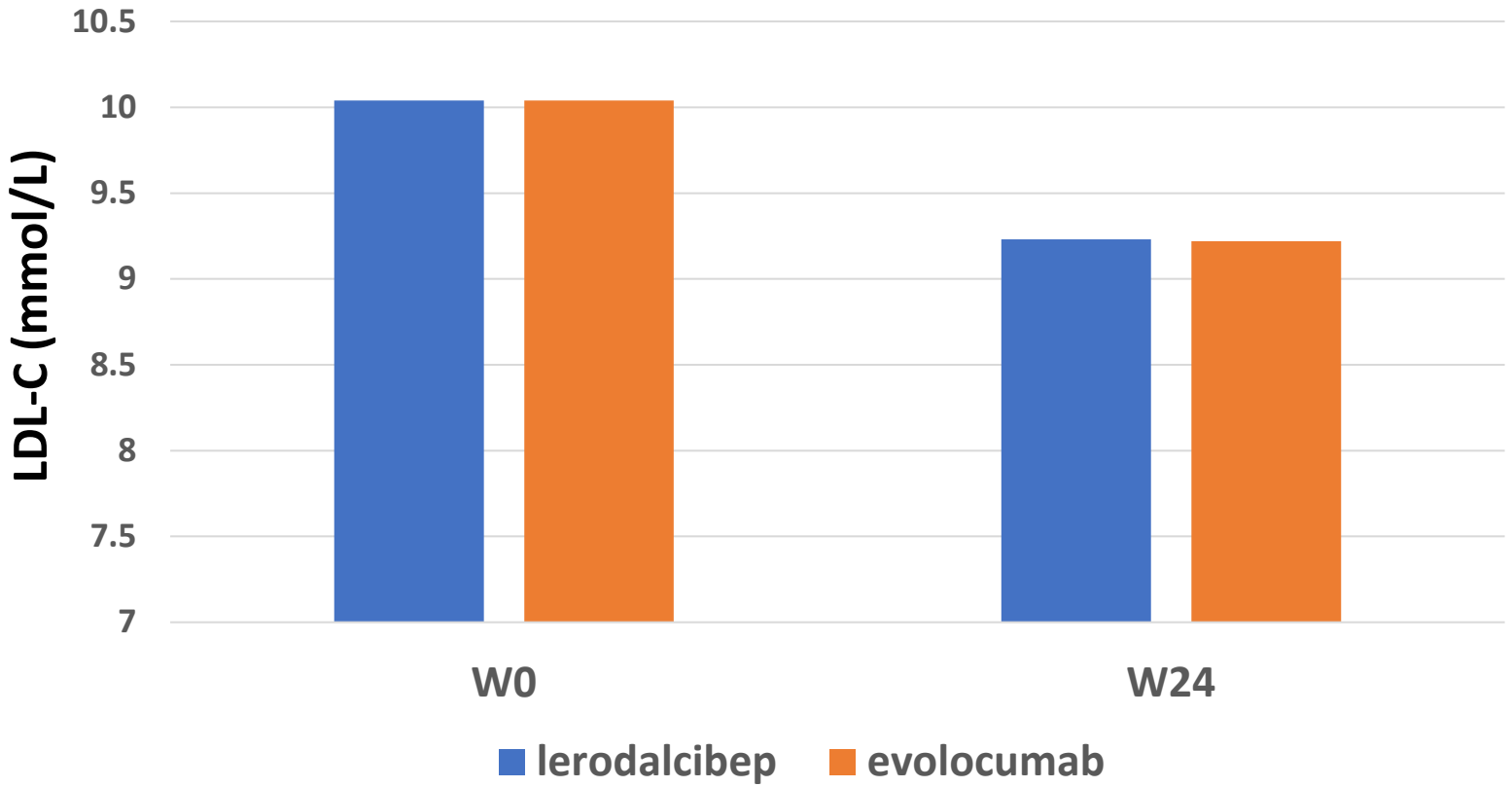
Baseline lipid and PCSK9 levels

Baseline lipids	
Total-cholesterol mmol/L; mean (SD)	11.96 (4.51)
Triglyceride mmol/L; mean (SD)	1.36 (0.88)
LDL-C (Friedewald) mmol/L; mean (SD)	10.35 (4.53)
LDL-C (ultracentrifugation) mmol/L; mean (SD)	10.04 (4.51)
HDL-C mmol/L; mean (SD)	0.95 (0.37)
Apolipoprotein B mg/dL; mean (SD)	241.4 (90.22)
Lipoprotein(a) nmol/L; (mean, median)	147.4 (116)
Baseline free PCSK9 ng/mL; mean (SD)	564.8 (280)

