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.:** SB-480848/026

**Title:** SB-480848/026: An international, multicenter, randomized, placebo controlled, parallel-group, 1 year treatment, integrated biomarkers and imaging study in subjects with angiographically documented coronary artery disease (CHD) to examine the effects of the novel lipoprotein-associated phospholipase A2 (Lp-$PLA_2$) inhibitor SB 480848 on intermediate cardiovascular endpoints, patient safety and tolerability.
**Short Title**: Integrated Biomarker and Imaging Study-2 (IBIS-2)

**Rationale:** Despite considerable progress in treating atherosclerotic vascular disease (ASVD), subjects at high risk continue to experience major cardiovascular events (e.g., cardiovascular death, myocardial infarction and stroke). Inflammation is a key process underlying the progression of atherosclerosis. Elevated plasma levels of Lp-$PLA_2$ are associated with an increased risk of cardiovascular disease. Clinical studies of SB-480848 have shown dose dependent inhibition of both plasma and intra-plaque levels of Lp-$PLA_2$ activity. The study was therefore conducted to evaluate the potential effect of SB-480848 on intermediate cardiovascular endpoints including circulating inflammatory biomarkers and coronary plaque biomechanical properties, as well as endothelial function, coronary plaque volume and composition.

**Phase:** IIb

**Study Period:** 10 Nov 2005 to 28 Aug 2007

**Study Design:** This study was an international, multicenter, randomized, double-blind, placebo-controlled, parallel group trial of SB-480848 in subjects with angiographically documented CHD. Subjects were randomized in a 1:1 ratio to receive oral doses of either 160 mg SB-480848 or placebo once-daily for 52 weeks. The study population was stratified into two groups: 1) subjects with acute coronary syndrome (ACS) and evidence of myocardial necrosis and 2) non-ACS subjects and those ACS subjects without evidence of myocardial necrosis.

**Centres:** The study was conducted in 23 centers in 10 countries: Austria, Belgium, Czech Republic, Denmark, Germany, The Netherlands, Norway, Poland, Spain, and Switzerland.

**Indication:** Atherosclerosis

**Treatment:** Subjects were randomized in a 1:1 ratio to receive oral doses of either 160 mg SB-480848 Enteric Coated tablets or placebo once-daily for 52 weeks**.**

**Objectives:** The primary objective of this study was to examine, in an exploratory fashion, whether darapladib provided measurable benefit on intermediate CV endpoints (plasma hsCRP levels and the density of high strain in the non-intervened segment of coronary arteries characterized by palpography) following 52 weeks of treatment.

**Primary Outcome/Efficacy Variables:**
This study had two, independent, co-primary endpoints in order to assess intermediate CV endpoints:

- Circulating hsCRP at the end of Week 52.
- Change from Baseline in the density of Rotterdam Classification (ROC) grade III/IV strain /10mm within the region of interest (ROI) on intravascular ultrasound (IVUS)-palpography at the end of Week 52.

**Secondary Outcome/Efficacy Variable(s):**
Key secondary efficacy endpoints included the following:
Imaging assessments: All imaging assessments were based on the same ≥ 10mm ROI of the non-intervened coronary arterial segment, unless otherwise stated.

- Changes from Baseline in IVUS Virtual Histology (IVUS-VH) assessments including necrotic core volume and necrotic core as a percent of IVUS-VH plaque at the end of Week 52.
- Changes from Baseline in IVUS-grey scale assessments including total atheroma volume and percent atheroma volume at the end of Week 52.
- Changes from Baseline in IVUS-grey scale assessments including vessel volume, lumen volume, mean plaque area, mean vessel area and mean lumen area at the end of Week 52.
- Changes from Baseline in IVUS-VH assessments including fibrous tissue volume, fibro-fatty volume, fibrous tissue as a percent of IVUS-VH plaque and fibro-fatty as a percent of IVUS-VH plaque at the end of Week 52.

