Synopsis

Identifier: CM2007/00149/00 **Study Number:** PMK103351

Title: A 28-day, randomized, double-blind, placebo-controlled study to assess the safety, tolerability, anti-inflammatory effect and steady-state pharmacokinetics of SB-681323 (7.5mg) in subjects with coronary heart disease (CHD) undergoing elective percutaneous coronary interventions (PCI)

Investigators: Multicentre study

Study Centres: 10 centres in 3 countries (Denmark, Poland and Spain).

Publications: None at the time of this report.

Study Period: 2 May 2006 - 3 August 2007

Phase of Development: II

Objectives:

Primary

- To determine the safety and tolerability of SB-681323 administered for 28 days in subjects with coronary heart disease (CHD) on statin therapy.
- To estimate the effect of 7.5mg orally (PO) (5mg am, 2.5mg pm) of SB-681323, compared to placebo, in reducing the acute increase in high sensitivity C-reactive protein (hsCRP) observed following PCI in subjects with angiographically documented CHD.

Secondary

- To characterise the chronic effect of 7.5mg PO of SB-681323, compared to placebo, on stable hsCRP after 28 days of administration.
- To evaluate the chronic effect of 7.5mg PO of SB-681323, compared to placebo, on the array of soluble biomarkers.
- To evaluate the effect of 7.5mg PO of SB-681323, compared to placebo, on endothelial function utilizing peripheral arterial tonometry.
- To evaluate the pharmacokinetics (PK) of 7.5mg PO of SB-681323 in subjects under going elective PCI.

Exploratory

- To evaluate the effect of 7.5mg PO of SB-681323, compared to placebo, on messenger ribonucleic acid mRNA expression of inflammatory and proatherogenic genes using microarray or TaqMan technology.
- To explore the correlation between concentrations of 7.5mg PO of SB-681323 and concentrations of hsCRP.

Methodology:

This was a randomized, double-blind, placebo-controlled, parallel-group study in subjects with angiographically documented CHD, on statin therapy for >5 days prior to an elective PCI.

Each subject attended a screening visit within 14 days prior to Day 0 (day of randomisation). Subjects enrolled in the study participated in a single 28-day study treatment session. Subjects with CHD, referred for elective PCI with a hsCRP concentration of <10mg/L, were randomized on Day 0 to either SB-681323, 7.5mg per day orally (administered as 5mg each morning and 2.5mg each evening), or to placebo in a ratio of 1:1 for 28 days. After three days of treatment subjects underwent PCI and continued with their randomized treatment.

Subjects had a final follow-up visit 14 days after their last dose of study medication. The total scheduled duration of each subject's participation in the study, from screening through to follow-up was approximately 8 weeks.

Number of Subjects:

Number of Subjects	Placebo	SB-681323 7.5mg	Total
Planned, N	45	45	90
Randomized, N	46	47	93
Completed, n (%)	35 (76.1)	39 (83.0)	74 (79.6)
Prematurely Withdrawn, n (%)	11 (23.9)	8 (17.0)	19 (20.4)
Primary Reason for Withdrawal from Study			
Adverse event, n (%)	3 (6.5)	2 (4.3)	5 (5.4)
Protocol violation, n (%)	5 (10.9)	2 (4.3)	7 (7.5)
Subject decided to withdraw from the study, n (%)	0	1 (2.1)	1 (1.1)
Other, n (%)	3 (6.5)	3 (6.4)	6 (6.5)

Diagnosis and Main Criteria for Inclusion:

A subject was eligible for inclusion if all of the following criteria applied:

1. Male adults, or female adults of non-child-bearing potential, aged >18 years of age at screening.
2. Female subjects had to have a negative pregnancy test (i.e. serum β human chorionic gonadotropin [hCG] test) and had to be of non-childbearing potential (i.e. physiologically incapable of becoming pregnant, including any female who was surgically sterile via hysterectomy or bilateral ligation or who is post-menopausal. For the purposes of this study, postmenopausal was defined as one year without menses).
3. Subjects who were scheduled to undergo elective PCI to be performed ≤12 weeks after diagnostic coronary angiography confirming obstructive CHD.
4. Subjects had to be on a stable dose of a statin for the 28 day duration of the study. Subjects who were on any stable therapeutic dose of any statin for ≥4 weeks prior to PCI were eligible for participation. Subjects whose statin treatment was initiated <4 weeks prior to PCI were to be started on a submaximal statin dose (e.g. atorvastatin ≤20mg or simvastatin ≤40mg) which was to be carried through the end of the study. Subjects whose statin treatment was initiated <5 days prior to PCI were excluded from the study.
5. Subjects with low density lipoprotein (LDL) at the screening visit <190mg/dL (<5.0mmol/L).
6. Subjects capable of providing signed written informed consent to participate.
7. Subjects with hsCRP concentration of <10mg/L at the screening visit.

Treatment Administration:

Subjects were randomized (1:1) to receive one of the following regimens for the duration of the 28-day treatment period:

- SB-681323 7.5mg: 1 x 5mg tablet (batch number 041026486) each morning and 1 x 2.5mg tablet (batch number 041026485) each evening.
- Placebo: placebo tablets (batch number 031002312) to match SB-681323 5mg and 2.5mg tablets twice daily.

Criteria for Evaluation:

Primary Endpoints

- Assessment of post-PCI cardiovascular events, the incidence of liver function abnormalities (alanine transaminase (ALT]) and other safety assessments based on subject symptoms and routine laboratory values including creatine kinase.
- Baseline corrected hsCRP concentrations at 2 days after PCI (i.e. 5 days on treatment).

Secondary Endpoints

- Baseline corrected hsCRP concentration at 3, 4, 10/11, 16/17, 21/22 and 28 days.
- Baseline corrected blood concentration of other protein inflammatory biomarkers at 3, 5, and 28 days. These biomarkers included the following: interleukin (IL)-6, IL-8, IL-1β, lipoprotein-associated phospholipase A_2 ($LpPLA_2$), and paraoxonase 1 (PON-1).
- Additional exploratory protein expression studies may have been conducted. If necessary, these studies were to be conducted using proteomics technology. The plasma inflammation markers could include but were not limited to the following: fibrinectin, plasminogen activator inhibitor (PAI)-1, IL-18, IL-4, IL-10, matrix metalloproteinase (MMP)-1, MMP-13, secreted phosphoprotein(SPP)-1, soluble intercellular adhesion molecule (sICAM), soluble vascular cell adhesion molecule (sVCAM), myeloperoxidase (MPO), fibronectin, CD40L and tumor necrosis factor (TNF)α.
- Baseline corrected mRNA blood levels of inflammatory biomarkers at 3, 5, and 28 days. These biomarkers included the following: IL-1β, intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), matrix metalloproteinase (MMP)9, MMP1 and control house keeper genes β-actin, cyclophilin, ribosomal protein (RP)L32, and RPL27.
- Baseline corrected endothelial function was measured using peripheral arterial tonometry (PAT) on Day 5 and at the end of drug therapy period (Day 28).

Exploratory Endpoints

- The effects of SB-681323 on additional proteins and mRNA biomarkers was to be explored based upon genes known to be regulated by p38 mitogen-activated protein kinase (MAPK) (approximately 600 genes), the associated proteins that are secreted into the blood (approximately 160 proteins), some of which are also expressed in human carotid plaque (34 known genes). These genes and proteins have the highest potential to be present in blood products and correlate with inhibition of p38 MAPK. If necessary, these exploratory studies were to be conducted using proteomics technology and microarray and/or TaqMan technology.

Statistical Methods:

The main endpoints for this study were safety parameters (the incidence of ALT concentrations ≥3 x ULN) and CRP concentrations, but precision estimates were based on the log-transformed ratio to baseline in serum CRP concentration post PCI after treatment with SB-681323 or placebo. The sample size for this study was based on feasibility and was determined using the variability seen in the IBIS-1 trial dataset for subjects with elevated CRP at baseline (i.e. CRP >3mg/L), using data up to the 3 month follow-up period. Based on a standard deviation of 0.85 in log ratio to baseline of CRP and a sample size of 40 subjects per treatment arm, it was estimated that the precision for the comparison of interest (SB-681323: placebo) would be approximately 46% of the observed point estimate, when precision was expressed as the half-width of the 95% CI. That is, the lower and upper bounds of the 95% CI for the ratio of SB-681323: placebo would be within approximately 46% of the observed ratio. For example, for an observed ratio of 0.50 (i.e. a 50% reduction in CRP for SB-681323 relative to placebo), the corresponding 95% CI would be (0.34, 0.73) (or from a 27% to a 66% reduction in CRP for SB-681323 relative to placebo).