Results: Mean (SE) LDL-C (Friedewald) at Monthly visits

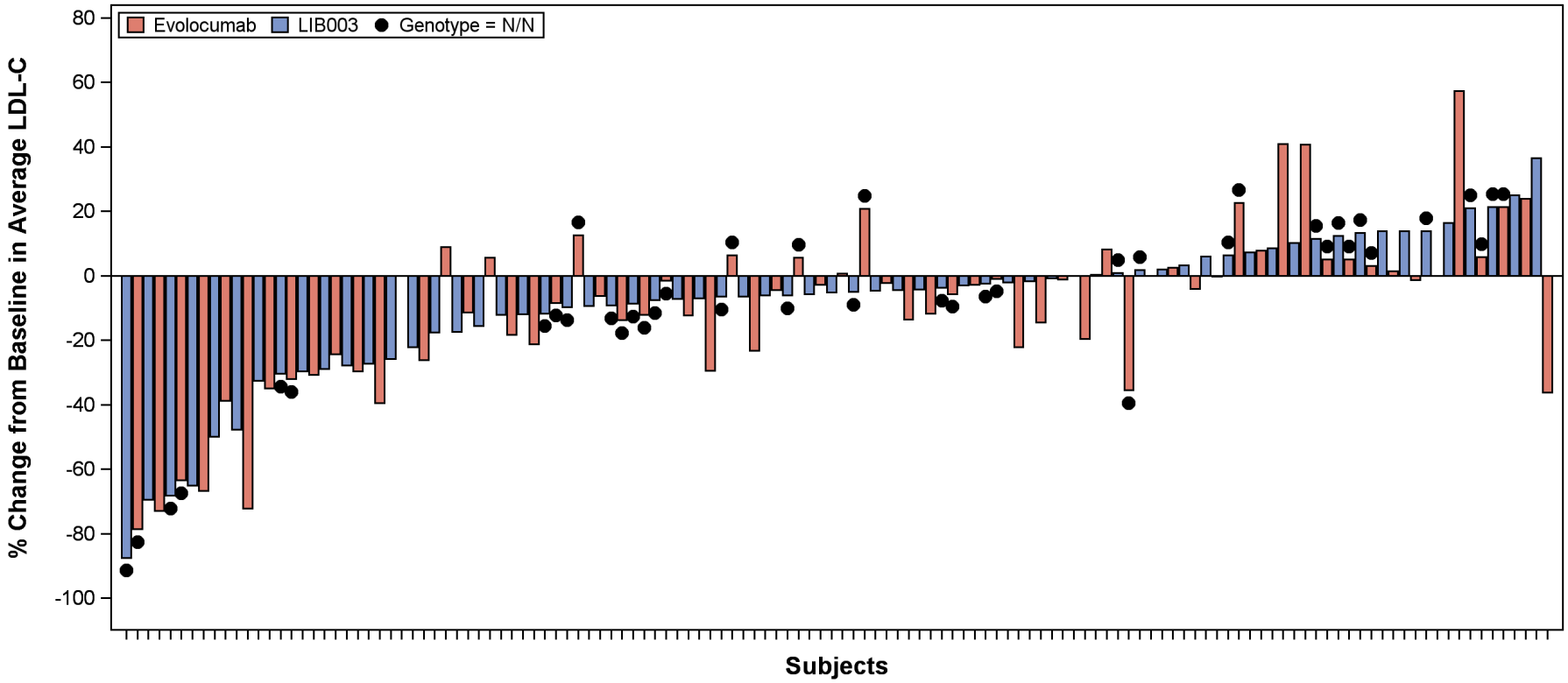


Results: Mean LDL-C by ultracentrifugation at baseline and Week 24



Waterfall plot showing individual patient responses of % change from baseline in average LDL-C