Biomarker assessments:

- Circulating hsCRP at the end of Week 26.
- Lp-$PLA_2$ activity at the end of Week 26 and Week 52.
- Circulating biomarkers associated with inflammatory burden (IL-6, ICAM-1, sCD40L, MPO), plaque

instability (MMP-9 activity) and Lp-PLA$_2$ related targets (oxidized non-esterified fatty acids (NEFA), oxidized LDL, and oxPL/apoB) at the end of Week 26 and Week 52.

**Statistical Methods:** The sample size was determined using an estimation approach because the effects of an Lp-PLA$_2$ inhibitor on novel imaging parameters were unknown. For imaging endpoints, within treatment group change from baseline comparisons were evaluated by paired t-tests and between treatment group comparisons of change from baseline in IVUS measures were analyzed using an analysis of covariance (ANCOVA) modelling approach, adjusting for ACS status, pooled country, baseline value and matched segment length. Biomarkers generally followed skewed distributions; hence log transformations were applied prior to analysis. Between treatment group comparisons of the log transformed data were analyzed by visit using ANCOVA, adjusting for ACS status and pooled country. For the primary analyses, missing efficacy biomarker data from 3 months onwards was imputed using last observation carried forward (LOCF). No multiplicity adjustments were applied; two-sided p-values and 95% confidence intervals are presented.

**Study Population:** Main criteria for inclusion: Male or female subjects between the ages of 18 and 80 years of age were eligible if they had undergone clinically indicated cardiac catheterization for ACS (non-S-T elevation myocardial infarction [NSTEMI] or S-T elevation myocardial infarction [STEMI]) or non-ACS (e.g., chronic stable angina or troponin-negative resting chest pain). The protocol specified 50% of randomized subjects to have troponin-positive ACS. Eligible subjects were required to be on at least one oral antiplatelet agent (e.g., aspirin, clopidogrel) at the time of randomization.

| | **Placebo** | **SB-480848 160 mg EC** |
|---|---|---|
| Planned, N | 150 | 150 |
| Randomised, N | 155 | 175 |
| Number of Subjects (ITT) | 151 | 172 |
| Completed, n (%) | 130 (86) | 152 (88) |
| Total Number Subjects Withdrawn, N (%) | 21 (14) | 20 (12) |
| | **Placebo** | **SB-480848 160 mg EC** |
| Withdrawn due to Adverse Events n (%) | 11 (7) | 7 (4) |
| Subject Decided to Withdraw from Study | 5 (3) | 11 (6) |
| Withdrawn for other reasons n (%) | 5 (3) | 2 (1) |
| **Demographics** | **Placebo** | **SB-480848 160 mg EC** |
| N (ITT) | 151 | 172 |
| Females: Males | 25:126 | 32:140 |
| Mean Age, years (SD) | 57.3 (10.86) | 59.4 (9.81) |
| Race, n (%) | | |
| White | 146 (97) | 171 (>99) |
| Asian | 2 (1) | 1 (<1) |
| Japanese/East Asian Heritage/ South East Asian Heritage | 1 (<1) | 1 (<1) |
| Central/South Asian Heritage | 1 (<1) | 0 |
| African American/ African Heritage | 3 (2) | 0 |

**Co-Primary Efficacy Results: Change from Baseline in High Strain/10mm within the Region of Interest (Imaging Evaluable Population: SB-40848/026)**

| **IVUS-Palpography/High Strain Spots** | **Placebo N=121** | **SB-480848 160 mg EC N=146** |
|---|---|---|
| **n** | 115 | 131 |
| Baseline Mean (SD) | 0.440 (0.6409) | 0.427 (0.6343) |
| End of Study Mean (SD) | 0.438 (0.7112) | 0.353 (0.5493) |
| p-value vs. Baseline[1] | 0.964 | 0.138 |
| Change from Baseline Mean (SD) | -0.003 (0.6014) | -0.074 (0.5705) |
| Least Square Mean (LSM) for Treatment Difference[2] (95% CI) | -0.082 (-0.214, 0.049) | |
| p-value vs. Placebo | 0.220 | |

Note: N=number of subjects in the population; n= number of subjects with imaging at Baseline and end of study

