Safety, Tolerability and LDL-C Reduction with a Novel Anti-PCSK9 Recombinant Fusion Protein (LIB003): Results of a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study

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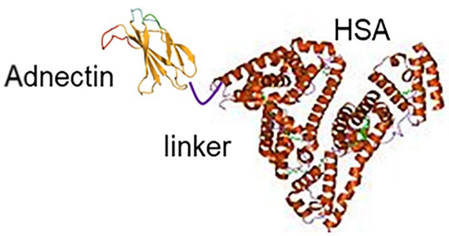
*Founder/partner LIB Therapeutics. Received consulting fees related to development of PCSK9 inhibitors from Amgen, Regeneron/Sanofi, Genentech/Roche, Medicines Co and BMS and other LDL drugs from AstraZeneca, Catabasis, CymaBay and Gemphire. Lipid Advisory Panel for CVS/Caremark

LIB003 Phase 2 dose ranging trial: *Background*

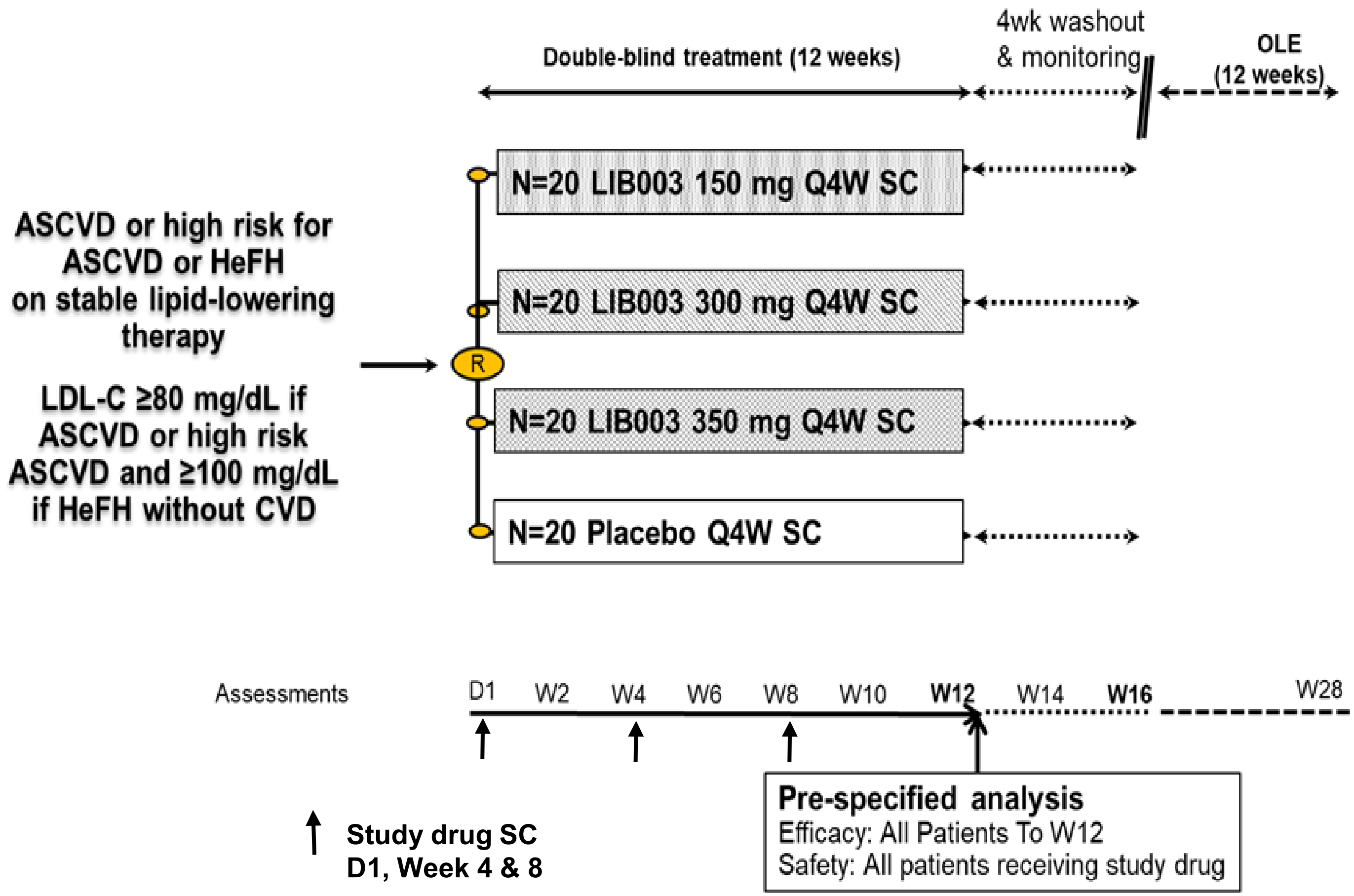
- LIB003 is a Chinese hamster ovary-cell line-derived recombinant fusion protein therapeutic agent consisting of a PCSK9-binding domain and human serum albumin (HSA).



