Synopsis

Identifier: SM2007/00007/00 **Study Number:** RA1100849

Title: A randomised, parallel group, placebo-controlled, double blind study to assess the safety and tolerability of SB-681323 at 7.5mg daily dose for 28 days and its effects on the levels of serum C-reactive protein (CRP) in subjects with rheumatoid arthritis (RA)

Investigator(s): Multi-centre study

Study center(s): Denmark (1), Germany (6), Hong Kong (1), Italy (3), Norway (3), Poland (2), Spain (5), Sweden (2) and the UK (3).

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

Study period:

[14 Nov 2005] - [19 Oct 2006]

Phase of development: IIa

Objectives:

Primary:

- To assess the effect of SB-681323 on the serum levels of C-reactive protein (CRP) in subjects with RA.

A significant reduction in serum CRP would be considered a clinical response to treatment.

Secondary:

- To assess the effect of SB-681323 on Disease Activity Score based on 28 joint count (DAS28).
- To assess the safety and tolerability of SB-681323 in subjects with RA.
- To assess the effect of SB-681323 on American College of Rheumatology (ACR) 20% response in a core set of rheumatologic assessments (ACR20).
- To assess the effect of SB-681323 on fatigue in subjects with RA.
- To assess the effect of SB-681323 on relevant biomarkers of inflammation and joint damage.
- To assess pharmacokinetics of SB-681323 in this subject population.
- To explore the potential effects of concomitant medication on the pharmacokinetics of SB-681323.

- To explore the potential correlation between plasma exposure to SB-681323 and disease surrogate (CRP) and clinical endpoints (ACR20 and DAS28).

Methodology:

This was a randomized, parallel group, placebo-controlled, double-blind study to assess the safety and tolerability of SB-681323 at 7.5mg daily dose for 28 days and its effects on levels of serum C-reactive protein (CRP) in subjects with rheumatoid arthritis (RA). Seventy-nine subjects experiencing the signs and symptoms of RA were enrolled into the study. Subjects were on stable anti-rheumatic therapy, including disease modifying anti-rheumatic drugs (DMARDs), but excluding biologicals.

Following screening, eligible subjects were randomised on Day 1 (within 14 days of screening) to receive either placebo or SB-681323 (7.5mg/day) (1:1 ratio) in addition to their stable anti-rheumatic therapy for 28 days.

Number of subjects:

Number of Subjects	Placebo	SB-681323 7.5mg/day	Total
Planned, N	41	41	82
Randomized, N	40	39	79
Modified Intent-to-Treat (mITT) Population[1], N	40	38	78
Completed[2] n (%)	38 (95%)	37 (97%)	75 (96%)
Total Withdrawn (any reason), n (%)	2 (5%)	1 (3%)[3]	3 (4%)
Withdrawn due to Serious Adverse Event, n (%)	0	1 (3%)	1 (1%)
Withdrawn due to Adverse Events, n (%)	0	1 (3%)	1 (3%)
Withdrawn due to: protocol violation, n (%) subject withdrew, n (%)	 1 (3%) 1 (3%)	 0 0	 1 (1%) 1 (1%)

1. Subjects who received at least one dose of study medication and have a baseline measurement and at least one on-treatment assessment measure.
2. Percentage based on mITT population
3. Excludes subject with SAE as not included in mITT population

Diagnosis and main criteria for inclusion:

This study was conducted in subjects with active rheumatoid arthritis, diagnosed according to the American College of Rheumatology (ACR) criteria. Subjects who were on stable anti-rheumatic therapy which included methotrexate (within permitted dosages) but not anti-rheumatic biologicals were eligible for inclusion. Despite their anti-rheumatic therapy, the subjects still had active disease. Male or female subjects ≥18 years of age were to be included if they had a body weight of ≥50kg for males and ≥45kg for females and BMI within the range of 18.5 to 35 kg/m^2 inclusive. Female subjects were to use adequate contraception to ensure no pregnancies occurred during the study and for 2 weeks following the end of the treatment phase.