1. Data analysed using paired t-test.
2. Data analysed using ANCOVA, with ACS status, pooled country, Baseline value, matched segment length and treatment included as covariates. Difference in adjusted means is shown [(SB-480848-Placebo). Display based on imaging evaluable population: observed case ≥6 month and ≥10 mm ROI.

| **Co-Primary Efficacy Results: hsCRP at the End of Week 52 (Biomarker Evaluable Population: SB-480848/026)** | | |
|---|---|---|
| **hsCRP** | **Placebo N=140** | **SB-480848 160 mg EC N=162** |
| **Week 52 LOCF, n** | 140 | 162 |
| Geometric Mean (mg/L) (95% CI) | 1.034 (0.854, 1.251) | 0.913 (0.765, 1.090) |
| Adjusted % Change[1] (95% CI) | -11.717 (-31.995, 14.607) | |
| p-value vs. Placebo | 0.348 | |
| Note: N=number of subjects in the population; n= number of subjects with an hsCRP value at Baseline and at least one other visit data for that assessment.<br>1. Data analysed using ANCOVA, with ACS status, pooled country and treatment included as covariates. Adjusted percent change is shown [(SB-480848-Placebo)-1 *100]. Display based on Last Observation Carried Forward (≥3 month). hsCRP had 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 Outcome Results: Imaging Assessments** | | |
| **Change from Baseline to the End of Study in Necrotic Core Volume and Necrotic Core as a Percent of VH Plaque (Imaging Evaluable Population: SB-480848/026)** | | |
| **IVUS-VH Assessment in ≥ 10 mm ROI** | **Placebo N=121** | **SB-480848 160 mg EC N=146** |
| **Necrotic Core Volume ($mm^3$), n** | 110 | 129 |
| Baseline Mean (SD) | 21.455 (21.9343) | 22.848 (24.4692) |
| End of Study Mean (SD) | 25.996 (25.3210) | 22.396 (25.8304) |
| p-value vs. Baseline[1] | 0.009 | 0.712 |
| Change from Baseline Mean (SD) | 4.540 (17.8824) | -0.452 (13.8734) |
| LSM for Treatment Difference[2] (95% CI) | -5.165 (-9.185, -1.145) | |
| **Necrotic Core as a % of VH Plaque, n** | 110 | 129 |
| Baseline Mean (SD) | 13.136 (7.6280) | 13.435 (6.5324) |
| End of Study Mean (SD) | 15.676 (8.8281) | 13.937 (7.6508) |
| p-value vs. Baseline[1] | 0.006 | 0.453 |
| Change from Baseline Mean (SD) | 2.540 (9.5789) | 0.502 (7.5812) |
| LSM for Treatment Difference[2] (95% CI) | -1.967 (-3.912, -0.022) | |
| Note: N=number of subjects in the population; n= number of subjects with imaging at Baseline and end of study.<br>1. Data analysed using paired t-test.<br>2. Data analysed using ANCOVA, with ACS status, pooled country, Baseline value, matched segment length and treatment included as covariates. Difference in adjusted means is shown (SB-480848-Placebo). Display based on imaging evaluable population: observed case ≥6 month and ≥10 mm ROI. | | |
| **Change from Baseline in Total Atheroma (Plaque) Volume and Percent Atheroma Volume at the End of Study (Imaging Evaluable Population: SB-480848/026)** | | |
| **IVUS-Grey Scale Assessment in ≥ 10 mm ROI** | **Placebo N=121** | **SB-480848 160 mg EC N=146** |
| **Total Atheroma (Plaque) Volume ($mm^3$), n** | 118 | 143 |
| Baseline Mean (SD) | 312.581 (148.8384) | 326.819 (188.9235) |
| End of Study Mean (SD) | 307.650 (147.5924) | 321.785 (187.7835) |
| p-value vs. Baseline[1] | 0.104 | 0.033 |
| Change from Baseline Mean (SD) | -4.932 (32.6958) | -5.034 (28.0180) |
| LSM for Treatment Difference[2] (95% CI) | 0.253 (-6.998, 7.504) | |
| **Percent Atheroma Volume, n** | 118 | 143 |
| Baseline Mean (SD) | 42.189 (9.9644) | 40.705 (10.1011) |
| End of Study Mean (SD) | 42.174 (9.5660) | 40.669 (10.1450) |
| p-value vs. Baseline[1] | 0.968 | 0.914 |
| Change from Baseline Mean (SD) | -0.015 (4.0442) | -0.036 (4.0061) |
| LSM for Treatment Difference[2] (95% CI) | -0.062 (-1.009, 0.886) | |

