Synopsis

Identifier: GM2006/00365/00 **Study Number:** MKC101614

Title: A 28-day, randomised, double-blind, placebo-controlled study to assess the safety, tolerability, anti-inflammatory effect and steady-state pharmacokinetics of SB-681323 7.5 mg per day in patients with chronic obstructive pulmonary disease.

Investigator(s): Multicentre study

Study center(s): This study was conducted in 5 countries at 16 sites: Denmark (2), Finland (1), Germany (3), Netherlands (4), United Kingdom (6).

Publication(s): None at the time of this report

Study Period: 22Sept2005 – 02Mar2006

Phase of Development: IIa

Objectives: The primary objective was to assess the safety and tolerability of SB-681323 administered orally for 28 days in subjects with chronic obstructive pulmonary disease (COPD).

Secondary objectives were to assess the:

- Systemic anti-inflammatory activity of SB-681323 by serum concentrations of C-reactive protein (CRP) and other inflammatory markers
- Pulmonary anti-inflammatory activity
- Effect on pulmonary function and Dyspnoea
- Pharmacokinetics of SB-681323
- Potential correlation between plasma concentrations of SB-681323 and serum concentrations of CRP

Methodology: This was a Phase IIa, randomised, double-blind, placebo-controlled, parallel-group study in subjects with moderate stable COPD. Following a two week run-in period, subjects with a serum CRP concentration ≥ 1 mg/L were randomised to receive one of the following two treatments in a 1:1 ratio:

- SB-681323 7.5mg tablets (administered as 2.5mg each morning and 5mg each evening) for 28 days
- Placebo tablets to match for 28 days

During the 28-day treatment period, subjects were assessed on Days 3, 7, 10, 14, 17, 21, 24 and on Day 28. Assessments on days 3, 7, 10, 17, 21 and 24 could be completed at the subject's home. A follow-up visit was attended two weeks after the end of study medication. The expected total duration of the subject's participation in the study was approximately 56 days (8 weeks).

Number of subjects:

Number of Subjects	Placebo	SB681323
Planned, N	33	33
Randomised, N	37	34
Completed, n (%)	32 (86)	31 (91)
Total Number of Subjects Withdrawn, n (%)	5 (14)	3 (9)
Withdrawn due to Adverse Events, n (%)	1 (3)	3 (9)
Withdrawn for not meeting Treatment Eligibility Criteria, n (%)	2 (5)	0
Withdrawn for other reasons, n (%)	2 (5)	0

Diagnosis and main criteria for inclusion: Male or female subjects between 40 and 75 years of age with a clinical diagnosis of COPD, a cigarette smoking history of ≥ 10 pack years, a post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio (FEV1:FVC) < 0.7 and a post-bronchodilator FEV1 ≥ 50% and < 80% of predicted normal. Prior to randomisation subjects were required to demonstrate a serum CRP concentration of ≥ 1mg/L.

Treatment administration: Study medication was administered twice daily. Subjects were instructed to take one tablet (SB-681323 2.5 mg (batch number 0410264850) or placebo (batch number 031002312)) each morning approximately 30 minutes prior to breakfast and one tablet (SB-681323 5 mg (batch number 041026486) or placebo (batch number 031002312)) in the evening approximately 30 minutes prior to the evening meal. In addition subjects could continue to use their salbutamol inhalers (metered dose inhaler (MDI), DISKHALER™ or DISKUS™) on a PRN basis and, if required, their stable dose of ipratropium bromide (MDI) for relief medication.

Criteria for evaluation: The primary endpoint for this study was the safety and tolerability of SB-681323 as assessed by the incidence of alanine aminotransferase (ALT) concentrations >3 x the upper limit of normal (ULN). (NB: Serum CRP was changed from a co-primary endpoint to a main secondary endpoint in Protocol Amendment 02 because subjects were showing lower than expected serum CRP levels at the end of the run-in period resulting in a high screening failure rate. To address this issue, the inclusion criterion for subjects to have a serum CRP concentration of > 3mg/L at the end of the run-in period was lowered to ≥ 1 mg/L).