r=0.79



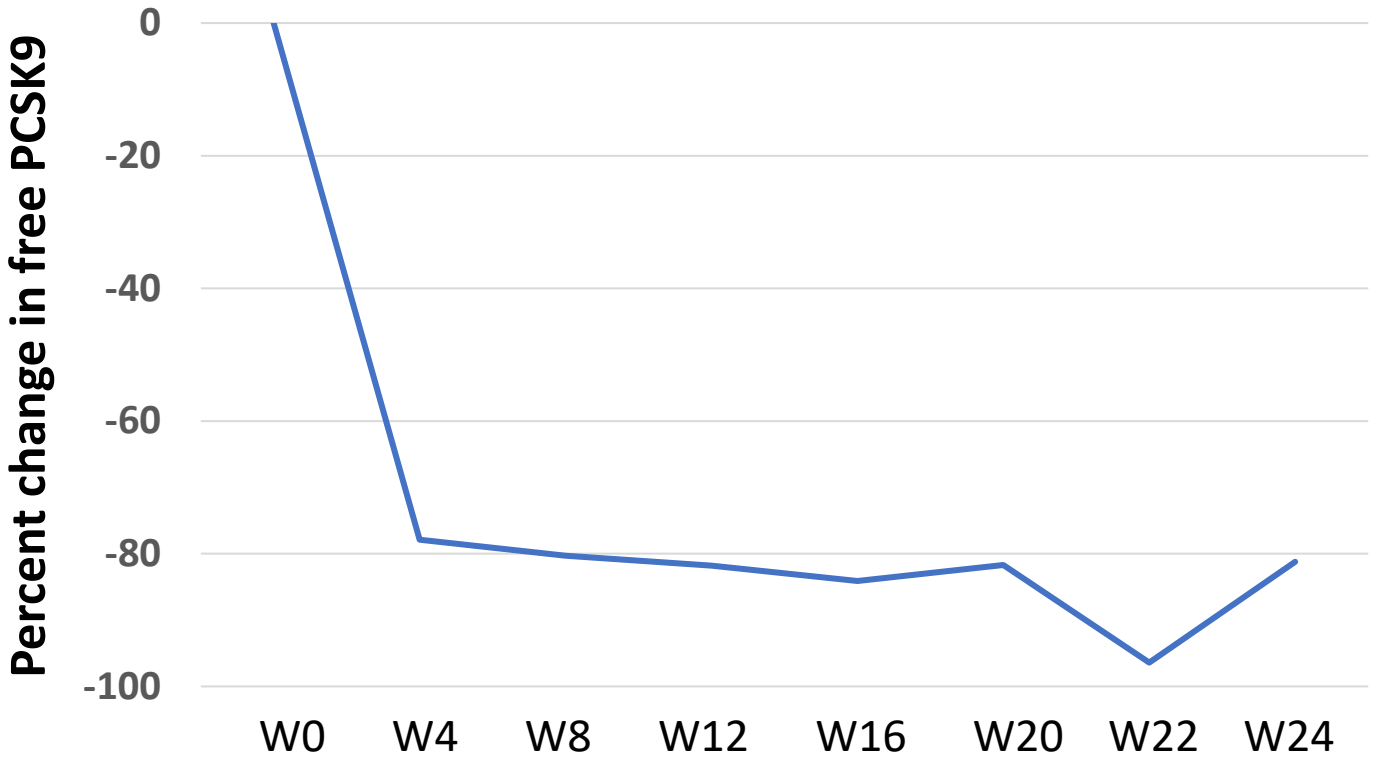
- Note: Subjects sorted by % reduction in Lerodalcibep group. Adjacent boxes in the plot represent % reductions in Lerodalcibep and Evolocumab for the same patient.

