The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: LPL104884

Title: LPL104884: A multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study of SB-480848, an oral lipoprotein-associated phospholipase A_2 (Lp-PLA_2) inhibitor, in subjects with stable coronary heart disease (CHD) or CHD-risk equivalent to examine chronic inhibition of Lp-PLA_2, effects on circulating biomarkers associated with cardiovascular risk, safety and tolerability over 12 weeks.

Rationale: Elevated plasma levels of Lp-PLA_2 are associated with an increased risk of cardiovascular events. Short term (2 and 4 weeks) clinical studies of SB-480848 have shown dose-dependent inhibition of both plasma and intra-plaque Lp-PLA_2 activity. Consequently, this longer term (12 week) dose-ranging study of SB-480848, administered in conjunction with standardized statin therapy, was conducted to explore the dose response relationship of SB-480848 and plasma Lp-PLA_2 activity when administered with statin therapy, and to assess if inhibition of plasma Lp-PLA_2 activity remains sustained.

Phase: IIb

Study Period: 7 Nov 2005 to 27 Sep 2006

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study. Subjects who were not receiving statin therapy at the time of entry into the study were first given atorvastatin 20 mg for a two-week period. All subjects were randomized to the atorvastatin dose (20 mg or 80 mg), which was taken for the remainder of the study. The "Baseline" visit occurred after completion of the 4-week randomized atorvastatin dosing period, when subjects were randomized to one of four treatment arms (see "Treatment," below).

Centres: One hundred and fourteen centers from 15 countries: Argentina, Australia, Bulgaria, Canada, Denmark, Estonia, France, Germany, Hungary, Netherlands, New Zealand, Pakistan, Romania, Spain, and the United States.

Indication: Atherosclerosis

Treatment: Subjects were randomized 1:1:1:1 to SB-480848 Enteric Coated tablets 40 mg, 80 mg, 160 mg, or matching placebo for a period of 12 weeks.

Objectives: The primary study objective was to assess the ability of SB-480848 to produce sustained inhibition of plasma Lp-PLA_2 activity in subjects receiving concomitant atorvastatin therapy.

Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the on treatment sustained inhibition of plasma Lp-PLA_2 activity at trough levels of SB-480848 assessed by the difference in plasma Lp-PLA_2 activity from week 4 to the end of Week 12 in subjects on stable atorvastatin background treatment.

Secondary Outcome/Efficacy Variables:

Biomarker assessments

- Difference in dose dependent effects of SB-480848 on plasma Lp-PLA2 activity in the presence of 2 different regimens of background statin therapy (atorvastatin 20mg and 80mg) over 12 weeks of dosing.
- Difference in Baseline corrected values of plasma high sensitivity C reactive protein (hsCRP) between placebo and SB-480848 groups over 12 weeks of dosing.
- Difference in the proportion of subjects achieving prespecified targets of hsCRP (<1mg/L or <2mg/L) between placebo and SB-480848 groups over 12 weeks of dosing.
- Difference in Baseline-corrected values of other circulating inflammatory biomarkers (interleukin [IL]-6, matrix metalloproteinase-9 [MMP-9], and myeloperoxidase [MPO]) between placebo and SB-480848 groups over 12 weeks of dosing.

Pharmacokinetic assessments

- Estimation of pharmacokinetic (PK) parameters of SB-480848.

Statistical Methods: The primary comparison was based on two-sided 95% confidence intervals (CIs) for the change in log-transformed Lp-PLA_2 activity from Baseline [Week 4 (Visit 5)] to Week 12 (Visit 8) for each SB-480848 group. If the CI lay within equivalence limits of 0.883 to 1.132 (equivalent to ±0.124 on the log scale) the effect of SB-480848 inhibition of Lp-PLA_2 activity was considered to be sustained for that dose of SB-480848. The secondary endpoint was dose-response of SB-480848 over log-transformed Lp-PLA_2 activity. It was anticipated from previous PK/PD modeling that for the range of SB 480848 doses used in this study, the effect on change from Baseline (Visit 4) to Week 12 (Visit 8) in log-transformed Lp-PLA_2 activity would be linear against log-dose. Linear regressions of change from Baseline (Visit 4) to Week 12 (Visit 8) in log-transformed Lp-PLA_2 activity against log-dose of SB-480848 were fitted for each atorvastatin dose group. Atorvastatin level (20 mg and 80 mg) and treatment group were included in all statistical models. Interactions for atorvastatin level by treatment group were

tested at the 10% significance level. Eleven populations were defined for this study: Enrolled, Open-label Atorvastatin, Atorvastatin, Randomized Atorvastatin, Randomized and Dosed Atorvastatin, Atorvastatin Only, Randomized, Intent-to-Treat (ITT), Per-Protocol (PP), Safety, and Questionnaire Populations.
For the primary comparison, using a standard deviation (SD) for change in log-transformed Lp-PLA_2 activity values of 0.34 from Study SB-480848/005, an equivalence limit of +/-0.124 (equivalent to a 13% effect on inhibition) and 90% power, 196 evaluable patients per group were required, without adjustment for multiplicity or atorvastatin dose. Assuming a 15% dropout rate, 230 subjects per SB-480848 group (920 total) were planned to be randomized.