- The PCSK9-binding domain (Adnectin) in LIB003 is derived from the 10th type III domain of human fibronectin modified by mRNA display technology to bind with high affinity to human PCSK9 with picomolar affinity in a concentration-dependent manner.
- HSA linkage to the adnectin provides increases LIB003 half-life of 12 to 15 days
- The binding of LIB003 to PCSK9 blocks the interaction between PCSK9 and LDLR
- The small size (77 KD) and high solubility of LIB003 allows for a smaller injection volume than achievable with mAbs in order to achieve stable and prolonged duration of LDL-C reduction between injections
- Based on the phase 1 SAD study[1] with SC doses ranging from 25 to 600 mg, doses of LIB003 150 to 350 mg were selected for Q4W dosing in phase 2

[1]Turner T, Biernat L, Dimova D, et al. Abstract 1051-05, Annual Scientific Sessions of the American College of Cardiology, 16-18 March 2019, New Orleans, USA

LIB003 Phase 2 dose ranging trial: *Study Design & Entry Criteria*



ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; OLE = optional longer-term extension; Q4W = every 4 weeks; SC = subcutaneous

LIB003 Phase 2 dose ranging trial: *Objectives*

- **Primary Objective:**

The co-primary endpoint was percent change from baseline in calculated LDL-C level of the mean of Weeks 10/12 and Week 12

- **Secondary Objectives:**
  - unbound (free) PCSK9 concentrations
  - LDL-C by both preparative ultracentrifugation (PUC) and Hopkins formula;
  - Other lipids and apolipoproteins; TC, HDL-C, non-HDL-C, VLDL-C, TG, ApoA1 and B and Lp(a)
  - Immunogenicity: occurrence and frequency of ADAs and NAbs
  - Safety: Clinical and laboratory adverse events and injection site assessments

LIB003 Phase 2 dose ranging trial:

Demographic and Baseline Characteristics

Demographic/Characteristic	Placebo (N = 20)	LIB003 150 mg (N = 21)	LIB003 300 mg (N = 19)	LIB003 350 mg (N = 21)
Age Mean (range) years	66.6 (52-85)	65.0 (31-79)	61.9 (38-76)	65.5 (53-78)
Gender Male/Female	10/10	12/9	10/9	6/15
Race N (%) White	14 (70.0%)	15 (71.4%)	12 (63.2%)	19 (90.5%)
African American	5 (25.0%)	6 (28.6%)	7 (36.8%)	1 (4.8%)
Other	1 (5.0%)	0 (0.0)	0 (0.0)	1 (4.8%)
BMI (kg/m ^{2}) Mean (SD)	29.59 (4.5)	31.10 (4.6)	29.55 (3.3)	29.36 (5.3)
CVD n (%)	9 (45%)	10 (48%)	7 (37%)	10 (48%)
Diabetes n (%)	8 (40.0%)	11 (52.4%)	10 (52.6%)	10 (47.6%)
Smoking n (%): Never	12 (60.0%)	12 (57.1%)	11 (57.9%)	15 (71.4%)
Former	6 (30.0%)	7 (33.3%)	6 (31.6%)	4 (19.0%)
Current	2 (10.0%)	2 (9.5%)	2 (10.5%)	2 (9.5%)
Statin n (%): High intensity	7 (35.0%)	13 (61.9%)	6 (31.6%)	11 (52.4%)
Mod/low intensity	9 (45.0%)	5 (23.8%)	6 (31.6%)	8 (38.1%)
None	4 (20.0%)	3 (14.3%)	7 (36.8%)	2 (9.5%)
Current ezetimibe use – n (%)	6 (30.0%)	4 (19.0%)	3 (15.8%)	3 (14.3%)
Baseline LDL-C mg/dL*				
Friedewald formula Mean (SD)	119.2 (34.20)	119.5 (37.45)	128.9 (39.28)	115.7 (30.53)
Hopkins formula Mean (SD)	119.3 (34.03)	120.5 (37.73)	130.5 (38.36)	116.9 (32.02)
Ultracentrifugation Mean (SD)	119.2 (32.29)	121.2 (35.03)	129.4 (38.64)	119.1 (32.05)
Lp(a) nmol/L mean (SD)**	113.2 (132.29)	107.1 (96.45)	116.7 (137.80)	124.3 (102.42)

*To convert to mmol/L ÷ by 38.6:

**To convert to mg/dL ÷ by 2.4

LIB003 Phase 2 dose ranging trial:

Subject Disposition – All Enrolled Subjects

	Placebo n (%)	LIB003 150mg n (%)	LIB003 300mg n (%)	LIB 003 350mg n (%)
Subjects randomized	20	21	19	21
Subjects receiving ≥1 dose of study drug	20 (100.0)	21 (100.0)	19 (100.0)	21 (100.0)
Subjects completing study	20 (100.0)	20 (95.2)	19 (100.0)	20 (95.2)
Subjects withdrew(awn) from study	0 (0.0)	1 (4.8)*	0 (0.0)	1 (4.8)**

*Patient received prescription PCSK9 mAb **Patient lost to follow-up

LIB003 Phase 2 dose ranging trial: *Results*

Co-primary end points:

Percent Changes in Low-Density Lipoprotein Cholesterol (mg/dL) by Friedewald Formula – ITT Population

