Low Density Lipoprotein Cholesterol Reduction and Safety with LIB003, an anti-Proprotein Convertase Subtilsin/Kexin Type 9 Fusion Protein (PCSK9): Results of a Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study

1051-05

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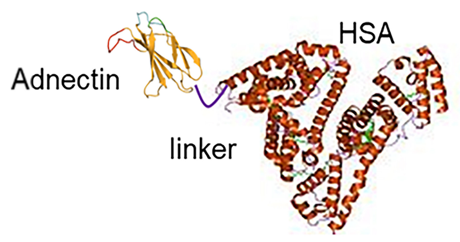
Introduction

- Based on >200,000 patients in randomized clinical trials, for every 1 mmol/L (~39 mg/dL) reduction in LDL-C, the risk of major CVD events is reduced by 24%[1]
- Recent CVD outcome studies, FOURIER and ODYSSEY Outcomes, with PCSK9 monoclonal antibodies (mAbs), confirmed this relationship for PCSK9 mediated LDL-C reduction[2,3]
- Two PCSK9 mAbs, evolocumab and alirocumab, are currently marketed and a siRNA, inclisiran, is in Phase 3 development[4]
- LIB003 is a recombinant 77 kDa fusion protein consisting of a PCSK9-binding domain and human serum albumin (HSA); it is being developed for the reduction of LDL-C in patients with heterozygous and homozygous FH, CVD, or those at high risk of CVD who require additional LDL-C reduction



Objective

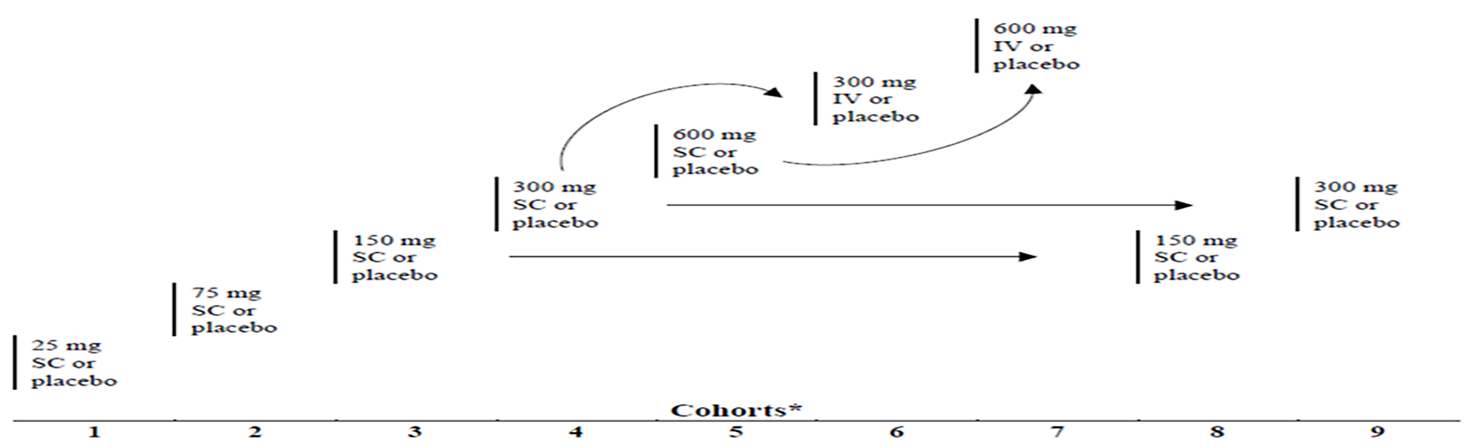
- Primary Objective: To evaluate the safety, tolerability, pharmacokinetics and LDL-C lowering of single subcutaneous (SC) or intravenous (IV) doses of LIB003 25 mg to 600 mg in subjects with LDL-C ≥100 mg/dL on diet or statin therapy
- Secondary Objectives:
  - To assess the PD effects on serum unbound/total PCSK9 and LDL-C levels
  - To assess effects on total cholesterol (TC), HDL-C, VLDL-C,TG, Apo A1 and B, and Lp(a)
  - To assess PK, bioavailability and dose proportionality of SC and IV dosing
  - To assess immunogenicity; frequency of anti-drug antibodies (ADAs) to LIB003
- Exploratory Objective: To compare the PD effects on non-statin and statin treated subject