Study Population: Male or female subjects between the ages of 18 and 80 years of age with established, stable CHD or CHD-risk equivalent on a stable dose of a statin for ≥4 weeks prior to screening, with statin tolerability and low-density lipoprotein (LDL) <130 mg/dL (3.4mmol/L) or off statin therapy for ≥4 weeks with LDL <160 mg/dL (4.1 mmol/L) at the Prescreen Visit were allowed to participate.

Number of Subjects:	**Placebo**	**SB-480848 40 mg**	**SB-480848 80 mg**	**SB-480848 160 mg**
Planned, N	230	230	230	230
Randomized, N	242	240	240	242
Completed, n (%)	231 (95)	222 (93)	223 (93)	220 (92)
Total Number Subjects Withdrawn, n (%)	11 (5)	18 (8)	16 (7)	18 (8)
Withdrawn due to AEs, n (%)	4 (2)	9 (4)	9 (4)	12 (5)
Withdrawn for other reasons n (%)	7 (3)	9 (4)	7 (3)	6 (3)
Demographics				
N (ITT)	242	240	239	238
Females: Males	72:170	69:171	66:173	67:171
Mean Age, years (SD)	63.2 (8.48)	62.6 (9.13)	63.0 (9.04)	62.3 (8.68)
Race				
n	242	238	239	237
White	234 (97)	227 (95)	228 (95)	225 (95)
All Other[1]	8 (3)	11 (5)	11 (5)	12 (5)

1. Includes: African American/African Heritage, American Indian or Alaska Native, Asian (Central/South Asian Heritage; Japanese/East Asian Heritage/ South East Asian Heritage) American Indian or Alaska Native & White, Asian & White.

Primary Efficacy Results: Summary of the Analysis of Change in Plasma Lp-PLA_2 Activity from Week 4 to Week 12: Adjusted for Atorvastatin Level (Colorimetric assay method [CAM] Assay; ITT Population)

Treatment	**N**	**n**	**Week 4 Geometric Mean (95% CI)**	**Week 12 Geometric Mean (95% CI)**	**Adjusted Ratio (Week 12 vs. Week 4) (95% CI)**	**Adjusted Treatment Effect Ratio vs. Placebo (95% CI)**
Evaluation of Sustained Inhibition: Change from Week 4 to Week 12						
Placebo	242	174	124.59 (120.37, 128.96)	124.00 (120.00, 128.14)	0.996 (0.98, 1.01)	-
SB-480848 40 mg	240	152	69.23 (66.11, 72.50)	68.70 (65.51, 72.06)	0.992 (0.96, 1.03)	0.996 (0.96, 1.03)
SB-480848 80 mg	239	147	55.19 (51.74, 58.88)	55.93 (52.50, 59.59)	1.013 (0.97, 1.06)	1.017 (0.97, 1.07)
SB-480848 160 mg	238	145	42.49 (40.01, 45.12)	42.09 (39.46, 44.91)	0.990 (0.94, 1.04)	0.994 (0.94, 1.05)

Data analysed using analysis of covariance (ANCOVA), with Atorvastatin Level and Treatment included as covariates.

Secondary Efficacy Results: Biomarker Assessments: Difference in dose dependent effects of SB-480848 on plasma Lp-PLA_2 activity in the presence of 2 different regimens of background statin therapy (atorvastatin 20mg and 80mg) over 12 weeks of dosing (Colorimetric assay method [CAM] Assay Results)

Summary of the Analysis of Change in Plasma Lp-PLA_2 Activity from Baseline Adjusted for Atorvastatin Level (CAM Assay; ITT Population)

Treatment	N	n	Adjusted Ratio (95% CI)	Adjusted Treatment Effect Ratio vs. Placebo (95% CI)
Change from Baseline to Week 12				
Placebo	242	178	0.996 (0.98, 1.01)	-
SB-480848 40 mg	240	165	0.566 (0.55, 0.59)	0.569 (0.55, 0.59)
SB-480848 80 mg	239	160	0.450 (0.43, 0.47)	0.451 (0.43, 0.47)
SB-480848 160 mg	238	160	0.339 (0.32, 0.36)	0.340 (0.32, 0.36)

Summary of the Analysis of Change in Plasma Lp-PLA_2 Activity from Baseline Adjusted for Atorvastatin Level (Radiometric Assay)