Subjects were to have:

- active RA defined as:

  CRP ≥ 10mg/L and a DAS28 score ≥ 3.2 or

  CRP ≥ 5mg/L, ESR ≥ 28mmHr and a DAS28 score ≥ 3.2.
- normal liver function tests (LFTs; i.e. ALT, AST, ALP, GGT and total bilirubin within normal limits) at screening.
- for those on DMARDs (which may have included, but was not limited to, oral or parenteral methotrexate, sulphasalazine, hydroxychloroquine) must have been on stable dosing regimens for at least eight weeks prior to screening and continued on stable dosing regimens during the screening and study treatment period. This may have included monotherapy or combination therapy. The subjects may have been using methotrexate up to 25mg/week or sulphasalazine up to 3g/day.
- for those on other anti-rheumatic therapies (which may have included but was not limited to, NSAIDs, COX-2 inhibitors and oral glucocorticoids) must have been on stable dosing regimens for at least 4 weeks prior to screening and continued on stable dosing regimens during the screening and study treatment period. The subject may have been using oral prednisolone at doses up to 10mg/day.
- the subjects on stable doses of methotrexate must also have been on stable folate supplements with normal red cell folate levels at screening.

The subjects had to be capable of giving informed consent and able to comply with the study requirements and timetable.

Treatment administration:

Subjects were randomised to receive either SB-681323 administered orally at 7.5mg/day or placebo for 28 days. Subjects took one 2.5 mg tablet (or placebo) on the morning of each dosing occasion and one 5mg tablet (or placebo) 12 hours later (e.g. at bedtime).

Treatment	Dose/Form/Route	Frequency/Duration	Batch Number
SB-681323 7.5mg/Day)			
Morning dose	2.5mg/tablet/oral	OD for 28 days	041026485
Evening dose	5mg/tablet/oral	OD for 28 days	041026486 051092134
Placebo			
Morning dose	-/tablet/oral	OD for 28 days	031002312
Evening dose	-/tablet/oral	OD for 28 days	031002312

Criteria for evaluation:

Endpoints:

Primary:

- Serum levels of CRP at the end of study (after 28 days of treatment) following repeat dosing with SB-681323 (7.5mg/day) compared with placebo.

Secondary:

- Serum levels of CRP at other available time points.

The following secondary endpoints were analysed at all available time points:

Clinical Symptoms:

- DAS28 clinical scores.
- American College of Rheumatology (ACR) defined improvements of 20% in a core set of secondary rheumatologic endpoints (ACR20 response).
- Tender/painful joints count and swollen joints count.
- Subject's and physician's global assessment of arthritis condition (visual analogue scale; VAS).
- Subject's assessment of pain (visual analogue scale; VAS).

Safety and Biomarkers:

- Safety and tolerability of oral SB-681323: adverse events (AE), vital signs, 12-lead ECGs and laboratory assessments (including liver function tests, LFTs; i.e. alanine amino transferase (ALT), aspartate amino transferase (AST), alkaline phosphatase (ALP) gamma glutamyl transferase (GGT) and total, direct and indirect bilirubin).
- Erythrocyte sedimentation rate (ESR).
- Population pharmacokinetic (PK) parameters for SB-681323.
- Potential correlation between systemic exposure to SB-681323 and disease surrogate (CRP) and clinical endpoints (ACR20 and DAS28).
- Biomarkers of inflammation (Serum IL-6, TNF-α, and Matrix metalloproteinase (MMP)-3) as well as protein and mRNA levels of certain other candidate genes and exploratory biomarkers associated with RA will also be assessed after treatment with SB-681323 compared with placebo.
- Samples will be stored for measurement of exploratory biomarkers of cartilage damage, bone formation and bone resorption.

Health Outcomes:

- Functional disability index (Health Assessment Questionnaire).
- Changes in levels of fatigue (Multidimensional Assessment of Fatigue).

Statistical methods:

The sample size calculation was based on estimates of between subject variability of CRP concentrations seen in four previous GSK studies in patients with Rheumatoid Arthritis. From these previous studies, 0.9 appeared to be an appropriate estimate of the standard deviation of log CRP.

