Long-term Efficacy and Safety of Lerodalcibep in Heterozygous Familial Hypercholesterolemia

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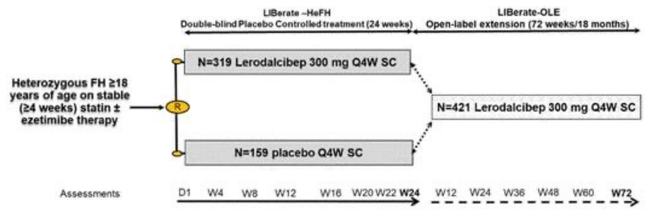
BACKGROUND

Lerodalcibep, a novel small recombinant fusion protein of a PCSK9-binding domain (adnectin) and human serum albumin reduced LDL-cholesterol (LDL-C) compared to placebo by a mean (SE) of 58.61 (3.25)% with a monthly (QM) 300 mg SC dose of 1.2 mL in the Phase 3, 24-week trial in heterozygous familial hypercholesterolemia (HeFH), LIBerate-HeFH[1].

We report on assessment of longer-term safety and efficacy from the open label extension trial, LIBerate-OLE, in those subjects from LIBerate-HeFH continuing on Lerodalcibep and those who switched from placebo to active drug.

METHODS



Of 478 participants in the LIBerate-HeFH trial, 421 (88%) continued into the 72 week LIBerate-OLE trial, including 281 patients who had been treated with Lerodalcibep and 140 with placebo for the 24 week base trial period – Table 1.

All participants received open label Lerodalcibep 300 mg in a SC dose of 1.2 mL monthly (QM ≤31 days) starting immediately on completion of the base trial or within 28 days.

Participants were dosed in clinic monthly through Week 12 after which they were able to self-dose and return to clinic every 12 weeks.

RESULTS

Mean age (range) was 52.8 (18-79) years, 51.3% female, 86% white and 14% South Asian, multiracial or black, with 88% on statins, 50.6% on ezetimibe and mean (SD) LDL-C of 153.4 (67.0) mg/dL – **table 1.**

Mean reductions with lerodalcibep from baseline, based on intention to treat, through 48 weeks in the OLE in LDL-C of approximately 50% - **Figure 1**.

ApoB was reduced by approximately 35% and Lp(a) by 20% consistent with the reductions in the base trial – **table 2.**

Percent change in LDL-cholesterol from baseline to week 48 for individual subjects is shown in **Figure 2**.

SAFETY: Apart from minor injection site reactions, not of which were severe or persistent, there were no significant additional safety concerns.

Long-term Treatment up to 18 months with Lerodalcibep, a novel anti-PCSK9 small binding protein dosed monthly and stable at ambient temperature for patient convenience, significantly and persistently reduces LDL-C, apo-B and Lp(a) with no attenuation in subjects with heterozygous familial hypercholesterolemia (HeFH) with a safety profile similar to placebo.

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TABLE 1

Demographic Data

Demographic data at entry of original LIBerate-HeFH trial of participants continuing in LIBerate-OLE			
Characteristic	**Placebo (N=140)**	**Lerodalcibep (N=281)**	**Total (421)**
Age – yr (range)	54.1 (18-79)	52.2(19-76)	52.8 (18-79)
Female sex – (%)	52.9	50.5	51.3
Race White (%)	89.3	84.3	86.0
Black/Multiracial (%)	8.6	8.9	8.8
South Asian (%)	2.1	6.8	5.2
Body mass Index – kg/m² mean(SD)	29.0(5.1)	28.8 (5.1)	28.9(5.1)
Diabetes Mellitus (%)	12.1	9.6	10.5
Very-high risk for ASCVD %	69.3	68.7)	68.9
High risk for ASCVD %	30.7	31.3	31.1
Lipid modifying therapy - %			
Statin; any dose	88.6%	89.0%	88.8%
High intensity statin	62.1%	69.4%	67.0%
Ezetimibe	52.1%	49.8%	50.6%
Baseline Lipids –mg/dL; mean(SD)			
LDL-cholesterol (calculated Friedewald)	146.1 (55.6)	153.3 (68.8)	150.9 (64.7)
LDL-cholesterol (Ultracentrifugation)	144.3 (52.1)	150.2 (65.3)	148.2 (61.2)
Total cholesterol	222.6 (59.5)	231.0 (72.6)	228.2 (68.6)
HDL-Cholesterol	50.7 (14.9)	50.6 (16.0)	50.6 (15.6)
Triglycerides	129.7(79.2)	135.7(81.9)	133.7 (81.0)

FIGURE 1

Percent Change in LDL-C in OLE from Baseline for Lerodalcibep and from Week 24 for Placebo

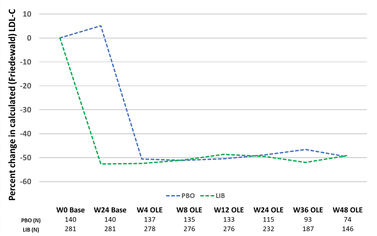


TABLE 2

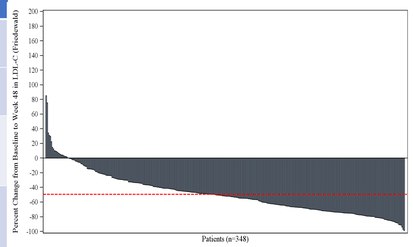
Summary of Changes in Lipoproteins from Baseline to Week 48 (ITT population)

	Baseline	Week 48	% Change
LDL-cholesterol* (mg/dL)	148.5	72.5	**-48.5%**
Apolipoprotein B (mg/dL)	120.7	76.0	**-36.1%**
Total Cholesterol (mg/dL)	225.8	152.8	**-31.3%**
Non HDL-cholesterol (mg/dL)	174.6	99.6	**-42.5%**
Triglyceride (mg/dL)	130.1	119.9	**-10.2%**
HDL-cholesterol (mg/dL)	51.3	55.6	**+9.9%**
Lipoprotein(a) (nmol/L)	112.1	93.0	**-19.1%**

* LDL-cholesterol by Friedewald formula

FIGURE 2

Waterfall Plot of % Change in LDL-C from Baseline to Week 48 by Friedewald Formula



CONCLUSION

In this large open label extension trial, Lerodalcibep, a novel anti-PCSK9 small binding protein dosed monthly for an additional 48 weeks and up to 18 months in total, significantly and persistently reduced LDL-C, apo-B and Lp(a), with no attenuation in subjects with HeFH with good tolerability and no new safety concerns identified.

These results support the use of Lerodalcibep in addition to existing maximally tolerated statins, ezetimibe and other lipid-lowering therapy for the management of HeFH.

References

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

DISCLOSURE INFORMATION

This clinical trial was funded by LIB Therapeutics, Inc.