Randomized, Double-Blind, Placebo-Controlled, Phase 3, Study to Evaluate the Long-Term Efficacy and Safety of Lerodalcibep in Heterozygous Familial Hypercholesterolaemia Patients (LIBerate-HeFH)

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LIBerate HeFH: Background and rationale

- **HeFH is a genetic disorder affecting ~1 in 300 or over 30 million people worldwide**
  - Life-long cumulative exposure to elevated LDL-C, starting at birth drives early onset, accelerated atherosclerotic cardiovascular disease (ASCVD).[1]
  - Untreated, or under treated, HeFH 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 HeFH patients with ASCVD or an additional ASCVD risk factor, the ESC consensus target is an absolute LDL-C of < 1.4 mmol/L, plus at least a 50% reduction in LDL-C from baseline.[3]
  - For HeFH patients without ASCVD or an additional risk factor, the target is a LDL-C of <1.8 mmol/L together with a reduction of ≥50% from baseline.[3]

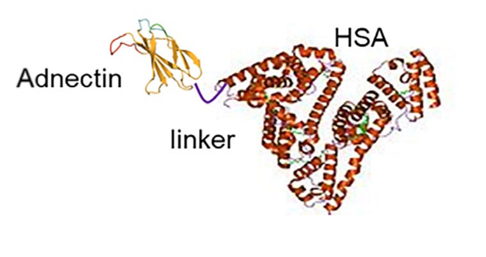
1. Ference BA et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. *Eur Heart J* 2017;38(32):2459-72.
2. Vallejo-Vaz AJ et al . Global perspective of familial hypercholesterolaemia. *Lancet* 2021;398:1713-1725.
3.. Mach F, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;41(1):111-88.

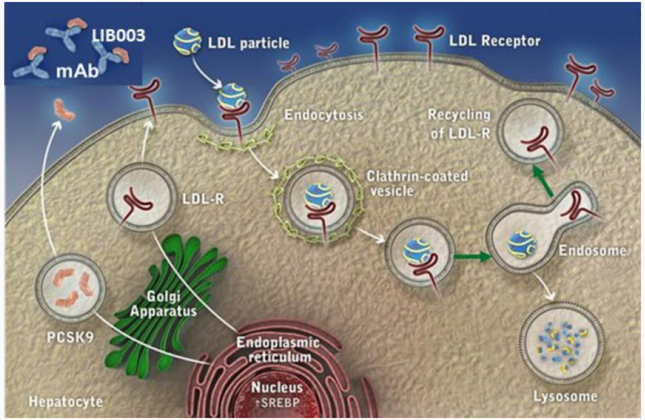
LIBerate HeFH: Background and rationale

- **Management is prevention of ASCVD through LDL-C lowering therapy**
  - ➢ High intensity statins, ezetimibe and/or other oral lipid lowering agents.
  - ➢ Despite this therapy, the majority of HeFH patients fail to achieve sufficient LDL-C reduction and additional therapies to inhibit PCSK9 in the circulation, or reduce its hepatic production, and enhance LDL clearance are required.
  - ➢ **In this global Phase 3 trial, we evaluated the safety and efficacy of lerodalcibep in HeFH patients requiring additional LDL-C lowering.**

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.



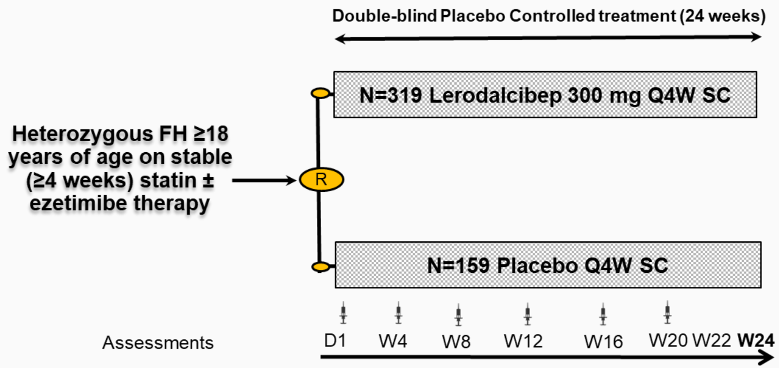


- Similar to mAbs, Lerodalcibep binds to PCSK9, blocks the interaction between PCSK9 and LDLR, preventing LDLR degradation, increasing LDLR recycling, enhancing LDL-C clearance, and lowers LDL-C levels.
- Prolonged stability at ambient temperature, small size (77kDa) and high solubility allows for a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

LIBerate HeFH: Methods

- Patients were randomized 2:1 to monthly 1.2 mL SC injections of either lerodalcibep 300mg or placebo for 24 weeks.