Note: N=number of subjects in the population; n= number of subjects with imaging at Baseline and end of study

1. Data analysed using paired t-test.
2. Data analysed using ANCOVA. Adjusted for ACS status, pooled country, Baseline value, matched segment length and treatment. Difference in adjusted means is shown [(SB-480848-Placebo). Display based on imaging evaluable population: observed case ≥6 month.

**Other Secondary Outcome Results: Other Imaging Assessments**

**Change from Baseline in vessel volume ($mm^3$), lumen volume (mm3), mean plaque area (mm2), mean vessel area (mm2) and mean lumen area ($mm^2$) at the End of Study (Imaging Evaluable Population: SB-480848/026)**

| IVUS-Grey Scale Assessment in ≥ 10 mm ROI | Placebo N=121 | SB-480848 160 mg EC N=146 |
|---|---|---|
| **Vessel Volume ($mm^3$), n** | 118 | 143 |
| Baseline Mean (SD) | 740.797 (310.4198) | 785.914 (379.2070) |
| End of Study Mean (SD) | 729.432 (307.9515) | 776.588 (381.8082) |
| Change from Baseline Mean (SD) | -11.366 (47.7463) | -9.325 (65.4456) |
| LSM for Treatment Difference[2] (95% CI) | 1.758 (-12.675, 16.192) | |
| **Lumen Volume ($mm^3$), n** | 118 | 143 |
| Baseline Mean (SD) | 428.255 (192.7913) | 459.160 (226.3259) |
| End of Study Mean (SD) | 421.836 (188.5428) | 454.870 (227.1584) |
| Change from Baseline Mean (SD) | -6.420 (42.6566) | -4.291 (65.3315) |
| LSM for Treatment Difference[2] (95% CI) | 2.627 (-11.171, 16.425) | |
| **Mean Plaque Area ($mm^2$), n** | 118 | 143 |
| Baseline Mean (SD) | 6.754 (2.7365) | 6.682 (3.0420) |
| End of Study Mean (SD) | 6.641 (2.6323) | 6.559 (2.9685) |
| Change from Baseline Mean (SD) | -0.113 (0.7098) | -0.123 (0.5601) |
| LSM for Treatment Difference[2] (95% CI) | -0.012 (-0.160, 0.136) | |
| **Mean Vessel Area ($mm^2$), n** | 118 | 143 |
| Baseline Mean (SD) | 15.772 (4.8245) | 16.042 (5.3557) |
| End of Study Mean (SD) | 15.521 (4.7509) | 15.856 (5.6405) |
| Change from Baseline Mean (SD) | -0.251 (0.9939) | -0.186 (1.3984) |
| LSM for Treatment Difference[2] (95% CI) | 0.048 (-0.258, 0.354) | |
| **Mean Lumen Area ($mm^2$), n** | 118 | 143 |
| Baseline Mean (SD) | 9.019 (2.9520) | 9.361 (3.1612) |
| End of Study Mean (SD) | 8.882 (2.8874) | 9.298 (3.5299) |
| Change from Baseline Mean (SD) | -0.137 (0.9692) | -0.063 (1.3671) |
| LSM for Treatment Difference[2] (95% CI) | 0.061 (-0.237, 0.360) | |

Note: N=number of subjects in the population; n= number of subjects with imaging at Baseline and end of study

1. Data analysed using paired t-test.
2. Data analysed using ANCOVA. Adjusted for ACS status, pooled country, Baseline value, matched segment length and treatment. Difference in adjusted means is shown [(SB-480848-Placebo). Display based on imaging evaluable population: observed case ≥6 month.