Methods

Study Design

- Placebo (PBO)-controlled, double-blind, single ascending dose (SAD) study
- All subjects in-patients for 72 hrs post dose and followed as out-patients on days 5, 8, 11, 15, 18, 22, 29, 36 and 43
- All cohorts enrolled sentinel group (3 subjects; 2 LIB003:1 PBO)
- Randomization to next cohort dose commenced after safety review at day 8 of ≥5 subjects in a cohort

Figure 1. LIB003 Single Ascending Dose Schedule



IV = intravenous; SC = subcutaneous

Cohorts 1-7 diet only: Cohort 1: 25 mg SC, Cohort 2: 75 mg SC, Cohort 3: 150 mg SC, Cohort 4: 300 mg SC, Cohort 5: 600 mg SC, Cohort 6: 300 mg IV infusion, and Cohort 7: 600 mg IV infusion

Cohorts 8 - 9 stable on statin: Cohort 8: 150 mg SC and Cohort 9: 300 mg SC

Patient Population

Key inclusion criteria

- Screening LDL-C ≥100 mg/dL and ≤190 mg/dL in non-statin groups and LDL-C ≥100 mg/dL in statin groups; TG ≤250 mg/dL in all groups
- Subjects on a stable dose of no more than 1 antihypertensive drug in the non-statin-treated cohorts and 2 antihypertensive agents in the stable statin cohorts

Key exclusion criteria

- Systolic blood pressure <90 mmHg or >160 mmHg or diastolic blood pressure <50 mmHg or >100 mmHg at screening
- Screening AST or ALT >2 × ULN, total bilirubin >1.5 × ULN,TSH >1.5 × ULN, CK >3 × ULN, GFR <60 ml/min

Statistical Analysis

- All subjects who received ≥1 dose of study drug-TEAE, clinical laboratory, vital sign, ECG etc. were summarized
- All subjects with valid PK parameters (Cmax and AUC)-Concentrations summarized by nominal time, parameters calculated by standard non-compartmental methods (NCA) and summarized and analyzed for dose proportionality and bioavailability using power model and t-test respectively
- All subjects with a post-baseline PD measurement-PCSK9 concentration and lipid panel were summarized, plotted, and tested using ANOVA model as appropriate

Results

- Screened 104 subjects, 63 subjects were randomized, 18 randomized to placebo and 45 to LIB003
- All 63 (100%) subjects completed the study and all visits; adherence to study drug was 100% as given in the unit

Table 1: Baseline Demographics and LDL-C

Characteristics	Cohort: 25 mg D SC N=5	75 mg D SC N=5	150 mg D SC N=5	300 mg D SC N=5	600 mg D SC N=5	300 mg D IV N=5	600 mg D IV N=5	150 mg S SC N=5	300 mg S SC N=5	PBO N=18
Age (years) Mean (range)	42.8 (31-57)	48.8 (27-58)	46.8 (32-57)	54.6 (30-69)	46.0 (26-61)	52.8 (39-62)	48.8 (35-58)	52.2 (30-62)	50.6 (31-70)	54.7 (32-69)
Gender										
Female:male	0:5	2:3	1:4	4:1	3:2	3:2	1:4	3:2	3:2	4:14
Race White:African American	1:4	1:4	2:3	3:2	2:3	3:2	5:0	5:0	4:1	10:8
BMI (kg/m^2) Mean (SD)	30.78 (3.932)	28.81 (1.225)	26.80 (4.345)	24.13 (4.215)	25.86 (5.564)	26.19 (3.002)	29.50 (4.696)	30.46 (2.702)	29.16 (2.885)	29.49 (5.328)
LDL-C mg/dL Mean (SD)	124.6 (21.55)	128.2 (32.25)	132.9 (21.43)	124.8 (16.24)	130.3 (18.92)	118.2 (18.81)	133.0 (7.19)	123.8 (17.74)	119.7 (11.70)	134.4 (27.01)