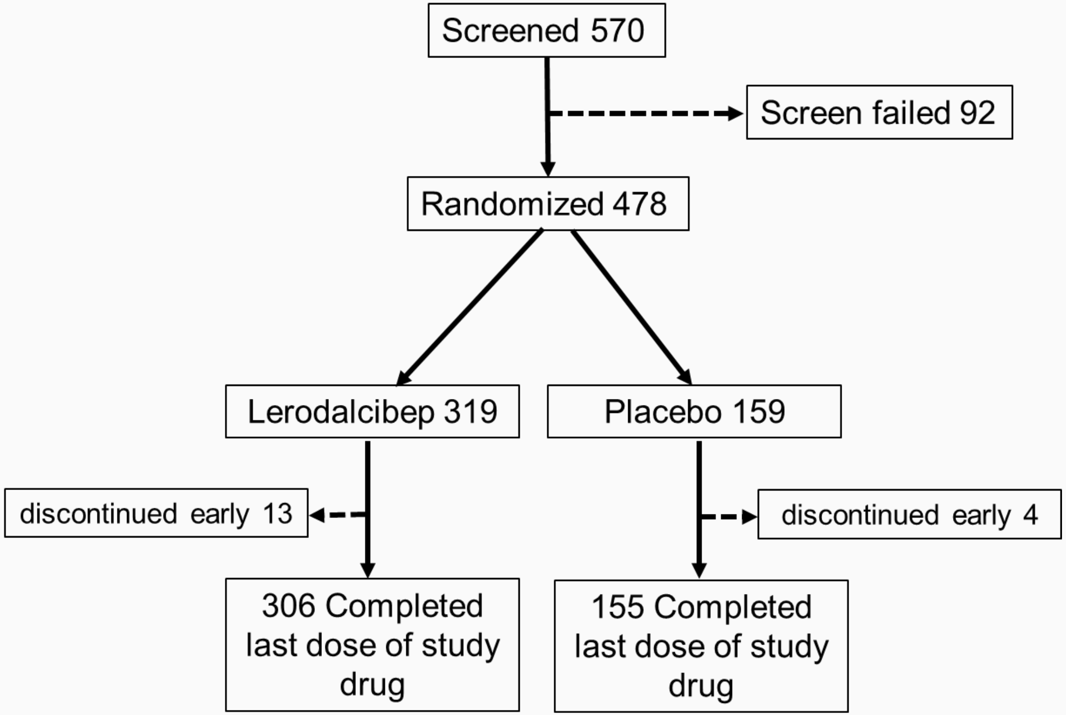
LIBerate-HeFH: Study Design



- The primary efficacy endpoints were the percent change from baseline in LDL-C at Week 24 and the mean of Weeks 22 and 24.
- Secondary efficacy end points included changes in apolipoprotein B, Lp(a) and achievement of ESC recommended LDL-C targets.

LIBerate HeFH: Results

Consort Diagram: Participant Disposition



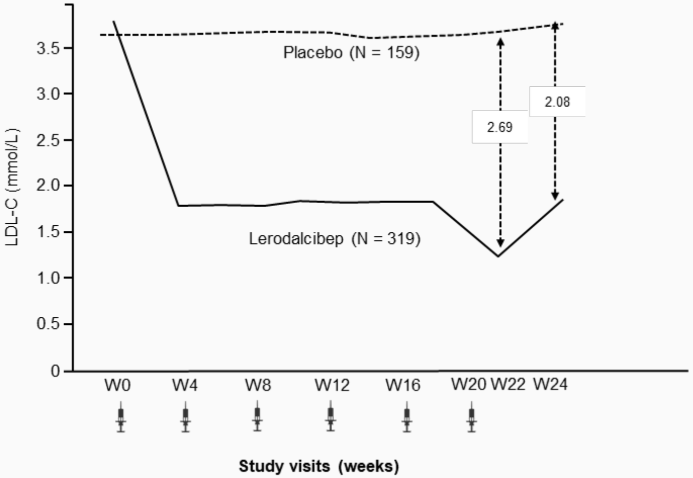
LIBerate HeFH: Results: Baseline characteristics