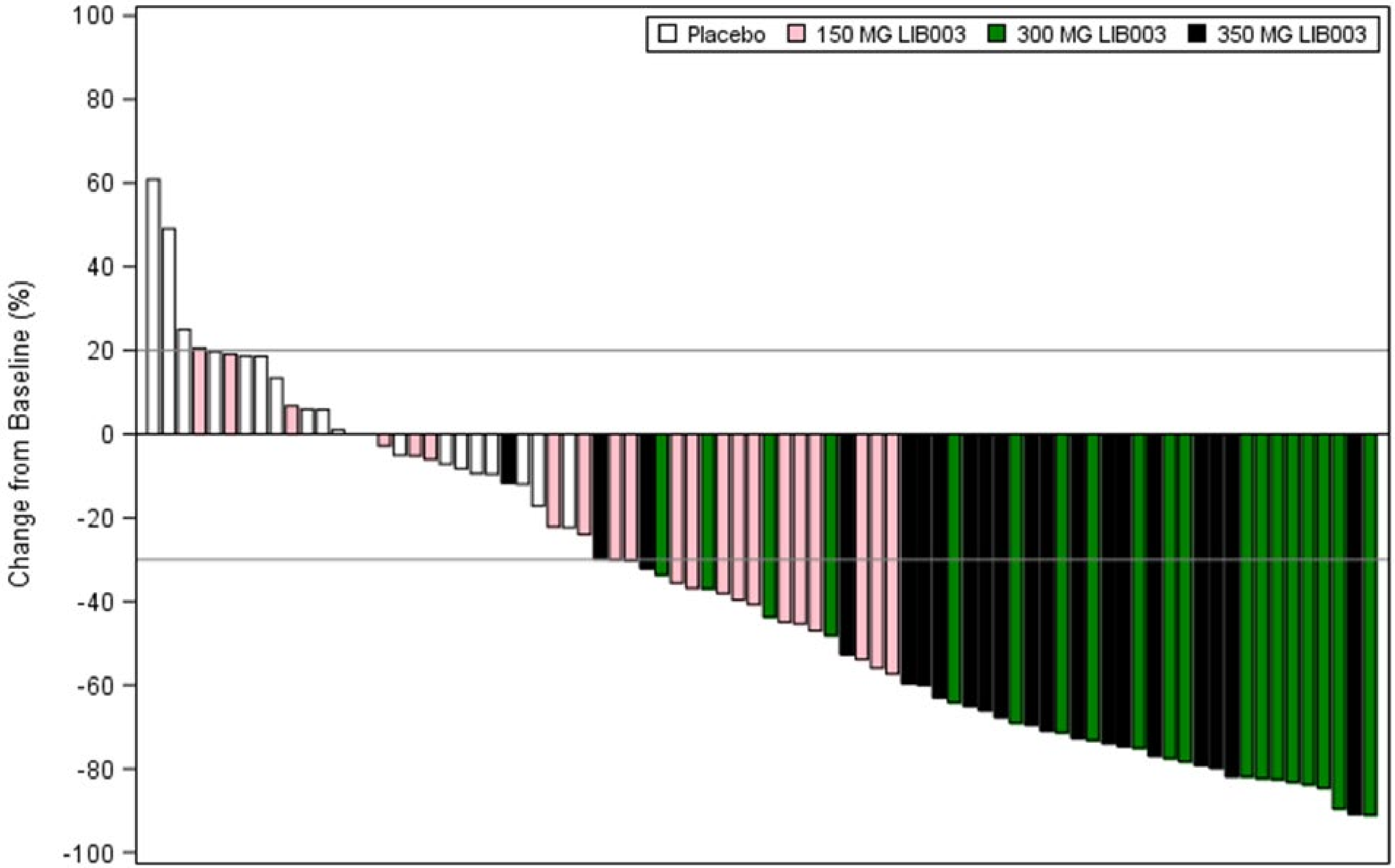
	Placebo (N = 20)	LIB003 150 mg (N = 21)	LIB003 300 mg (N = 19)	LIB003 350 mg (N = 20)
% change from baseline to average Wks 10/12 LOCF Mean (SD)	2.72 (15.6)	-45.26 (15.2)	-73.39 (15.6)	-67.54 (15.9)
Comparison LIB003 vs placebo: LS mean (SE)		-48.0 (4.87)	-76.1 (4.99)	-70.3 (4.93)
95% CI		(-57.7, -38.3)	(-86.0, -66.2)	(-80.1, -60.5)
p-value		<0.0001	<0.0001	<0.0001
% change from baseline to Wk 12 LOCF Mean (SD)	6.36 (21.2)	-27.10 (23.72)	-70.98 (17.7)	-63.76 (19.4)
Comparison LIB003 vs placebo: LS mean (SE)		-33.5 (6.5)	-77.3 (6.6)	-70.1 (6.5)
95% CI		(-46.3, -20.6)	(-90.5, -64.1)	(-83.2, -57.1)
p-value		<0.0001	<0.0001	<0.0001

n = number of subjects with measurements at both baseline and a post-baseline visit

LIB003 Phase 2 dose ranging trial:

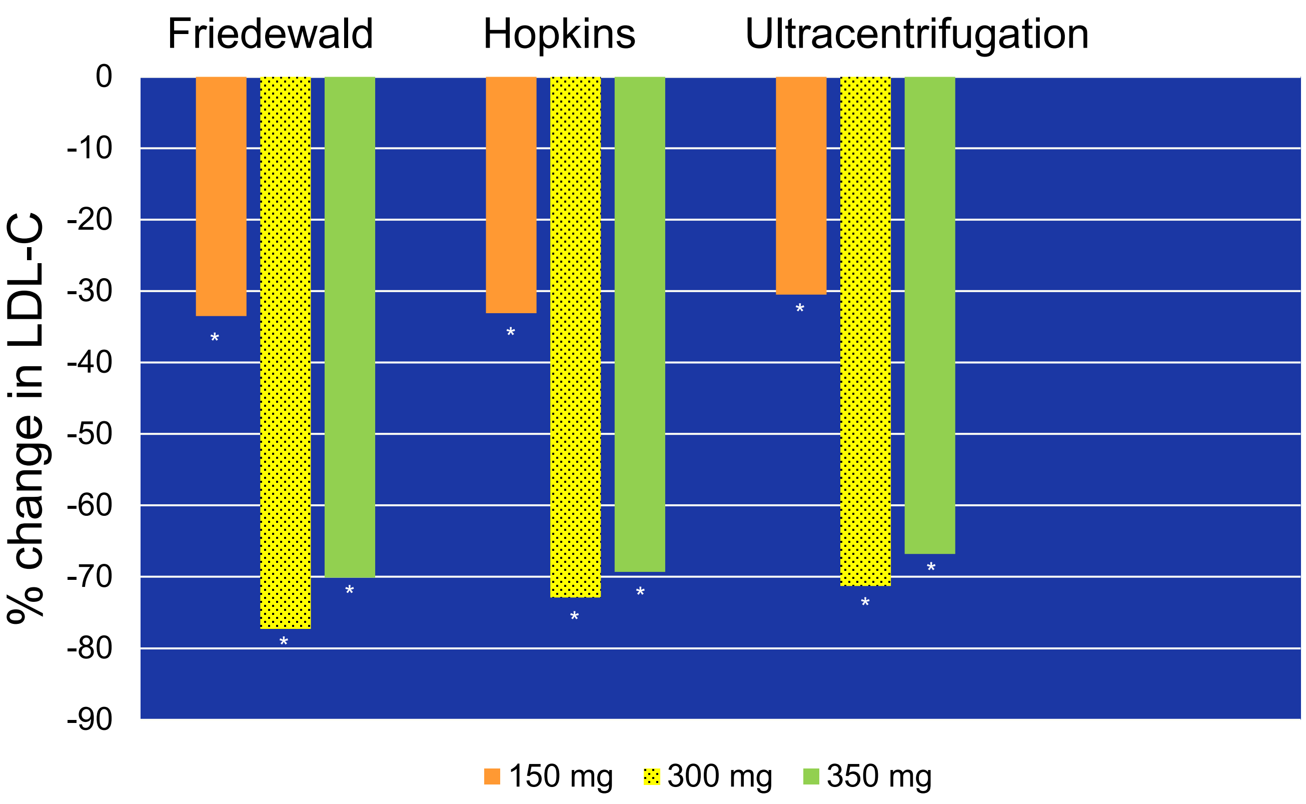
Results

Percent Changes in LDL-C by Friedewald Formula from baseline to wk 12 – ITT Population