**Summary of Analysis of Change and Within Treatment Change from Baseline to Week 52 in IVUS-VH Assessments ROI >=10mm (Imaging Evaluable Population: SB-480848/026)**

| | Treatment Group | |
|---|---|---|
| IVUS-VH Assessment | Placebo N=121 | SB-480848 160 mg EC N=146 |
| **Fibrous tissue volume ($mm^3$), n** | 110 | 129 |
| Baseline Mean (SD) | 91.230 (60.1157) | 97.369 (80.7854) |
| End of Study Mean (SD) | 84.611 (58.3332) | 89.487 (76.6034) |
| Change from Baseline Mean (SD) | -6.619 (22.7201) | -7.882 (26.9678) |
| LSM for Treatment Difference[1] (95% CI) | -0.584 (-6.819, 5.650) | |

Note: N=number of subjects in the population; n= number of subjects with imaging at Baseline and end of study.

1. Data analysed using ANCOVA, with ACS status, pooled country, Baseline value, matched segment length and treatment included as covariates. Difference in adjusted means is shown [(SB-480848-Placebo)]. Display based on imaging evaluable population: observed case ≥6 month and ≥10 mm ROI.

| IVUS-VH Assessment | Treatment Group | |
|---|---|---|
| | Placebo N=121 | SB-480848 160 mg EC N=146 |
| **Fibrous tissue as a % of IVUS-VH plaque, n** | 110 | 129 |
| Baseline Mean (SD) | 59.350 (7.9721) | 59.641 (7.1445) |
| End of Study Mean (SD) | 55.456 (7.7847) | 57.537 (8.0709) |
| Change from Baseline Mean (SD) | -3.895 (7.8373) | -2.103 (6.8131) |
| LSM for Treatment Difference[1] (95% CI) | 2 (0.299, 3.701) | |
| **Fibro-fatty volume ($mm^3$), n** | 110 | 129 |
| Baseline Mean (SD) | 31.663 (30.7560) | 31.769 (30.8236) |
| End of Study Mean (SD) | 28.358 (27.0171) | 30.323 (30.0061) |
| Change from Baseline Mean (SD) | -3.305 (22.0273) | -1.446 (18.1968) |
| LSM for Treatment Difference[1] (95% CI) | 1.926 (-2.748, 6.600) | |
| **Fibro-fatty as a % of IVUS-VH plaque, n** | 110 | 129 |
| Baseline Mean (SD) | 20.173 (10.0118) | 20.190 (9.4430) |
| End of Study Mean (SD) | 19.466 (11.3868) | 20.084 (9.7945) |
| Change from Baseline Mean (SD) | -0.707 (11.2946) | -0.106 (10.3309) |
| LSM for Treatment Difference[1] (95% CI) | 0.739 (-1.635, 3.114) | |

Note: N=number of subjects in the population; n= number of subjects with imaging at Baseline and end of study.

1. Data analysed using ANCOVA, with ACS status, pooled country, Baseline value, matched segment length and treatment included as covariates. Difference in adjusted means is shown [(SB-480848-Placebo)]. Display based on imaging evaluable population: observed case ≥6 month and ≥10 mm ROI.

**Secondary Outcome Results: Biomarker Assessments**

**hsCRP at Week 26 (Biomarker Evaluable Population: SB-480848/026)**

| hsCRP | Treatment Group | |
|---|---|---|
| | Placebo N=140 | SB-480848 160 mg EC N=162 |
| **Week 26 LOCF, n** | 140 | 162 |
| Geometric Mean (mg/L) (95% CI) | 0.924 (0.774, 1.102) | 0.960 (0.815, 1.131) |
| Adjusted % Change[1] (95% CI) | 3.977 (-18.331, 32.379) | |

Note: N=number of subjects in the population; n= number of subjects with an hsCRP value at Baseline and at least one other visit data for that assessment.

1. Data analysed using ANCOVA, with ACS status, pooled country and treatment included as covariates. Adjusted percent change is shown [(SB-480848-Placebo)-1 *100]. Display based on Last Observation Carried Forward (≥3 month). hsCRP had 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.