Characteristic	Placebo (N=159)	Lerodalcibep (N=319)
Age – yr (range)	53.8 (18-79)	52.5(19-80)
Female sex – no. (%)	83(52.2)	164(51.4)
Race White no. (%)	143 (89.9)	273(85.6)
Black/Multiracial no. (%)	12 (7.5)	25 (7.8)
South Asian no. (%)	4 (2.5)	21 (6.6)
Diagnosis of heterozygous FH no. (%)	159 (100)	319 (100)
on clinical criteria no. (%)	103 (64.8)	186 (58.3)
on genotyping no. (%)	56 (35.2)	133 (41.7)
Diabetes Mellitus no. (%)	18 (11.3)	31 (9.7)
Documented ASCVD no. (%)	49 (45.0)	108 (48.9)
Very-high risk for ASCVD no. (%)	109 (68.6)	221 (69.3)
High risk for ASCVD no. (%)	50 (31.4)	98 (30.7)
Lipid modifying therapy -no. (%)		
Statin; any dose	141 (88.7)	281 (88.1)
High intensity statin	101 (63.5)	218 (68.3)
Not high intensity statin	40 (25.2)	63 (19.7)
Ezetimibe	78 (49.1)	155 (48.6)
LDL-cholesterol (calculated)	**3.79 (1.47)**	**3.93 (1.74)**

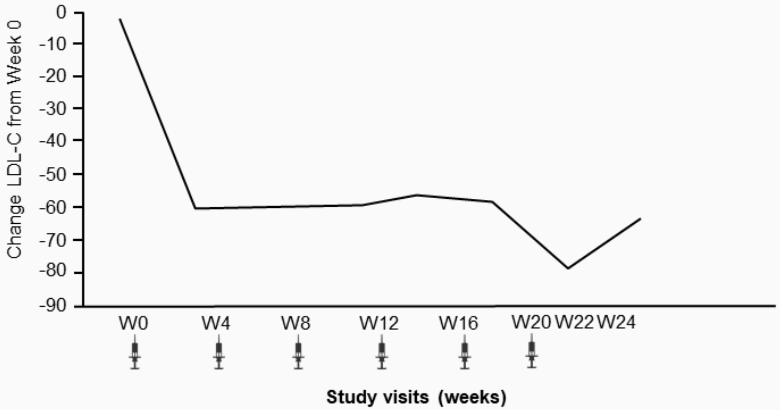
LDL-C (Friedewald) – ITT population

Co-primary endpoints	Lerodalcibep (n=319)	Placebo (n=159)	Placebo adjusted	P value
LDL-C Week 24	-50.5%	+8.1%	-58.6%	<0.0001
LDL-C Mean W22/24	-58.0%	+7.0%	-65.0%	<0.0001