This study was powered to detect a difference in mean ratio to baseline CRP between SB-681323 and placebo. An effect size of 50% appeared reasonable based on a study comparing 7.5mg prednisolone OD with placebo in patients with active RA. The study observed an estimated 66% decrease in CRP following prednisolone compared with placebo after 12 weeks treatment (and 50% reduction reported at 4 weeks). It was estimated that 37 subjects in each group would provide 90% power to detect a difference between SB-681323 and placebo based on a test of significance at the two-sided 5% level. To allow for an estimated 10% of patients withdrawing from treatment, 41 patients per arm were planned to be enrolled into the study.

There was no formal analysis of safety data, which were summarised descriptively.

Following log-transformation, CRP levels were analysed using repeated measures. Adjusted geometric means for SB-681323 and placebo and treatment differences were presented with the corresponding 95% confidence interval (CI) and p-values. Mean changes from baseline in modified Disease Activity Score (DAS28) and other relevant secondary efficacy endpoints were also compared between SB-681323 and placebo.

Summary:

Demographics

		Placebo N=40	SB-681323 (7.5mg/day) N=38
Sex, n (%)	Males Females	12 (30%) 28 (70%)	15 (39%) 23 (61%)
Age, years	Median Range	64 37-79	58 36-78
Race, n	African American/African Heritage	0	0
	American Indian or Alaskan Native	0	0
	Asian – East Asian Heritage	3 (8%)	2 (5%)
	Asian – Central/South Asian Heritage	0	0
	Asian – Japanese Heritage	0	0
	Asian – South East Asian Heritage	0	0
	Native Hawaiian or other Pacific Islander	0	0
	White – Arabic/North African Heritage	0	0
	White – White/Caucasian/European Heritage	37 (93%)	36 (95%)
Ethnicity	Hispanic or Latino	5 (13%)	4 (11%)
	Not Hispanic or Latino	35 (88%)	34 (89%)
Height, cm	Median	163	162.5
	Range	145-192	149-182
BMI, kg/m^2	Median	24.9	27.7
	Range	19.3-35.5	19.7-36.5

Data based on mITT population

Safety:

SB-681323 was well tolerated in these subjects with RA.

Most Frequent Adverse Events	Placebo N=40	SB-681323 (7.5mg/day) N=39
	n (%)	n (%)
Any AE	13 (33%)	13 (33%)
Any AE related to investigational product	5 (13%)	5 (13%)
Most Common AEs (≥5% in any treatment group):		
Diarrhoea	4 (10%)	2 (5%)
Abdominal pain	1 (3%)	2 (5%)
Nausea	0	2 (5%)
Headache	3 (8%)	1 (3%)
Urinary tract infection	1 (3%)	2 (5%)
Asthenia	0	2 (5%)

There was one SAE (sinus tachycardia) which was reported on Day 6 by a subject receiving SB-681323 (7.5mg/day). It was reported as not related to study medication and resolved the following day. Study medication was discontinued and the subject withdrew from the study on Day 17. There was one non-serious AE which resulted in withdrawal from the study (mild bradycardia). This event was reported as related to study medication and resolved in 4 days. The incidence of AEs of special interest such as diarrhoea and changes in red blood cell count was similar between the groups. There were no changes in liver function tests (e.g. ALT or AST) which were of clinical concern.

Pharmacokinetics:

A three compartment, first order absorption and elimination model with lag time was determined to adequately describe the PK of SB-681323 in RA subjects. SB681323 was quickly absorbed after oral administration of tablets, then distributed to peripheral compartments, and finally eliminated in a multi-exponential manner.

Compared to data from healthy subjects, plasma concentration data observed from RA subjects showed slightly higher systemic exposure to SB-681323 and a larger variability. Population PK predicted a slower oral clearance in RA subjects, which was largely due to the age distribution between the RA and healthy subjects. The exposure to SB-681323 at steady state would increase with increase in age. These findings may require further confirmation with more data. The estimated median steady-state AUC 0-24 was 177ng.h/mL (range 100-410 ng.h/mL).

Efficacy Results:

There was no evidence of an effect of SB-681323 (7.5mg/day) on serum CRP levels on Day 28 or on Day 22, 15 or 8 when compared with placebo.

SB-681323/Placebo	Adjusted Ratio to Baseline (95% CI)[0]	P value
Day 28	1.06 (0.77, 1.48)	0.71
Day 22	1.03 (0.76, 1.40)	0.84
Day 15	0.86 (0.61, 1.22)	0.39
Day 8	0.79 (0.56, 1.12)	0.19

Analysis adjusted for effects of treatment, day, baseline log(CRP), treatment by day and baseline log(CRP) by day interaction, use of methotrexate at screening and baseline swollen joint count.