LIB003 Phase 2 dose ranging trial: ***Results***

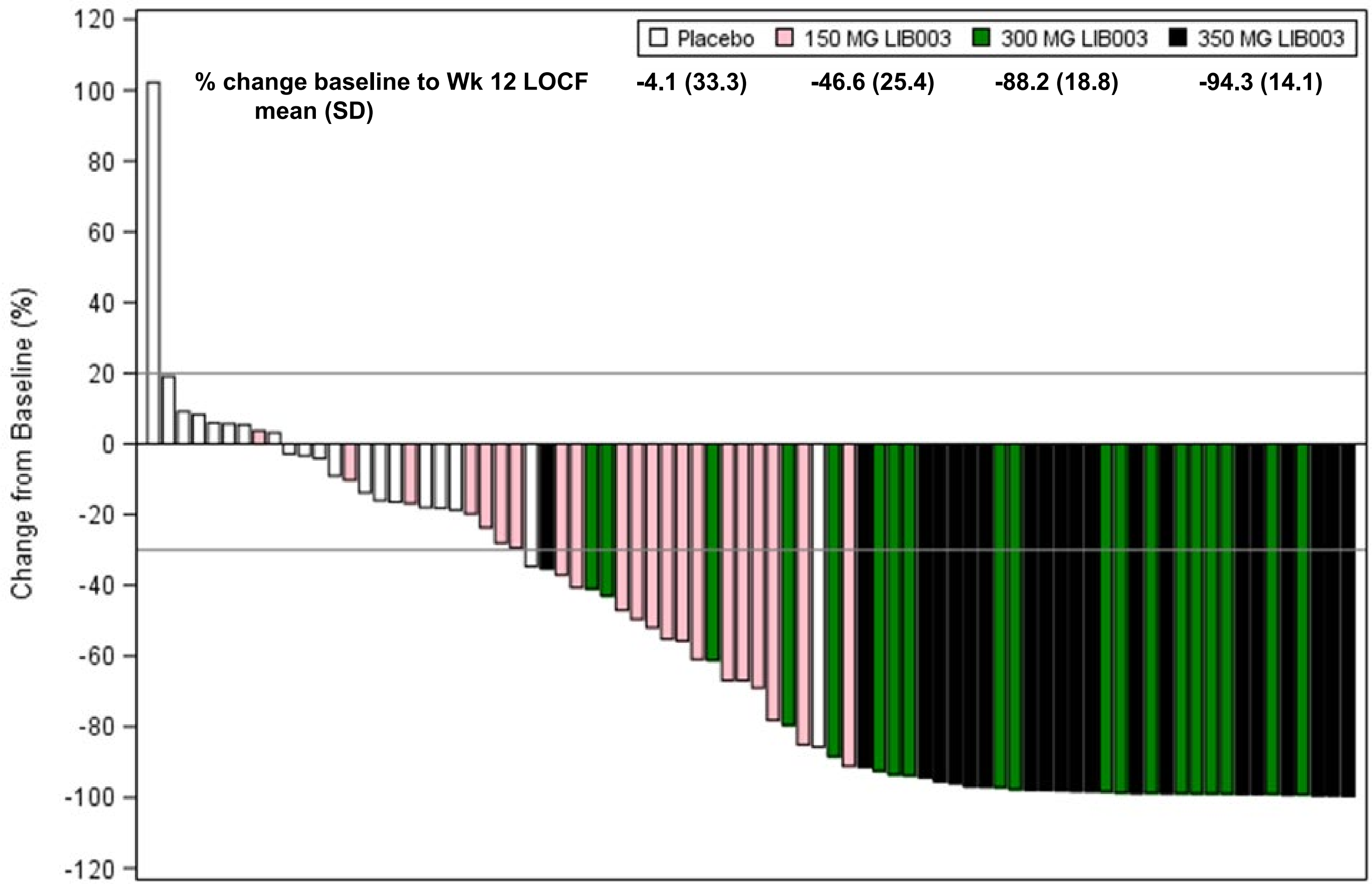
Percent Changes in LDL-C from baseline to week 12 versus placebo – ITT Population