Treatment	N	n	Adjusted Ratio (95% CI)	Adjusted Treatment Effect Ratio vs. Placebo (95% CI)
Change from Baseline to Week 12				
Placebo	242	91	1.020 (0.99, 1.05)	-
SB-480848 40 mg	240	80	0.331 (0.30, 0.37)	0.324 (0.29, 0.37)
SB-480848 80 mg	239	67	0.194 (0.17, 0.23)	0.190 (0.16, 0.22)
SB-480848 160 mg	238	85	0.120 (0.10, 0.14)	0.118 (0.10, 0.14)

Summary of the Analysis of Change in High Sensitivity C-Reactive Protein Adjusted for Atorvastatin Level-

Treatment	N	n	Adj. Treatment Effect Ratio vs. Placebo[1] (95% C-I)
Change from Baseline to Week 12			
Placebo	242	177	-
SB-480848 40 mg	240	166	0.940 (0.78, 1.13)
SB-480848 80 mg	239	161	0.997 (0.82, 1.20)
SB-480848 160 mg	238	161	0.870 (0.72, 1.05)

1. High sensitivity C-reactive protein (hsCRP) has a skewed distribution and values were log transformed before analysis. Analysis was performed on the log transformed data and back transformed for presentation in the summary tables.

Secondary Efficacy Results: Biomarker Assessments: Difference in the proportion of subjects achieving prespecified targets of hsCRP (<1mg/L or <2mg/L) between placebo and SB-480848 groups over 12 weeks of dosing.

Cochran-Armitage Trend Test for Treatment over Proportions of Subjects with Sensitivity C-Reactive Protein (hsCRP) Levels <1mg/L and <2mg/L over 12 weeks of dosing

Treatment	N	n	n (%) hsCRP<1 mg/L
Placebo	118	99	56 (57)
SB-480848 40 mg	109	89	49 (55)
SB-480848 80 mg	110	89	49 (55)
SB-480848 160 mg	115	94	50 (53)
Treatment	**N**	**n**	**n (%) hsCRP<2 mg/L**
Placebo	118	99	83 (84)
SB-480848 40 mg	109	89	71 (80)
SB-480848 80 mg	110	89	66 (74)
SB-480848 160 mg	115	94	74 (79)

Secondary Efficacy Results: Biomarker Assessments: Difference in Baseline-corrected values of other circulating inflammatory biomarkers (interleukin [IL]-6, matrix metalloproteinase- 9 [MMP-9], and myeloperoxidase [MPO]) between placebo and SB-480848 groups over 12 weeks of dosing.

Summary of Change From Baseline to Week 12 in Inflammatory Biomarkers (ITT Population)					
Interleukin 6 (ng/L)					
Treatment	**N**	**n**	**Baseline (Visit 4) Geometric Mean (95% CI)**	**Week 12 (Visit 8) Geometric Mean (95% CI)**	**Ratio (Week 12 vs. Baseline) (95% CI)**
Placebo	242	171	2.446 (2.25, 2.66)	2.278 (2.05, 2.53)	0.931 (0.85, 1.02)
SB-480848 40 mg	240	149	2.574 (2.32, 2.86)	2.173 (1.95, 2.42)	0.845 (0.77, 0.93)
SB-480848 80 mg	239	146	2.345 (2.13, 2.59)	2.165 (1.94, 2.42)	0.923 (0.84, 1.02)
SB-480848 160 mg	238	150	2.726 (2.43, 3.05)	2.141 (1.94, 2.36)	0.785 (0.72, 0.86)
MMP-9 (Total) (µg/L)					
Placebo	242	178	470.569 (422.45, 524.17)	479.101 (428.78, 535.33)	1.018 (0.92, 1.13)
SB-480848 40 mg	240	165	505.316 (444.94, 573.88)	494.542 (433.43, 564.27)	0.979 (0.87, 1.11)
SB-480848 80 mg	239	161	447.830 (398.09, 503.78)	420.552 (371.93, 475.53)	0.939 (0.84, 1.05)
SB-480848 160 mg	238	163	475.211 (422.49, 534.51)	504.819 (445.22, 572.40)	1.062 (0.94, 1.20)
Myeloperoxidase (MPO) (pmol/L)					
Placebo	242	179	507.521 (468.50, 549.80)	515.464 (472.80, 561.98)	1.016 (0.94, 1.10)
SB-480848 40 mg	240	165	557.826 (508.59, 611.83)	552.172 (501.16, 608.38)	0.990 (0.91, 1.08)
SB-480848 80 mg	239	162	524.276 (476.00, 577.45)	529.994 (478.81, 586.65)	1.011 (0.92, 1.11)
SB-480848 160 mg	238	163	587.509 (535.42, 644.66)	586.033 (533.41, 643.85)	0.997 (0.90, 1.10)

Secondary Efficacy Results: Pharmacokinetic Assessments: The pharmacokinetics of darapladib in patients with stable CHD or CHD-risk equivalent were influenced by age and CYP3A4 inhibitor co-medication. Darapladib CL/F for the typical patient in study LPL104884 (median age 64 years) was 255 L/h with CL/F changing approximately 1% per year (decreased for patients older than 64 years, increased for patients less than 64 years). CYP3A4 inhibitor co-medication was shown to decrease CL/F by approximately 20%. Effects of age and CYP3A4 inhibitor co-medication on darapladib exposure are minor and are not considered clinically significant.