Results - Efficacy

Primary/Key Secondary Endpoints	Lerodalcibep 300mg SC Q4W	Evolocumab 420mg SC Q4W	Mean Difference (SE) Lerodalcibep versus Evolocumab	95% CI	P-value
% change in average LDL-C	-9.26	-11.00	1.73 (2.24)	(-2.77, 6.23)	0.444
% change in average apolipoprotein B	-3.67	-7.77	4.10 (2.38)	(-0.67, 8.86)	0.091
% change in average total cholesterol	-7.20	-8.91	1.71 (1.93)	(-2.17, 5.59)	0.380
% change in average triglycerides	0.97	-0.22	1.19 (3.12)	(-5.07, 7.45)	0.705
% change in average HDL-C	0.17	-0.19	0.37 (1.33)	(-2.29, 3.02)	0.784
% change in average Lipoprotein(a)	-7.24	-11.44	4.20 (2.90)	(-1.62, 10.01)	0.154
Patients with ≥15% reduction in LDL-C n(%)	15 (26.8%)	21 (37.5%)			
Patients with ≥30% reduction in LDL-C n(%)	8 (14.3%)	12 (21.4%)			

Results: mean % change in free PCSK9 in the lerodacibep treated group

	W0	W4	W8	W12	W16	W20	W22	W24
absolute mean ng/mL	564.8	78.8	44.9	40.7	44.2	45.9	3.1	58.1
SD	279.6	147.8	101.2	78.6	97.5	104.8	2	143.3



Results – Safety (All randomized subjects)

Category	Lerodalcibep 300mg SC Q4W (N=65) n (%)	Evolocumab 420mg SC Q4W (N=62) n (%)
Patients with any TEAE	31 (47.7)	38 (61.3)
Discontinued due to an AE	2 (3.1)	0
Moderate or severe AE	21 (32.4)	20 (32.2)
Serious AE	5 (7.7)	2 (3.2)
Deaths	0	0
Most common AEs (incidence of >2 patients within a treatment group)		
Injection site reactions	**1 (1.5)**	**15 (24.2)**
Injection site erythema	0	5 (8.1)
Corona virus infection	4 (6.2)	4 (6.5)
Toothache	3 (4.6)	1 (1.6)
Headache	6 (9.2)	3 (4.8)
Alanine aminotransferase > 3X ULN	0 (0)	1 (1.6)
Aspartate aminotransferase > 3X ULN	1 (1.5)	0 (0)

Summary/Conclusions

- LIBerate-HoFH is the largest randomized and diverse global trial conducted in genetically confirmed HoFH patients and the first to compare two different PCSK9 inhibitors in this population.
- The LDL-C response was highly variable but similar with both drugs and unrelated to the robust PCSK9 suppression achieved with lerodalcibep.
- Both drugs were well tolerated and there were no drug-related serious adverse events. Injection site reactions were less frequent with lerodalcibep, but with either drug none were severe or persistent.
- However, given the marked reductions in LDL-C in one third of patients, PCSK9 inhibitors remain part of standard of care in HoFH as initial additive therapy to statins and ezetimibe, especially in patients with good residual LDLR activity.
- The unpredictable and sometimes excellent response even in those with null/null or novel variants with unknown LDLR activity are supportive of a trial of PCSK9 inhibition in HoFH patients.

HoFH, homozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; LDLR, LDL receptor; PCSK9, proprotein convertase subtilisin/kexin type 9.