**Lp-$PLA_2$ Activity at the End of Week 26 and Week 52 (Biomarker Evaluable Population: SB-480848/026)**

| Lp-$PLA_2$ Activity | Placebo N=140 | SB-480848 160 mg EC N=162 |
|---|---|---|
| **Week 26 LOCF, n** | 140 | 162 |
| Geometric Mean (µmol/min/L) | 151.98 | 59.26 |
| (95% CI) | (146.04, 158.16) | (55.94, 62.77) |
| Adjusted % Change[1] (95% CI) | -60.737 (-63.486, -57.780) | |
| **Week 52 LOCF, n** | 140 | 162 |
| Geometric Mean (µmol/min/L) | 152.81 | 61.59 |
| (95% CI) | (146.56, 159.34) | (58.01, 65.38) |
| Adjusted % Change[1] (95% CI) | -59.326 (-62.210, -56.222) | |

Note: N=number of subjects in the population; n= number of subjects with an Lp-$PLA_2$ value at Baseline and at least one other visit data for that assessment.

1. Data analysed using ANCOVA, with ACS status, pooled country and treatment included as covariates. Adjusted percent change is shown [(SB-480848-Placebo)-1 *100]. Display based on Last Observation Carried Forward (≥3 month). Lp-$PLA_2$ had 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.

| Other Secondary Outcome Results: Other Biomarker Assessments at the End of Weeks 26 and 52 | | |
|---|---|---|
| **Other Biomarker, Week 26 LOCF-** | | |
| | **Treatment Group** | |
| **Biomarker, Week 26 LOCF** | **Placebo N=140** | **SB-480848 160 mg EC N=162** |
| **IL-6, n** | 135 | 160 |
| Geometric Mean (ng/L) (95% CI) | 1.851 (1.609, 2.128) | 1.979 (1.741, 2.250) |
| Adjusted % Change[1] (95% CI) | 6.958 (-11.568, 29.364) | |
| **ICAM-1, n** | 140 | 161 |
| Geometric Mean (ng/mL) (95% CI) | 269.444 (258.932, 280.383) | 266.447 (256.744, 276.516) |
| Adjusted % Change[1] (95% CI) | -1.112 (-6.363, 4.433) | |
| **MPO, n** | 139 | 162 |
| Geometric Mean (pmol/L) (95% CI) | 324.534 (294.535, 357.589) | 378.811 (346.275, 414.405) |
| Adjusted % Change[1] (95% CI) | 16.725 (2.232, 33.271) | |
| **MMP-9 Activity, n** | 140 | 162 |
| Geometric Mean (µg/L) (95% CI) | 481.581 (429.483, 539.997) | 471.477 (423.894, 524.401) |
| Adjusted % Change[1] (95% CI) | -2.098 (-16.303, 14.517) | |
| **oxPL/apoB B100 Ratio, n** | 140 | 162 |
| Geometric Mean (RLU) (95% CI) | 3114.718 (2695.797, 3598.739) | 3106.872 (2716.642, 3553.156) |
| Adjusted % Change[1] (95% CI) | -0.252 (-18.151, 21.561) | |
| | **Treatment Group** | |
| **Biomarker, Week 52 LOCF** | **Placebo N=140** | **SB-480848 160 mg EC N=162** |
| **IL-6, n** | 137 | 161 |
| Geometric Mean (ng/L) (95% CI) | 2.019 (1.749, 2.331) | 2.267 (1.985, 2. 588) |
| Adjusted % Change[1] (95% CI) | 12.255 (-7.725, 36.562) | |
| **ICAM-1, n** | 140 | 161 |
| Geometric Mean (ng/mL) (95% CI) | 277.947 (265.822, 290.624) | 268.950 (257.998, 280.367) |
| Adjusted % Change[1] (95% CI) | -3.237 (-8.976, 2.865) | |
| **MPO, n** | 139 | 162 |
| Geometric Mean (pmol/L) (95% CI) | 370.999 (331.989, 414.592) | 405.339 (365.718, 449.253) |
| Adjusted % Change[1] (95% CI) | 9.256 (-6.136, 27.172) | |
| **MMP-9 Activity, n** | 140 | 162 |
| Geometric Mean (µg/L) (95% CI) | 488.998 (432.454, 552.935) | 498.709 (444.895, 559.032) |
| Adjusted % Change[1] (95% CI) | 1.986 (-13.807, 20.673) | |
| **oxPL/apoB B100 Ratio, n** | 140 | 162 |
| Geometric Mean (RLU) (95% CI) | 2711.118 (2017.411, 3643.363) | 2478.376 (1883.212, 3261.634) |
| Adjusted % Change[1] (95% CI) | -8.585 (-39.007, 37.012) | |