The pharmacokinetic/pharmacodynamic relationship between darapladib and plasma Lp-PLA2 activity was described by a sigmoid inhibitory Emax model. Baseline plasma Lp-PLA2 activity was influenced by gender and atorvastatin dose. Compared to male patients, baseline Lp-PLA2 activity levels were approximately 11% lower in females while patients receiving atorvastatin 80 mg showed approximately 10% lower baseline levels compared to patients receiving atorvastatin 20 mg.

Safety Results: A treatment-emergent AE was defined as an AE with onset on or after the start date of Investigational Product (IP) but not later than one day after the last date of study medication, including follow-up and post-study phases. A treatment-emergent serious adverse event (SAE) was defined as an SAE with onset on or after the start date of study medication and up to 28 days after the last dose of IP.

Most Frequent Treatment-emergent Adverse Events – (the most frequent 5 events in each treatment group)	**Placebo (N=242)**	**SB-480848 40mg (N=240)**	**SB-480848 80mg (N=239)**	**SB-480848 160mg (N=238)**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Subjects with Any AE(s), n (%)	124 (51)	144 (60)	156 (65)	138 (58)
Abnormal Feces	10 (4)	46 (19)	49 (21)	49 (21)
Urine Odor Abnormal	30 (12)	35 (15)	47 (20)	41 (17)
Dysgeusia	15 (6)	30 (13)	27 (11)	32 (13)
Breath Odor	11 (5)	24 (10)	15 (6)	27 (11)
Skin Odor Abnormal	7 (3)	23 (10)	21 (9)	25 (11)
Diarrhea	7 (3)	8 (3)	14 (6)	22 (9)
Serious Adverse Events: No treatment-emergent deaths occurred.				
	Placebo (N=242)	**SB-480848 40mg (N=240)**	**SB-480848 80mg (N=239)**	**SB-480848 160mg (N=238)**
	n (%) [related]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
Subjects with any Treatment-emergent SAE, n (%)[considered related by investigator]	7 (3) [0]	6 (3) [0]	7 (3) [0]	5 (2) [0]
Angina Pectoris	2 (<1) [0]	1 (<1) [0]	0	3 (1) [0]
Atrial fibrillation	1 (<1) [0]	1 (<1) [0]	0	0
Cardiac Failure Congestive	1 (<1) [0]	0	1 (<1) [0]	0
Angina Unstable	1 (<1) [0]	0	0	0
Cardiac Failure	1 (<1) [0]	0	0	0
Non-cardiac Chest Pain	0	0	2 (<1) [0]	0
Chest Pain	1 (<1) [0]	0	0	0
Loss of Consciousness	1 (<1) [0]	0	0	0
Sciatica	0	0	0	1 (<1) [0]
Syncope	0	0	1 (<1) [0]	0
Eye Hemorrhage	0	2 (<1) [0]	0	0
Appendicitis	0	0	0	1 (<1) [0]
Streptococcal Bacteremia	1 (<1) [0]	0	0	0
Fall	1 (<1) [0]	0	0	0
Femoral Neck Fracture	0	0	1 (<1) [0]	0
Asthma	0	0	1 (<1) [0]	0
Respiratory Distress	1 (<1) [0]	0	0	0
Hyponatremia	0	1 (<1) [0]	0	0
Prostate Cancer	0	1 (<1) [0]	0	0
Delusion	0	0	0	1 (<1) [0]
Renal Failure Acute	1 (<1) [0]	0	0	0
Subjects With Fatal SAEs Prior to Randomized IP	**n (%) [related]**			
	1 (<1) [0]			
Subjects with fatal SAEs, n (%)[considered related by investigator]	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**	**n (%) [related]**
	0	0	0	0
Conclusion: See publication listed below.				
Publication: Mohler ER, Ballantyne CM, Davidson MH, *et al*. The Effect of Darapladib on Plasma Lipoprotein-Associated Phospholipase A2 Activity and Cardiovascular Biomarkers in Patients With Stable Coronary Heart Disease or Coronary Heart Disease Risk Equivalent: The Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study. *JACC*. 2008. 51(17):1632-1641.				