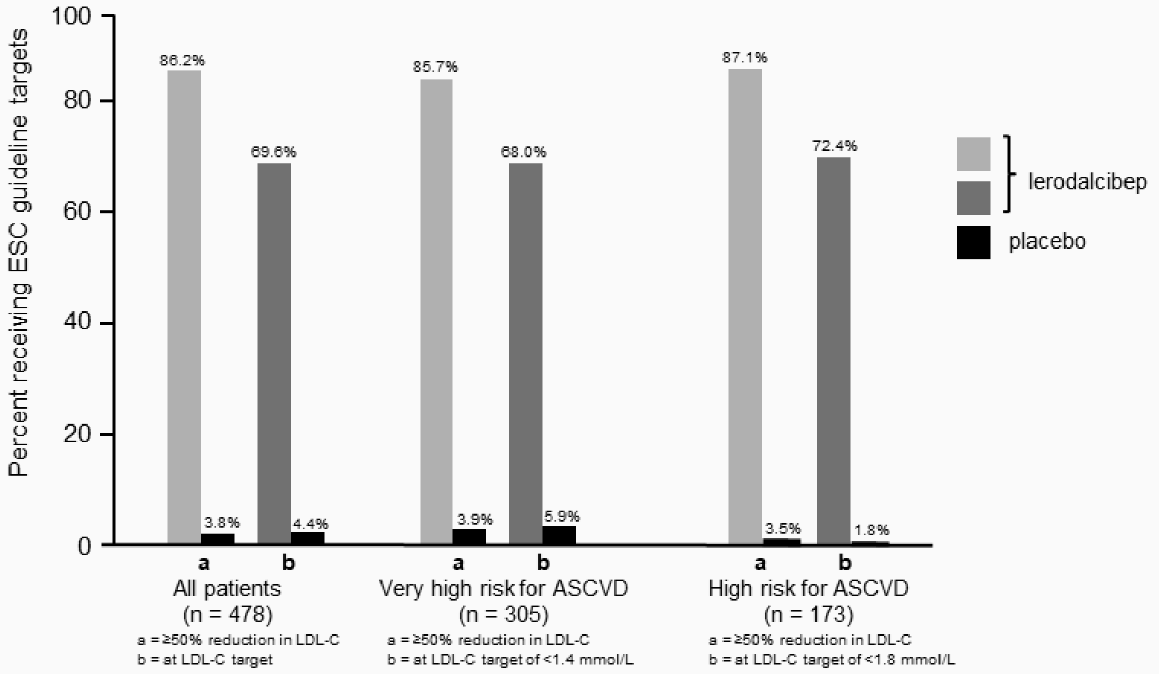
Absolute reduction in LDL-C all visits



Placebo adjusted percent reduction in LDL-C



Number (%) achieving a ≥50% reduction in LDL-C and ESC recommended LDL-C targets with lerodalcibep compared to placebo during the study



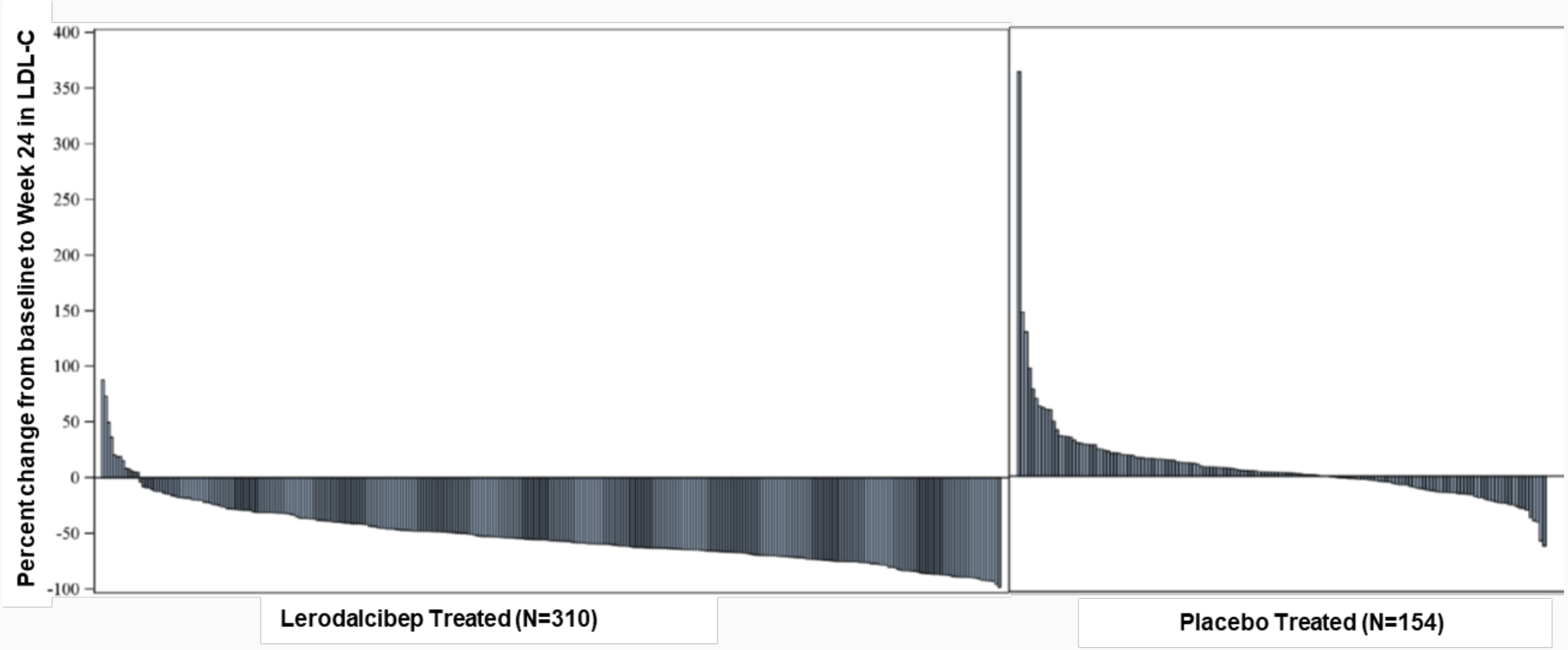
Percent Change from Baseline LDL-C (Friedewald) at W24 and Mean W22/24: Per-Protocol Population