D=diet only (non-statin); S=statin

Table 2: Treatment-Emergent Adverse Events by Treatment – Safety Population

Characteristics	Cohort: 25 mg D SC N=5 n (%)	75 mg D SC N=5 n (%)	150 mg D SC N=5 n (%)	300 mg D SC N=5 n (%)	600 mg D SC N=5 n (%)	300 mg D IV N=5 n (%)	600 mg D IV N=5 n (%)	150 mg S SC N=5 n (%)	300 mg S SC N=5 n (%)	All LIB N=45 n (%)	PBO N=18 n (%)
Subjects with any TEAE	2 (40.0)	0 (0.0)	2 (40.0)	2 (40.0)	0 (0.0)	3 (60.0)	3 (60.0)	1 (20.0)	2 (40.0)	**15 (33.3)**	**7 (38.9)**
Subjects with any TEAE by maximum severity											
Mild	2 (40.0)	0 (0.0)	1 (20.0)	2 (40.0)	0 (0.0)	2 (40.0)	3 (60.0)	1 (20.0)	2 (40.0)	**13 (28.9)**	**6 (33.3)**
Moderate	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	**2 (4.4)**	**1 (5.6)**
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**
Any drug-related TEAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	**2 (4.4)**	**1 (5.6)**
Subjects with any drug-related TEAE by maximum severity											
Mild	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	1 (20.0)	**2 (4.4)**	**1 (5.6)**
Moderate	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**
Subjects with any SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	**1 (2.2)**	**1 (5.6)**
Any drug-related SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**
TEAE related to ISR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0 (0.0)**	**0 (0.0)**

D=diet only (non-statin); S=statin

- Most commonly reported TEAEs:
  - headache (4 [8.9%] LIB003 and 2 [11.1%] placebo);
  - upper respiratory tract infection (2 [4.4%] LIB003 and 1 [5.6%] placebo);
  - vision blurred, diarrhea, nausea, (2 [4.4%] LIB003 and 0 [0%] placebo)
- No clinically significant trends in laboratory findings. Hepatic transaminases (ALT and AST), showed no difference between PBO and LIB003 with no subject having values >2 x ULN