Secondary efficacy endpoints were: mean ratio (endpoint to baseline) of serum CRP concentration; serum concentrations of CRP at other time points; parameters measured in induced sputum; plasma concentrations of fibrinogen and serum concentrations of proinflammatory cytokines; Lung function parameters (trough and post-bronchodilator): slow vital capacity (SVC), inspiratory capacity (IC), FVC, FEV_1, forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}), forced expiratory flow at 75% of vital capacity (FEF_{75}), peak expiratory flow (PEF); dyspnoea measured by the Baseline Dyspnoea Index (BDI)/Transition Dyspnoea Index (TDI).

Safety evaluations included incidence of adverse events (AEs) (specifically AEs of diarrhoea), incidence of liver function test rises, withdrawals due to adverse events/exacerbations of COPD, vital signs, clinical laboratory assessments and electrocardiogram (ECG) parameters. (NB: as a result of *in vitro* tests that indicated a potential risk of phototoxicity with SB-681323, Protocol Amendment 01 was implemented which added a precaution to the protocol asking patients to avoid exposure to sunlight and to promptly report any adverse skin effects).

Pharmacokinetic (PK) endpoints included population pharmacokinetic parameters of SB-681323 and model parameters for the correlation between plasma concentrations of SB-681323 and serum concentrations of CRP.

Statistical methods: As the primary endpoint for this study was a safety endpoint, based on clinical judgment, it was considered that 30 completed subjects per treatment arm would be required to demonstrate adequate safety and tolerability. Sensitivity sample size calculations were performed on the main secondary endpoint, serum CRP, and based on a 2-sided significance level of 5%, 30 completed subjects per arm were expected to provide 84% power to detect a 50% reduction in CRP at Day 28 on SB-681323 compared with placebo. To allow for an estimated 10% of subjects withdrawing from treatment, 33 randomised subjects per arm were planned for this study.

The primary population for efficacy was the Modified Intent-to-Treat (mITT) population, which included all subjects who received at least one dose of study medication and had a baseline and at least one on-treatment assessment measure. For the primary endpoint, the number and percentage of subjects with the liver function parameter ALT > 3 times ULN were tabulated at any time after the start of treatment and 95% confidence intervals around the difference in proportions between SB-681323 and placebo were planned.

For the main secondary endpoint, mean ratio to baseline of serum CRP concentration, a repeated measures analysis was used on log transformed data. The model included fixed effects for treatment, day, country, smoking status, treatment by day, baseline and baseline by day. The repeated measures fixed effects model was also used for analyzing induced sputum cell numbers, concentrations of inflammatory markers and lung function parameters (lung function variables were not log transformed). The Dyspnoea TDI scores were analysed using analysis of covariance with baseline BDI, treatment country and smoking status as covariates.

All other safety parameters were listed and summarized.

For PK parameters, plasma concentrations of SB-681323 were listed and summarised by sampling time and population parameters were estimated using a non-linear mixed-effect modelling approach. Effects of potential covariates, including baseline demographics, smoking status, serum CRP and lung function on pharmacokinetics were explored.

Summary: The two treatment groups were well matched for all demographic and baseline parameters.

Efficacy: For the main efficacy endpoint, mean ratio to baseline serum CRP concentration at end of treatment, there was no difference between the two treatment

groups. In addition, serum CRP concentrations at other time points gave no clear indication of a treatment effect. The proportion of sputum neutrophils showed an increase from baseline in the placebo group and a decrease from baseline following SB-681323 treatment (treatment difference: 9.4%; 95% CI: -0.6% to 19.5%; p=0.064). Treatment with SB-681323 also resulted in a statistically significant reduction in plasma fibrinogen concentrations after 14 and 28 days, relative to placebo (Day 28: 11% reduction, SB-681323/placebo ratio: 0.89; 95% CI: 0.81, 0.98; p-value 0.020). A panel of proinflammatory cytokines gave no indication of treatment effects. A trend in improvement in measurements of lung capacity (FVC and SVC) was shown following SB-681323 treatment compared with placebo but no other obvious changes were seen in lung function parameters. At the end of treatment, a small improvement in dyspnoea scores was shown in the placebo group with little change in the SB-681323 group and this difference was statistically significant in favour of placebo.