The primary pharmacodynamic variable was the change from baseline at the end of 5 days of double-blind treatment in plasma hsCRP. The difference between the two treatment groups for this variable was analyzed using general linear model methodology (PROC MIXED in SAS). The statistical model included the treatment, country and treatment-by-country interaction terms. Baseline was included as a covariate and other potential covariates such as BMI, body weight, and waist circumference were considered. If evidence of a treatment by country interaction was found (p-value <0.10), exploratory analyses were to be undertaken to describe the nature of the interaction and results were to be presented by country. The treatment by country interaction term was kept in the model.

Secondary pharmacodynamic variables were analyzed in a similar manner to the primary pharmacodynamic variable. Evaluations of interaction for the secondary variables were consistent with the primary variable evaluation.

Summary:

Demography

The placebo and SB-681323 groups were generally well matched with regard to demographic characteristics. For all randomized subjects, the mean age was 59 years and the majority of subjects (83%) were male.

Safety

Number (%) of Subjects with Common Adverse Events (Serious and Non-Serious) Reported by More Than One Subject Overall, by Preferred Term: Safety Population		
	Placebo N=46	SB-681323 7.5 mg N=46
	n (%)	n (%)
Any Event	26 (57)	19 (41)
Common AEs by Preferred Term (Reported by >1 Subject Overall)		
Angina pectoris	11 (24)	3 (7)
Headache	3 (7)	2 (4)
Fatigue	2 (4)	2 (4)
Bradycardia	2 (4)	1 (2)
Myocardial infarction	2 (4)	1 (2)
Constipation	1 (2)	2 (4)
Diarrhoea	1 (2)	2 (4)
Vessel puncture site haematoma	1 (2)	2 (4)
Depression	2 (4)	0
Myalgia	2 (4)	0
Non-cardiac chest pain	2 (4)	0
Urinary tract infection	2 (4)	0
Abdominal pain	1 (2)	1 (2)
Blood creatine phosphokinase increased	1 (2)	1 (2)
Influenza	1 (2)	1 (2)
Muscle fatigue	1 (2)	1 (2)
Nausea	1 (2)	1 (2)
Haematoma	0	2 (4)

Summary of the Number (%) of Subjects with Adverse Events (Serious and Non-Serious) by Preferred Term Leading to Withdrawal of Study Medication: Safety Population		
	Placebo N=46	SB-681323 7.5 mg N=46
	n (%)	n (%)
Any AE Leading to Withdrawal of Study Medication	3 (7)	4 (9)[1]
Preferred Term		
Angina pectoris	1 (2)	1 (2)
Myocardial infarction	1 (2)	1 (2)
Abdominal pain	1 (2)	0
Pancreatic carcinoma metastatic	0	1 (2)
Pharyngitis	0	1 (2)

1. Note that 2 of the subjects in the SB-681323 group who had an AE leading to withdrawal of study medication continued in the study after cessation of study medication (i.e. these subjects were not withdrawn from the study).

Number (%) of Subjects with Non-Fatal Serious Adverse Events by Preferred Term: Safety Population		
	Placebo N=46	SB-681323 7.5 mg N=46
	n (%)	n (%)
Any SAE	7 (15)	3 (7)
Preferred Term		
Angina pectoris	4 (9)	1 (2)
Myocardial infarction	2 (4)	1 (2)
Bradycardia	1 (2)	0
Myalgia	1 (2)	0
Myocardial ischaemia	1 (2)	0
Sepsis	1 (2)	0
Pancreatic carcinoma metastatic	0	1 (2)

No deaths were reported during this study.