	Lerodalcibep (n=269)	Placebo (n=130)	Placebo adjusted	P value
LDL-C Week 24	-56.2%	+7.5%	-63.6%	<0.0001
LDL-C Mean W22/24	-64.0%	+6.2%	-70.2%	<0.0001

Key lipid and free PCSK9 secondary endpoints: Week 24 (ITT population)

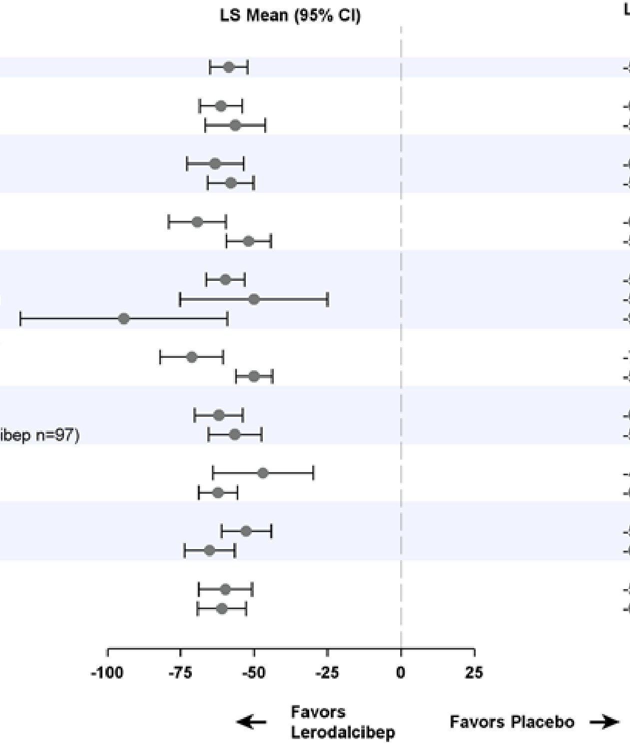
Parameter	Lerodalcibep (n=319)	Placebo (n=159)	Placebo adjusted	P value
LDL-C (UC)	-47.9%	+8.1%	-56.0%	<0.0001
Apolipoprotein B	-38.9%	+6.7%	-45.6%	<0.0001
Lp(a) (median)	-24.4%	-1.4%	-23.9%	<0.0001
Free PCSK9 (median)	-94.3%	-	-	<0.0001

Waterfall plot of percent change in LDL-C from baseline to Week 24 with lerodalcibep and placebo in individual patients