Figure 2: Changes in Free PCSK9

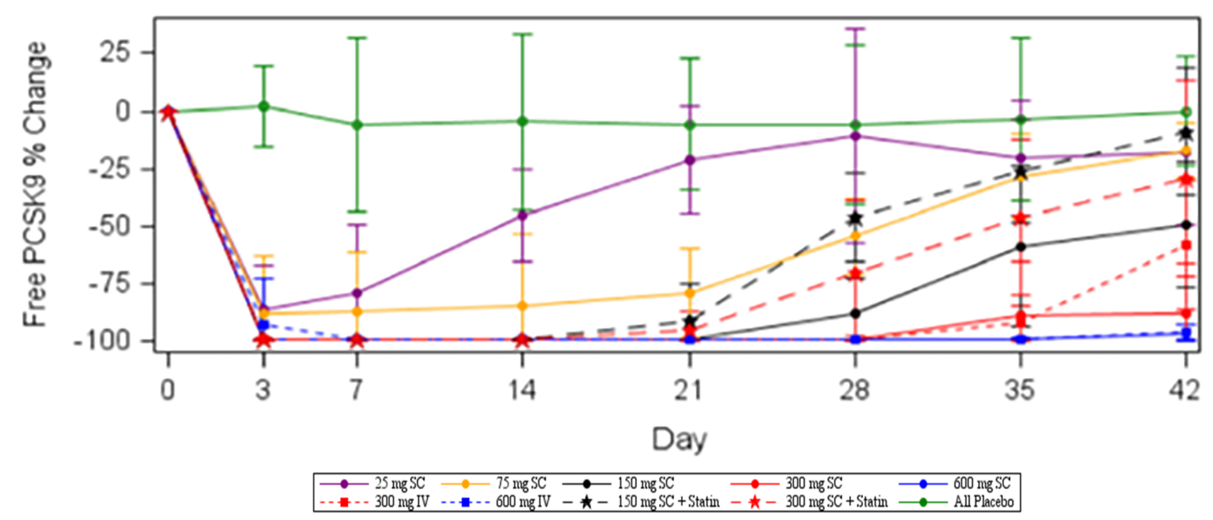


Figure 3: Changes in Calculated LDL-C

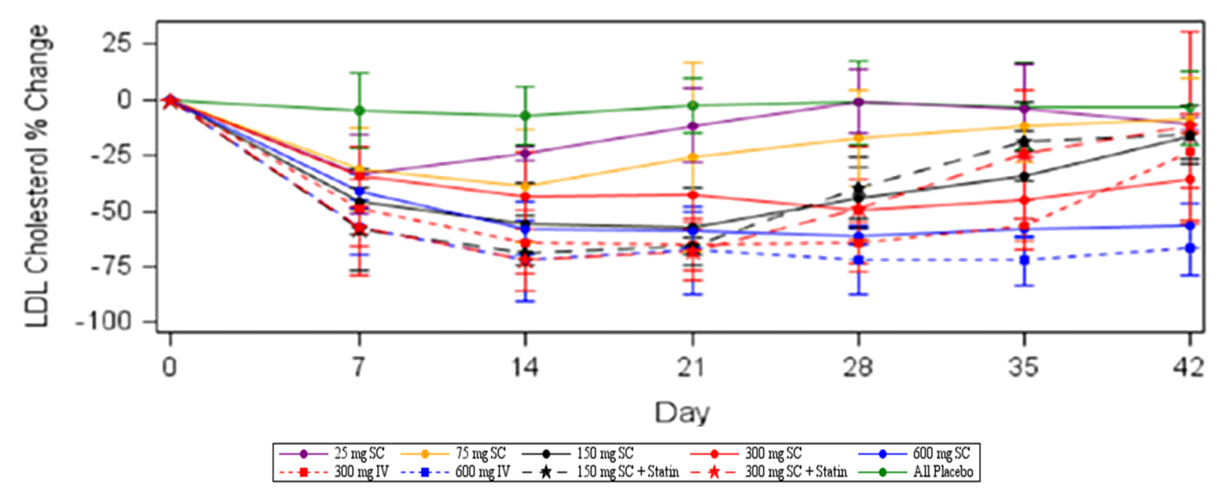


Table 3: Percent Changes in Apo B and Lp(a)

A. Apo B

Cohort	25 mg D SC N=5	75 mg D SC N=5	150 mg D SC N=5	300 mg D SC N=5	600 mg D SC N=5	300 mg D IV N=5	600 mg D IV N=5	150 mg S SC N=5	300 mg S SC N=5	PBO N=18
Baseline (mg/dL)										
Mean (SD)	96.6 (7.73)	91.8 (22.25)	98.6 (5.81)	91.6 (13.09)	99.6 (7.50)	85.4 (12.46)	102.4 (14.17)	99.8 (9.47)	96.8 (8.90)	105.5 (16.04)
% ↓ mean (min:max)										
Day 8	-28.82 (-33:-26)	-17.81 (-28:11)	-36.57 (-56:-19)	-29.35 (-43:12)	-30.29 (-42:-19)	-35.37 (-48:-17)	-42.86 (-54:-31)	-46.99 (-67:-40)	-47.48 (-59:-23)	-3.76 (-29:31)
Day 15	-21.51 (-27:-18)	-30.68 (-51:7)	-44.44 (-56:-33)	-34.90 (-58:-11)	-44.71 (-57:-36)	-46.68 (-59:-22)	-52.60 (-67:-35)	-54.91 (-66:-42)	-57.10 (-64:-49)	-3.13 (-19:28)
Day 29	-4.84 (-16:6)	-11.04 (-23 :11)	-36.81 (-52:-24)	-37.85 (-59:-23)	-46.10 (-54:-41)	-48.40 (-56:-37)	-56.21 (-66:-37)	-28.06 (-38:-13)	-42.64 (-67:-21)	-0.19 (-30:20)