There were no clinically relevant differences between the SB-681323 group and placebo group with regard to clinical laboratory tests (including liver function tests), vital signs, or 12-lead ECG abnormalities.

The number of subjects with abnormal liver function tests was low and similar in the placebo and SB-681323 groups. For those subjects with an ALT value ≥upper limit of normal (ULN), the abnormality was <2 x ULN in all cases.

Overall, approximately 50% of subjects had an increase in troponin I levels to >0.03 mcg/L 24 hours after the PCI. There were fewer subjects with an increase in troponin I levels to >0.03 mcg/L following the PCI in the SB-681323 group (17/43 subjects) compared to the placebo group (25/43 subjects). However, an elevation in troponin I levels to >1 mcg/L following the PCI was observed for 7 subjects in the SB-681323 group vs 5 subjects in the placebo group.

Pharmacodynamics

Change From Baseline in Plasma hsCRP at Day 3, Day 5 and Day 28

Mean plasma hsCRP levels were reduced from baseline in both the placebo and SB-681323 groups at Day 3 (the scheduled day for PCI); the magnitude of this reduction was larger in the SB-681323 group than the placebo group. In the placebo group, mean plasma hsCRP levels increased following PCI and peaked on Day 5; hsCRP levels then gradually declined back to baseline levels over the remainder of the 28-day treatment period. In the SB-681323 group, there was an increase in mean hsCRP levels on Day 5, but the magnitude of this increase was smaller than the placebo group. In the SB-681323 group, mean plasma hsCRP levels had declined to baseline levels or below by the time of the next assessment at Day 10/11.

On average, there was a 29% reduction in log-transformed hsCRP for SB-681323 relative to placebo at Day 3, a 37% reduction in the increase from baseline in hsCRP at Day 5 (primary pharmacodynamic endpoint) and a 40% reduction in the increase from baseline

in hsCRP at Day 28 (without last observation carried forward [LOCF]). Treatment differences for SB-681323 relative to placebo were statistically significant at each of these time points.

Results from ANCOVA of Percent Change from Baseline for Log-Transformed hsCRP at Day 3, Day 5 and Day 28 (Without LOCF): ITT Population

		Ratio to Treatment (% Difference from Placebo)[1]		
Biomarker	Visit	Geometric Mean	95% CI	P-Value
hsCRP	Day 3	0.71	0.534, 0.948	0.021
	Day 5	0.63	0.405, 0.967	0.035
	Day 28	0.60	0.425, 0.838	0.003

1. Based on analysis of covariance (ANCOVA): Log(value) - log(baseline) = log(baseline) + treatment + country

Change From Baseline in Other Protein Inflammatory Biomarkers

At Day 3, levels of other protein inflammatory biomarkers were generally reduced in the SB-681323 group compared to the placebo group. On average, IL-6 was reduced by 14%, IL-8 by 28%, $LpLPA_2$ by 5%, and MPO by 30% (without LOCF). Differences compared to placebo were statistically significant for IL-8, $LpLPA_2$ and MPO, but not for IL-6.

At Day 5, levels of IL-6 had increased from baseline in both treatment groups but the magnitude of this increase was smaller in the SB-681323 group than the placebo group (15% reduction on average, compared to placebo), although this difference was not statistically significant. Levels of other biomarkers were similar to placebo at Day 5 and Day 28.

Results were generally consistent when an LOCF analysis was performed, except that the comparison for $LpLPA_2$ was not statistically significant in the LOCF analysis.