Summary of Analyses of Secondary Efficacy Endpoints (Serum CRP, Induced Sputum Cell Counts, Lung Function Parameters, Dyspnoea) at Day 28 (modified ITT Population)

Parameter	Placebo (N=37)	SB-681323 (N=34)
Serum CRP concentration (mg/L)		
Adjusted ratio to B/L	1.010	1.076
SB-681323/placebo ratio (95% CI)	1.07 (0.74, 1.53)	
p-value	0.728	
Induced sputum cell counts		
Total cell count		
Adjusted ratio to B/L	0.99	0.96
SB-681323/placebo ratio (95% CI)	0.98 (0.47, 2.03)	
p-value	0.951	
Neutrophils		
Adjusted mean change (se)	3.46 (3.69)	-5.98 (3.34)
SB-681323-placebo difference (95% CI)	-9.44 (-19.5, 0.57)	
p-value	0.064	
Macrophages		
Adjusted mean change (se)	-3.98 (3.09)	2.37 (2.80)
SB-681323-placebo difference (95% CI)	6.35 (-2.05, 14.75)	
p-value	0.135	
Lymphocytes[1]		
Raw median change	-0.25	0.00
SB-681323-placebo difference (95% CI)	0.38 (0.00, 0.75)	
p-value	0.004	
Eosinophils		
Adjusted ratio to B/L	0.81	1.39
SB-681323/placebo ratio (95% CI)	1.73 (0.87, 3.42)	
p-value	0.115	

Plasma Fibrinogen Adjusted ratio to B/L	1.05	0.94
SB-681323/placebo ratio (95% CI) p-value	0.89 (0.81, 0.98) 0.020	
Lung Function Parameters FEV_1 Adjusted mean change (se)	-0.03 (0.04)	-0.00 (0.04)
SB-681323/placebo difference (95% CI) p-value	0.03 (-0.09, 0.15) 0.619	
FVC Adjusted mean change (se)	-0.10 (0.08)	0.11 (0.08)
SB-681323/placebo difference (95% CI) p-value	0.21 (-0.01, 0.42) 0.061	
SVC Adjusted mean change (se)	-0.08 (0.06)	0.01 (0.06)
SB-681323/placebo difference (95% CI) p-value	0.09 (-0.09, 0.27) 0.321	
PEF Adjusted mean change (se)	0.37 (12.21)	14.97 (12.46)
SB-681323/placebo difference (95% CI) p-value	14.60 (-20.39, 49.59) 0.407	
Dyspnoea TDI Focal Score Adjusted mean (se)	0.98 (0.34)	-0.27 (0.34)
SB-681323-placebo difference (95% CI) p-value	-1.25 (-2.23, -0.28) 0.013	

1. Non-parametric analysis was used as 21 subjects (41%) had zero lymphocytes in their sputum sample.
CRP=C-reactive protein; B/L=baseline; se=standard error; CI=confidence interval; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; SVC=slow vital capacity; PEF=peak expiratory flow; TDI=transition dyspnoea index

Safety: For the primary endpoint, incidence of ALT concentrations >3 x ULN, there were no such cases in either treatment group at any time point during the study. In general, mean values of all liver function parameters were similar in the two treatment groups with only minor fluctuations observed over time. The proportion of subjects with at least one AE that started during treatment was very similar in both treatment groups. No treatment emergent serious adverse events were reported in either treatment group and 3 subjects in each group were withdrawn due to an AE.

Most Frequent Adverse Events During Treatment (safety Population)

AE (occurring in >1 subject in either treatment group), n (%)	Placebo (N=37)	SB-681323 (N=34)
Subjects with any AE(s)	24 (65)	25 (74)
Headache	7 (19)	3 (9)
Nasopharyngitis	6 (16)	3 (9)
Cough	3 (8)	4 (12)
COPD	2 (5)	3 (9)
Nausea	2 (5)	3 (9)
Back pain	1 (3)	2 (6)
Blood creatinine phosphokinase increased	2 (5)	1 (3)
Productive cough	0	2 (6)
URTI	0	2 (6)
Blood triglycerides increased	0	2 (6)
Diarrhoea	0	2 (6)
Dyspnoea	2 (5)	0
Cystitis	2 (5)	0
Oedema peripheral	2 (5)	0