Note: N=number of subjects in the population; n= number of subjects with an hsCRP value at Baseline and at least one other visit data for that assessment.

1. Data analysed using ANCOVA, with ACS status, pooled country and treatment included as covariates. Adjusted percent change is shown [(SB-480848-Placebo)-1 *100]. Display based on Last Observation Carried Forward (≥3 month). Biomarkers had 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.

**Safety Results:** A treatment-emergent AE was an event that emerged at any time on or after first dose of IP, until 1 day after stopping study medication, having been absent pre-treatment, or worsened relative to the pre-treatment state. Treatment emergent summaries included AEs that occurred with an onset date up until 1 day after stopping Investigational Product.

| **Most Frequent Treatment Emergent Adverse Events – (>= 3% in any Treatment Group (Preferred Term)** | **Placebo (N=151)** | **SB-480848 160 mg EC (N=172)** |
|---|---|---|
| Subjects with any AE(s), n (%) | 105 (70) | 117 (68) |
| Angina pectoris | 18 (12) | 22 (13) |
| Abnormal faeces | 2 (1) | 18 (10) |

| **Most Frequent Treatment Emergent Adverse Events – (>= 3% in any Treatment Group (Preferred Term)** | **Placebo (N=151)** | **SB-480848 160 mg EC (N=172)** |
|---|---|---|
| Urine odour abnormal | 4 (3) | 17 (10) |
| Diarrhoea | 3 (2) | 13 (8) |
| Non-cardiac chest pain | 9 (6) | 12 (7) |
| Coronary artery disease | 3 (2) | 12 (7) |
| Fatigue | 10 (7) | 10 (6) |
| Oedema peripheral | 2 (1) | 9 (5) |
| Nasopharyngitis | 10 (7) | 7 (4) |
| Skin odour abnormal | 2 (1) | 7 (4) |
| Dizziness | 5 (3) | 6 (3) |
| Headache | 5 (3) | 6 (3) |
| Abdominal pain | 0 | 6 (3) |
| Flatulence | 0 | 6 (3) |
| Back pain | 6 (4) | 1 (<1) |
| In-stent coronary artery restenosis | 7 (5) | 0 |
| **Serious Treatment Emergent Adverse Events:** No deaths occurred during the study. | | |
| **Subjects with at least one SAE, n (%) [considered related by investigator]** | **Placebo (N=151)** | **SB-480848 160mg EC (N=172)** |
| | **n (%) [related]** | **n (%) [related]** |
| Subjects with non-fatal SAEs, n (%) | 45 (30) [5] | 46 (27) [2] |
| Coronary artery disease | 3 (2) [0] | 12 (7) [0] |
| Angina pectoris | 9 (6) [0] | 9 (5) [0] |
| Acute myocardial infarction | 4 (3) [2] | 3 (2) [0] |
| Angina unstable | 4 (3) [0] | 3 (2) [0] |
| Non-cardiac chest pain | 2 (1) [1] | 3 (2) [0] |
| Hypotension | 0 | 2 (1) [1] |
| Coronary artery restenosis | 3 (2) [0] | 1 (<1) [0] |
| Gastrointestinal haemorrhage | 1 (<1) [0] | 1 (<1) [0] |
| Arteriospasm coronary | 0 | 1 (<1) [0] |
| Basal cell carcinoma | 0 | 1 (<1) [0] |
| Bladder cancer | 0 | 1 (<1) [0] |
| Bladder tamponade | 0 | 1 (<1) [0] |
| Bradycardia | 0 | 1 (<1) [1] |
| Cardiac procedure complication | 0 | 1 (<1) [0] |
| Cellulitis | 0 | 1 (<1) [0] |
| Gastroenteritis | 0 | 1 (<1) [0] |
| Global amnesia | 0 | 1 (<1) [0] |
| Hypertension | 0 | 1 (<1) [0] |
| Ischaemic stroke | 0 | 1 (<1) [0] |
| Lower gastrointestinal haemorrhage | 0 | 1 (<1) [0] |
| Occult blood positive | 0 | 1 (<1) [0] |
| Pharyngeal disorder | 0 | 1 (<1) [0] |
| Polyarthritis | 0 | 1 (<1) [0] |
| Polycythaemia vera | 0 | 1 (<1) [0] |
| Postoperative wound infection | 0 | 1 (<1) [0] |
| Prostatic adenoma | 0 | 1 (<1) [0] |
| Radius fracture | 0 | 1 (<1) [0] |
| Sciatica | 0 | 1 (<1) [0] |
| Thrombosis in device | 0 | 1 (<1) [0] |
| Ulna fracture | 0 | 1 (<1) [0] |
| Upper gastrointestinal haemorrhage | 0 | 1 (<1) [1] |