Forest plot showing LDL-C reduction with lerodalcibep in different subgroups

Subgroup	LS Mean (95% CI)
All subjects (Placebo n=159, Lerodalcibep n=319)	-58.61 (-64.97, -52.24)
Age at Informed Consent	
<65 years (Placebo n=126, Lerodalcibep n=252)	-61.30 (-68.53, -54.07)
>=65 years (Placebo n=28, Lerodalcibep n=58)	-56.47 (-66.69, -46.25)
Sex	
Female (Placebo n=80, Lerodalcibep n=158)	-63.27 (-72.87, -53.67)
Male (Placebo n=74, Lerodalcibep n=152)	-58.02 (-65.80, -50.24)
Baseline BMI Group	
<= Median (Placebo n=74, Lerodalcibep n=158)	-69.36 (-79.15, -59.58)
> Median (Placebo n=80, Lerodalcibep n=152)	-51.94 (-59.50, -44.37)
Race	
White (Placebo n=138, Lerodalcibep n=264)	-59.83 (-66.39, -53.27)
Black or African American (Placebo n=12, Lerodalcibep n=25)	-50.15 (-75.29, -25.02)
Other (Placebo n=4, Lerodalcibep n=21)	-94.31 (-129.56, -59.06)
LDL-C Group at Baseline Calculated by Friedewald Formula	
<= Median (Placebo n=76, Lerodalcibep n=157)	-71.29 (-81.90, -60.68)
> Median (Placebo n=78, Lerodalcibep n=153)	-50.05 (-56.21, -43.89)
Baseline Statin Intensity	
High Intensity (Placebo n=99, Lerodalcibep n=213)	-62.01 (-70.15, -53.87)
No Statin or Not High Intensity Statin (Placebo n=55, Lerodalcibep n=97)	-56.58 (-65.55, -47.61)
Diabetes in Medical History	
Yes (Placebo n=17, Lerodalcibep n=31)	-47.02 (-64.06, -29.99)
No (Placebo n=137, Lerodalcibep n=279)	-62.31 (-68.92, -55.71)
Diagnosis of HeFH Made by Genotyping	
Yes (Placebo n=54, Lerodalcibep n=129)	-52.70 (-61.21, -44.18)
No (Placebo n=100, Lerodalcibep n=181)	-65.15 (-73.72, -56.59)
CVD Status from IRT	
High Risk for CVD (Placebo n=55, Lerodalcibep n=112)	-59.81 (-68.87, -50.76)
Very High Risk for CVD (Placebo n=99, Lerodalcibep n=198)	-60.95 (-69.21, -52.68)



Adverse events and key safety laboratory findings

	Placebo (N=159)	Lerodalcibep (N=318)	Risk Difference (95% CI)
Adverse events- n (%)			
Patients with at least one adverse event	109 (68.6)	230 (72.3)	3.8 (-5.9, 13.4)
Patients with at least one serious adverse event	9 (5.7)	9 (2.8)	
Frequent adverse events (5% or more in either)			
COVID-19	17 (10.7)	35 (11.0)	0.3 (-9.3, 10.0)
Upper respiratory tract infection	11 (6.9)	18 (5.7)	-1.3 (-10.9, 8.4)
Arthralgia	12 (7.5)	13 (4.1)	-3.5 (-13.1, 6.2)
Nasopharyngitis	3 (1.9)	16 (5.0)	3.1 (-6.5, 12.8)
Urinary tract infection	8 (5.0)	10 (3.1)	-1.9 (-11.5, 7.8)
Laboratory results – n (%)			
Liver Function ALT or AST >3x ULN	1(0.6)	0	
Muscle CK>5xULN	2 (1.3)	3 (0.9)	

Injection site reactions (ISRs) and anti-drug antibodies - safety population

Treatment	Lerodalcibep (N=318)	Placebo (N=159)
Patients with ISRs N(%)	32 (10.1%)	2 (1.3%)
ISR grade: Mild	28	1
Moderate	4	1
Severe	0	0
ISR type: Erythema	21	1
Bruising	6	1
Pruritus	4	0
Pain	1	0
Total doses administered:	1853	934
ISR events N(%)	**57(3.1%)**	**2(0.2%)**

- Low levels of transient and sporadic anti-drug antibodies were detected and 11 patients (3.4%) had *in-vitro* NAbs. **None of the NAbs were associated with in-vivo effects, specifically ISRs or any impairment in PCSK9 or LDL-C reduction efficacy.**

LIBerate HeFH: Summary

- Lerodalcibep 300mg monthly added to maximally tolerated oral lipid-lowering therapy, reduced LDL-C a further **60%**.
- Lerodalcibep resulted in approximately **70%** of HeFH patients achieving ***both*** a reduction in LDL-C of ≥50% **and** the 2019 ESC recommended LDL-C targets for those with ASCVD or high-risk for ASCVD.
- Lerodalcibep also reduced apoB by 46% and Lp(a) by 24%.
- Lerodalcibep was as well tolerated and had a safety profile similar to placebo.
- **These results support the use of lerodalcibep for the management of heterozygous FH.**

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