***p<0.0001**

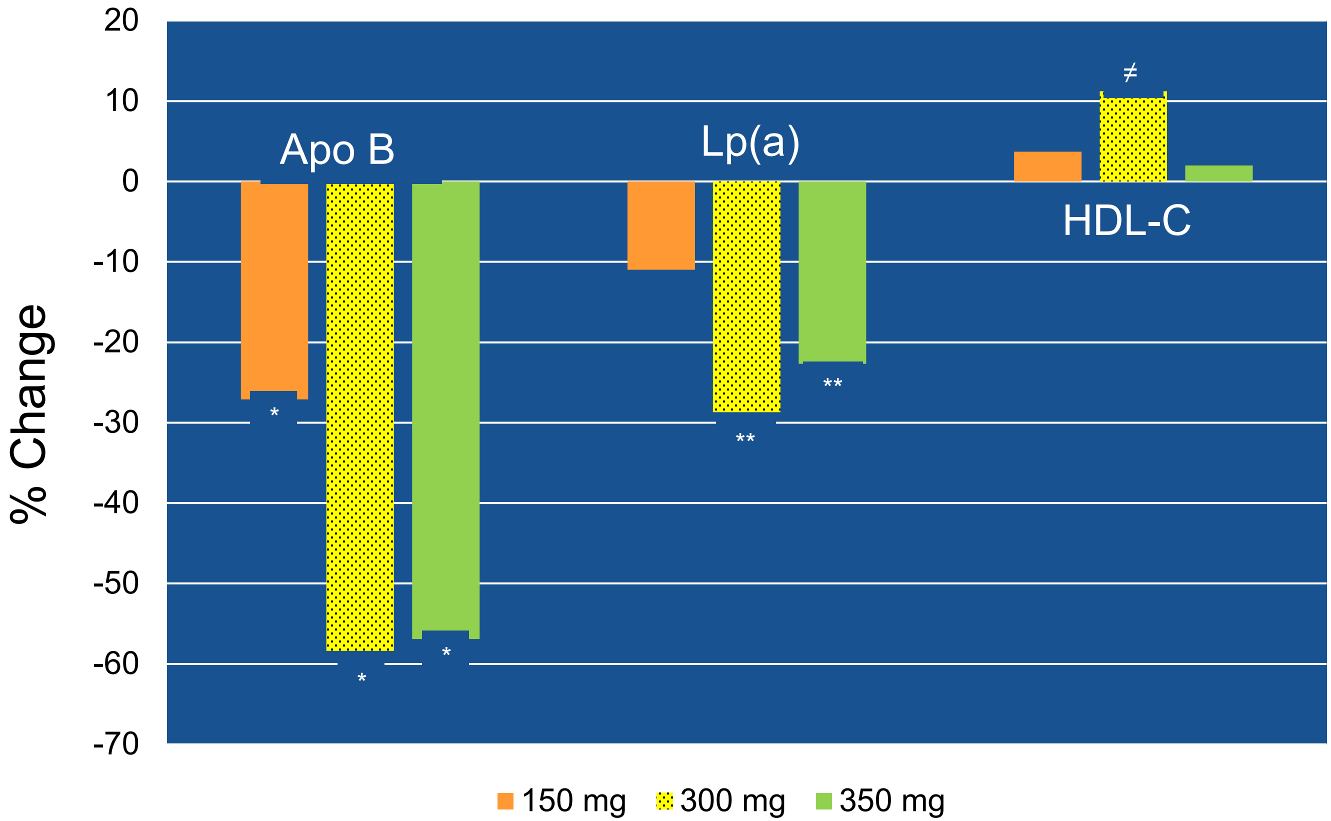
LIB003 Phase 2 dose ranging trial: *Results*

Percent Changes in free PCSK9 from baseline to week 12 – ITT Population



LIB003 Phase 2 dose ranging trial: ***Results***

Changes in Apo B, Lp(a) and HDL-C; baseline to week 12 versus placebo (ITT Population)



≠ p<0.02 ** p<0.001 * p<0.0001

LIB003 Phase 2 dose ranging trial:

Adverse Events – Safety Population

	Placebo (N = 20) n (%)	LIB003 150 mg (N = 21) n (%)	LIB003 300 mg (N = 19) n (%)	LIB003 350 mg (N = 21) n (%)
Any TEAE	10 (50.0)	9 (42.9)	11 (57.9)	13 (61.9)
TEAE by Maximum Severity: Mild	5 (25.0)	5 (23.8)	8 (42.1)	5 (23.8)
Moderate	4 (20.0)	3 (14.3)	2 (10.5)	5 (23.8)
Severe	1 (5.0)	1 (4.8)	1 (5.3)	3 (14.3)
study drug-related TEAE	2 (10.0)	1 (4.8)	1 (5.3)	2 (9.5)
by maximum severity Mild	1 (5.0)	1 (4.8)	1 (5.3)	2 (9.5)
Moderate	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
treatment-emergent SAE	1 (5.0)	1 (4.8)	2 (10.5)	2 (9.5)
study drug-related treatment-emergent SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
study drug-related TEAE leading to study drug discontinuation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The most commonly reported TEAEs were: fatigue in 5%; injection site bruising in 5%; upper respiratory tract infection in 5%; and dyspnea in 5%. All other TEAEs were reported by <5% subjects

LIB003 Phase 2 dose ranging trial:

Drug Related Adverse Events, Laboratory Safety and Immunogenicity

	Placebo (N = 20) n (%)	LIB003 150 mg (N = 21) n (%)	LIB003 300 mg (N = 19) n (%)	LIB003 350 mg (N = 21) n (%)
Any drug-related TEAE	2 (10.0)	1 (4.8)	1 (5.3)	2 (9.5)
Injection site reactions	1 (5.0)	1 (4.8)	1 (5.3)	2 (9.5)
Injection site erythema	0 (0.0)	0 (0.0)	1 (5.3)	2 (9.5)
Injection site bruising	0 (0.0)	1 (4.8)	0 (0.0)	0 (0.0)
Injection site pruritus	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.8)
Myalgia	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)

Laboratory Safety Tests:

- No clinically meaningful increases or trends in LFTs (ALT, AST, or bilirubin) in any treatment group or differences between placebo or LIB003-treated groups.
- No subject with ALT or AST >3 × ULN and no bilirubin >2 × ULN.
- A number of subjects in all treatment groups experienced non-sustained increases in CK, which were exercise- or activity related and none >5 × ULN.
- No clinically significant increases or differences between treatment groups in renal function, glucose, other chemistry or hematology parameters.

Immunogenicity:

- Two patients with ADAs >4 x MRD* = 3.3%: no NAbs and no attenuation of PCSK9 suppression or LDL-C reduction – all tested negative for ADA on 3 month follow up

*MDR = minimum required dilution: Kastelein JJK et al European Heart Journal (2016) 37, 1360–1369

LIB003 Phase 2 dose ranging trial: *Conclusions*

- **Monthly LIB003 doses of 150, 300 and 350 mg for 12 weeks were well tolerated with no significant safety concerns.**
- **All doses induced rapid, sustained, and significant mean decreases in LDL-C and serum unbound (free) PCSK9 levels**
- **Largest mean decrease of LDL-C observed in the 300 mg cohort and higher dose of 350 mg did not produce further LDL-C reduction indicating maximal suppression of PCSK9 was achieved with 300 mg after which no additional LDL-C reduction occurred.**
- **The 150 mg dose, although achieving similar reductions as 300 mg and 350 mg every 2 weeks post-dose, was insufficient to maintain maximal LDL-C reductions for the full 4 weeks between doses.**
- **ADAs above minimum required dilution (MRD) cut-point was 3.3% with no NAbs and no pharmacodynamics impairment on efficacy**
- **Based on these results, LIB003 300 mg SC Q4W dose was selected for the open-label extension and Phase 3 development.**