There was no evidence of any effect of SB-681323 (7.5mg/day) on the clinical scores of DAS28 or ACR20 when compared with placebo on Day 15 or Day 28.

DAS28	SB-681323 - Placebo Difference (95% CI)[0]	P value
Day 28	-0.09 (-0.50, 0.33)	0.68
Day 15	-0.04 (-0.35, 0.26)	0.79

Analysis adjusted for effects of treatment, day, baseline DAS28 (ESR), treatment by day and baseline log(CRP) by day interaction, region, baseline duration of early morning stiffness (mins) and age.

Similarly, there was no evidence of an effect of SB-681323 (7.5mg/day) on any of the individual components of RA disease measured, such as swollen joint count, tender/painful joint count, erythrocyte sedimentation rate or physician and patient assessment of RA, when compared with placebo on Day 15 and Day 28.

Serum levels of biomarkers IL-6, TNF-α, MMP-3, A-SAA and Fibrinogen were not significantly different when comparing SB-681323 (7.5mg/day) and placebo on Day 15 and Day 28. In addition, there was no evidence of any change in mRNA levels of cyclo-oxygenase-2, IL-6, TNF-α, IL-1β and IL-8 following SB-681323 (7.5mg/day) on Day 28 when compared with placebo.

The health outcome measures of Functional Disability Index and Global Fatigue Index were not significantly different when comparing SB-681323 (7.5mg/day) and placebo on Day 15 and Day 28.

Conclusions:

Efficacy and Biomarkers

- There was no evidence of a significant effect of SB-681323 (7.5mg/day for 28 days) on serum CRP levels when compared with placebo on Day 28, Day 22, Day 15, and Day 8.
- There was no evidence of a significant effect of SB-681323 (7.5mg/day for 28 days) on clinical scores DAS28 (ESR) and ACR20 when compared with placebo on Day 15 or Day 28.

- There was no evidence of a significant effect of SB-681323 (7.5mg/day for 28 days) on the individual components of RA activity of swollen joint count, tender/painful joint count, patient's global assessment of RA, physician's global assessment of RA, patient's assessment of pain and ESR, when compared with placebo Day 15 or Day 28.
- There was no evidence of a significant effect of SB-681323 (7.5mg/day for 28 days) on the levels of serum biomarkers (IL-6, TNF-α, MMP-3, A-SAA or fibrinogen) when compared with placebo on Day 15 and Day 28.
- There was no evidence of significant effect of SB-681323 (7.5mg/day for 28 days) on the gene expression (mRNA levels) of COX-2, IL-1β, IL-6, IL-8 and TNF-α compared with placebo on Day 15 and Day 28.
- No clear trends were found with respect to the expression of these genes over the 28 day period.
- The dose of SB-681323 (7.5mg/day for 28 days) may have been too low to result in significant efficacy (biomarker or clinical outcomes) in these subjects with RA.

Pharmacokinetics

- Population PK analysis showed that a three compartment, first order absorption and elimination model with lag time adequately described the PK of SB-681323 in RA subjects.
- Steady state plasma levels of SB-681323 were reached and maintained.
- Observed PK data from this study showed slightly higher exposure in these RA subjects when comparing to data in healthy subjects. Population PK analysis results indicated that this difference was largely due to the difference in the distribution of subject's age between RA and healthy subjects.
- There was a trend for association of negative correlation of age with oral clearance. Methotrexate or glucocorticoids usage and other demographic characteristics did not have significant impact on the oral clearance and volume distribution of SB681323. However, more patient data will be needed to evaluate the covariate effects.

Safety and Health Outcomes

- There was no evidence of a significant effect of SB-681323 (7.5mg/day for 28 days) on the Functional Disability Index and Global Fatigue Index health outcome measures when compared with placebo on Day 15 or Day 28.
- SB-681323 (7.5mg/day for 28 days) was well tolerated in this RA population. There was no evidence for adverse effects on liver function. There was one SAE which was not attributed to study medication.

Date of Report: **15-JUL-2007**