COPD = chronic obstructive pulmonary disease; URTI = upper respiratory tract infection

The number of subjects reporting a drug-related AE was 12 (32%) in the placebo group and 12 (35%) in the SB-681323 group. In the placebo group, the most commonly reported drug-related events were headache (6 (16%) subjects) and cough (2 (5%) subjects); in the SB-681323 group the most common events were headache (3 (9%) subjects), nausea (3 (9%) subjects), diarrhoea (2 (6%) subjects) and increased blood triglycerides (2 (6%) subjects).
Of the AEs of special interest, the incidence of diarrhoea was higher in the SB-681323 group compared with placebo (reported by 2 subjects during treatment and one post-treatment vs. 0 subjects respectively). In addition, one subject reported normal but more frequent bowel movements during SB-681323 treatment. The incidence of other AEs of special interest (muscle-related AEs, red blood cell parameters and skin abnormalities) was very low with no differences observed between SB-681323 and placebo treatments There were no clinically significant changes in routine haematology or chemistry laboratory parameters, vital signs or 12 lead ECG results in either treatment group throughout the study.
PK Endpoints: SB-681323 was quickly absorbed after oral administration of tablets, then distributed to peripheral compartments, and finally eliminated in a multi-exponential manner. Population PK analysis did not show any difference in the absorption and elimination of SB-681323 between COPD patients in the present study when compared with historical data in healthy subjects. Based on the limited data in this study, the population oral clearance (CL/F) of SB-681323 was found to be associated with body mass index (BMI). With every 10 unit of increase in BMI, there was a 30% reduction in CL/F and therefore a 30% increase in systemic exposure. However, the interpretations of these findings need confirmation when more data are available, and it is not recommended to adjust the dose at this stage of the drug development based on this analysis.

Conclusions:

- Treatment with SB-681323 7.5mg daily for 28 days in subjects with COPD was generally well tolerated, showing no effects on liver function tests.
- There was an increased incidence of diarrhoea in the SB-681323 group compared with placebo but there were no other AE differences between the groups or clinically significant changes in routine laboratory parameters, vital signs or 12 lead ECG results throughout the study.
- At the end of 28 days, treatment with SB-681323 showed no effect on serum CRP concentrations compared with placebo
- A 9.4% reduction in the number of sputum neutrophils with borderline significance (95% CI -0.06, 19.5; p=0.064) was observed at the end of treatment with SB-681323 compared with placebo.
- An increase in the number of sputum lymphocytes was observed at the end of treatment with SB-681323 compared with placebo. However, as lymphocyte numbers were low in this population (21 subjects (41%) had zero lymphocytes), the relevance of this finding is unclear.
- Treatment with SB-681323 resulted in a statistically and clinically significant reduction in plasma fibrinogen compared with placebo (11% reduction, SB-681323/placebo ratio: 0.89; 95% CI: 0.81, 0.98; p-value 0.020).
- Treatment with SB-681323 did not have a statistically significant effect on a panel of proinflammatory cytokines.
- There was a significant difference at 14 days, and a near significant difference at 28 days, between SB-681323 and placebo for changes in FVC (Day 14 treatment difference: 0.25L; 95% CI 0.07, 0.43; p=0.008 and Day 28 treatment difference: 0.21L; 95% CI -0.01 to 0.42; p=0.061). This was supported by a trend for a difference between treatments for SVC (Day 14 treatment difference: 0.18L; 95% CI 0.02, 0.34; p=0.024 and Day 28 treatment difference: 0.09L; 95% CI -0.09 to 0.27, p=0.321). No treatment changes were observed for FEV_1.
- At the end of treatment there was a mean improvement in dyspnoea scores in the placebo group of 1 with little change in the SB-681323 group (treatment difference: -1.25; 95% CI -2.23, -0.28; p=0.013).
- Population PK analysis did not show any difference in the absorption and elimination of SB-681323 between healthy subjects and COPD patients. There was a trend for association of body mass index (BMI) with oral clearance but more patient data will be needed to evaluate this potential covariate effect. Therefore, it is not recommended to adjust the dose at this stage of the drug development based on this analysis.
- The results of this study support the progression of the SB-681323 programme into longer term studies in this patient population.

Date of Report: October 2006