| Subjects with at least one SAE, n (%) [considered related by investigator] | Placebo (N=151) | SB-480848 160mg EC (N=172) |
|---|---|---|
| | n (%) [related] | n (%) [related] |
| Ventricular extrasystoles | 0 | 1 (<1) [0] |
| Ventricular tachycardia | 0 | 1 (<1) [0] |
| Vertigo | 0 | 1 (<1) [0] |
| In-stent coronary artery restenosis | 7 (5) [1] | 0 |
| Pulmonary embolism | 3 (2) [0] | 0 |
| Bronchitis | 2 (1) [0] | 0 |
| Coronary artery stenosis | 2 (1) [0] | 0 |
| Myocardial infarction | 2 (1) [0] | 0 |
| Anaphylactic shock | 1 (<1) [0] | 0 |
| Aortic aneurysm rupture | 1 (<1) [0] | 0 |
| Cardiac asthma | 1 (<1) [0] | 0 |
| Cardiac failure congestive | 1 (<1) [0] | 0 |
| Cardiac pseudoaneurysm | 1 (<1) [0] | 0 |
| Cervicobrachial syndrome | 1 (<1) [0] | 0 |
| Chest pain | 1 (<1) [0] | 0 |
| Coronary artery dissection | 1 (<1) [0] | 0 |
| Depression | 1 (<1) [0] | 0 |
| Diverticulitis | 1 (<1) [0] | 0 |
| Headache | 1 (<1) [1] | 0 |
| Leukoplakia oral | 1 (<1) [0] | 0 |
| Mitral valve incompetence | 1 (<1) [0] | 0 |
| Multiple myeloma | 1 (<1) [0] | 0 |
| Muscle haemorrhage | 1 (<1) [0] | 0 |
| Myalgia | 1 (<1) [1] | 0 |
| Post procedural myocardial infarction | 1 (<1) [0] | 0 |
| Pyelonephritis | 1 (<1) [0] | 0 |
| Rectal haemorrhage | 1 (<1) [0] | 0 |
| Syncope | 1 (<1) [0] | 0 |
| Tachycardia | 1 (<1) [0] | 0 |
| Tension headache | 1 (<1) [1] | 0 |
| Urosepsis | 1 (<1) [0] | 0 |
| **Subjects with fatal SAEs** | **n (%) [related]** | **n (%) [related]** |
| | 0 | 0 |
| **Conclusion:** See publication listed below. | | |
| **Publication:** Serruys PW, Garcia-Garcia HM, Buszman P, et al. Effects of the Direct Lipoprotein-Associated Phospholipase A2 Inhibitor Darapladib on Human Coronary Atherosclerotic Plaque. *Circulation*. 2008;118(11):1172-1182. | | |