Results from ANCOVA of Percent Change from Baseline for Log-Transformed Protein Inflammatory Biomarkers at Day 3, Day 5 and Day 28 (Without LOCF): ITT Population

		Ratio to Treatment (% Difference from Placebo)[1]		
Biomarker	Visit	Geometric Mean	95% CI	P-Value
IL-6	Day 3	0.86	0.709, 1.040	0.117
	Day 5	0.85	(0.597, 1.199)	0.342
	Day 28	1.15	(0.849, 1.544)	0.368
IL-8	Day 3	0.72	0.579, 0.888	0.003
	Day 5	0.98	(0.762, 1.263)	0.880
	Day 28	0.89	(0.669, 1.189)	0.429
$LpPLA_2$	Day 3	0.95	0.904, 0.999	0.046
	Day 5	0.96	(0.908, 1.014)	0.139
	Day 28	0.96	(0.906, 1.021)	0.198
MPO	Day 3	0.70	0.500, 0.973	0.034
	Day 5	0.94	0.715, 1.245	0.678
	Day 28	1.10	0.764, 1.591	0.596

1. Based on ANCOVA: Log(value) - log(baseline) = log(baseline) + treatment + country.

Change From Baseline in Peripheral Arterial Tonometry

A decrease in the PAT ratio is indicative of a decrease in endothelial function. The change from baseline in the PAT ratio at Day 5 and Day 28 was similar for the placebo group and SB-681323 group. The adjusted mean change from baseline at Day 5 was 3% in the placebo group and -9% in the SB-681323 group (treatment difference -12%, 95% CI: -25%, 1%) and at Day 28 was 8% in the placebo group and -2% in the SB-681323 group (treatment difference -9%, 95% CI: -28%, 10%). Neither of these comparisons was statistically significant.

Exploratory Results

The effect of SB-681323, compared to placebo, on mRNA expression of inflammatory and proatherogenic genes was to be evaluated using microarray or TaqMan technology. Samples were analyzed, but the mRNA data obtained was of poor quality and no inferences were drawn from this data.

Conclusions:

Safety

- The safety and tolerability profile of SB-681323 7.5mg for 28 days was similar to that of placebo in this study of subjects with CHD undergoing elective PCI.
- AEs were reported for a larger proportion of subjects in the placebo group (57%) than the SB-681323 group (41%).
- Angina pectoris was the most commonly reported AE; this event was reported for a larger proportion of subjects in the placebo group (24%) than the SB-681323 group (7%).
- No subject died during this study.
- SAEs were reported for a larger proportion of subjects in the placebo group (7 subjects, 15%) than the SB-681323 group (3 subjects, 7%). Angina pectoris was the most commonly reported SAE and was reported for a larger proportion of subjects in the placebo group (4 subjects, 9%) than the SB-681323 group (1 subject, 2%).
- The number of subjects with abnormal liver function tests was low and similar in the placebo and SB-681323 groups. For those subjects with an ALT value ≥ULN, the abnormality was <2 x ULN in all cases.
- Fewer subjects had an increase in troponin I levels to >0.03 mcg/L following the PCI in the SB-681323 group (17/43 subjects) compared to the placebo group (25/43 subjects). However, an elevation in troponin I levels to >1 mcg/L following the PCI was observed for 7 subjects in the SB-681323 group vs 5 subjects in the placebo group.
- There were no clinically relevant differences between the SB-681323 group and placebo group with regard to clinical laboratory tests (including liver function tests), vital signs, or 12-lead ECG abnormalities.

Pharmacodynamics

- On average, there was a 29% reduction in log-transformed hsCRP for SB-681323 relative to placebo at Day 3, a 37% reduction in the increase from baseline in hsCRP at Day 5 (primary pharmacodynamic endpoint) and a 40% reduction in the increase from baseline in hsCRP at Day 28; the treatment differences for SB-681323 relative to placebo were statistically significant.
- At Day 3, levels of other protein inflammatory biomarkers were generally reduced in the SB-681323 group compared to the placebo group. On average, IL-6 was reduced by 14%, IL-8 by 28%, $LpLPA_2$ by 5%, and MPO by 30%. Differences compared to placebo were statistically significant for IL-8, $LpLPA_2$ and MPO, but not for IL-6. At Day 5, on average there was a 15% reduction in the increase from baseline in levels of IL-6 in the SB-681323 group, compared to placebo, although this difference was not statistically significant. Levels of other biomarkers were similar to placebo at Day 5 and Day 28.
- Treatment comparisons for the change from baseline in the PAT ratio at Day 5 and Day 28 were not statistically significant.
- Pharmacodynamic results were generally consistent when with or without LOCF analyses were performed.

Date of Report: September 2008