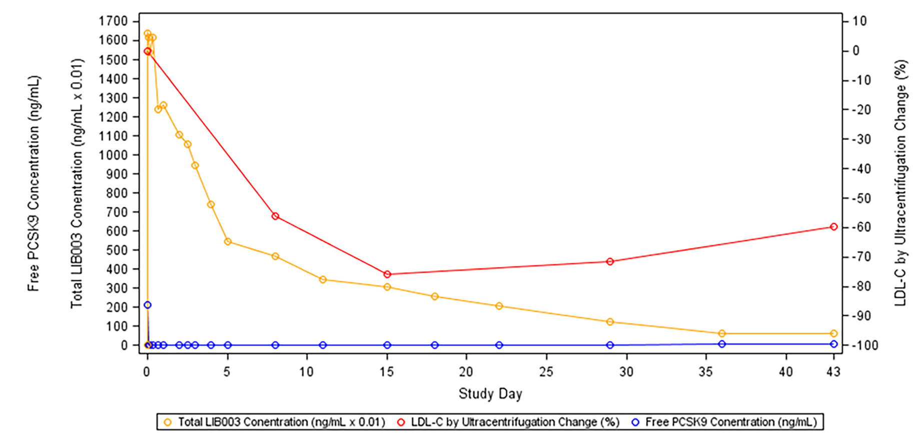
B.Lp(a)

Cohort	25 mg D SC N=5	75 mg D SC N=5	150 mg D - SC N=5	300 mg D - SC N=5	600 mg D - SC N=5	300 mg D - IV N=5	600 mg D - IV N=5	150 mg S - SC N=5	300 mg S - SC N=5	PBO N=18
Baseline (nmol/L)										
Median	46.0	18.0	57.0	25.0	35.0	41.0	125.0	44.0	66.0	41.0
% ↓ median										
Day 15	0.00	-22.22	-17.54	-41.18	-3.00	-25.77	-32.14	-36.52	-28.43	-7.74
Day 29	-3.03	8.82	-25.00	-37.78	-12.81	-22.68	-25.51	-31.82	-21.62	-12.40

D=diet only (non-statin); S=statin

Immunogenicity

- Anti-LIB003 antibodies (ADAs) detected in 2 subjects
- Subject in the 25 mg SC cohort developed low titer ADAs at Day 43; low and stable at follow-ups for 3 months
- Subject in 600 mg IV cohort developed ADA response at Day 22, which increased to a titer of 2560 by Day 43. Patient was followed at weekly then monthly intervals for 2.5 months. ADAs reached a maximal titer of 5120 at Day 113, then declined by 50% on Day 142. No neutralizing Abs detected and no apparent effect on or attenuation of free PCSK9 or LDL-C through Day 43



Conclusions

- Single doses of LIB003 from 25 to 600 mg were safe and well tolerated following SC and IV administration in healthy subjects and in subjects on statin therapy
- Treatment emergent AEs, all mild or moderate, were reported in 15 (33.3%) subjects with LIB003 and 7 (38.9%) subjects on placebo
- ADAs were detected in 2 subjects (25 mg SC and 600 mg IV) without NAbs and no apparent impact on free PCSK9 or LDL-C efficacy
- LIB003 given either SC or IV, resulted in rapid, significant, and substantial reductions in unbound (free) PCSK9 and LDL-C, Apo B and Lp(a) in a dose dependent manner
- At doses ≥150 mg maximal free PCSK9 and LDL-C reductions were maintained for 22 to 43 days in both non-statin and statin-treated patients.
- Based on these results LIB003 was considered both safe and effective with sufficient information to select appropriate doses for maximal and stable LDL-C reductions with SC dosing every 4 weeks.

References

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Disclosures

E.A. Stein: LIB Therapeutics (Cofounder, equity holder, and CEO), Amgen Inc., Adnexus Therapeutics/Bristol-Meyers Squibb, Genentech/Roche, Medicines Co and Regeneron/Sanofi (Consultant)

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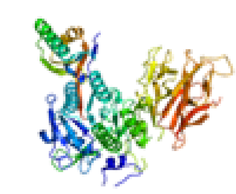

Lower is Better!