Synopsis

Identifier: SM2006/00034/00 **Study Number:** RA1104046

Title: A randomised, placebo-controlled, parallel group single dose study of SB-681323 in patients with active RA to investigate the CRP dose response relationship.

Investigator(s): Multicentre study

Study center(s): Four centres in the UK, 1 centre in France, 7 centres in Germany, 2 centres in Australia and 3 centres in Russia.

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

Study period:

[21 Jun 2005] - [03 Aug 2006]

Phase of development: IIa

Objectives:

Primary

- To describe the single dose-response relationship of the dose range of 7.5 to 25 mg of SB-681323 on circulating serum CRP levels.

Secondary

- To describe the single dose-response relationship of the dose range of 10 to 50 mg of prednisolone on circulating serum CRP levels.
- To explore the relationship between the dose of SB-681323 and the dose of prednisolone that gives the same response in terms of circulating serum CRP levels.
- To describe the single dose-response relationship of SB-681323 or prednisolone on circulating serum IL-6 levels.
- To describe the effect of SB-681323 or prednisolone on circulating biomarker levels

Methodology:

This was a randomised, placebo-controlled, parallel group single dose study of SB-681323 in patients with active RA to investigate the CRP dose-response relationship. Seventy-eight patients experiencing the signs and symptoms of RA, and who were on stable doses of methotrexate, were randomised into the study to receive single doses of either SB-681323 (7.5mg, 15mg or 25mg), prednisolone (10mg, 20mg or 50mg) or placebo. Treatment commenced between the patient's weekly doses of methotrexate (Day 3) and the last blood sample was drawn prior to taking the next methotrexate dose (Day 7). Patients were recruited into the study for 1 week in total.

Number of patients:

		SB-681323			Prednisolone		
Number of Patients	Placebo	7.5mg	15mg	25mg	10mg	20mg	50mg
Planned, N	11	11	11	11	11	11	11
Randomised, N	11	12	11	11	11[1]	11	11
Completed, n (%)	11 (100%)	12 (100%)	11 (100%)	11 (100%)	10 (91%)	11 (100%)	11 (100%)
Total Withdrawn[2] (any reason), n (%)	0	0	0	0	0	0	0

Data source: Table 9.1 and 9.4

1. [redacted]
2. Withdrawal data based on the mITT population and only includes patients who received study medication.

Diagnosis and main criteria for inclusion:

Seventy-eight male or female patients aged ∅18years and BMI within the range 18.5 – 35 kg/m^2 were recruited. Female patients were to use adequate contraception to ensure no pregnancies occurred during the study or for 5 half-lives after the end of the study period. The patients were to have:

- ∉# a diagnosis of RA according to the revised 1987 criteria for the American College of Rheumatology (ACR)
- ∉# serum CRP at screening ∅10mg/L
- ∉# ∅3/66 swollen or ∅3/68 tender/painful joints at screening
- ∉# urea and creatinine within normal range at screening
- ∉# liver function tests ALT, AST and νGT within 1.5 times the upper limit of normal; ALP within 2 times the upper limit of normal and total bilirubin within normal range at screening
- ∉# QT_c(b) of less than 430msec for males and 450msec for females at screening

Patients had to be on stable weekly methotrexate (2.5 – 25mg) for at least eight weeks prior to screening. Any additional oral anti-rheumatic therapies (which may have included sulphasalazine [Ω2g/day] or hydroxychloroquine) had to be stable for at least eight weeks prior to screening. Any additional oral symptomatic relief therapy (which

may have included NSAIDs or COX-2 inhibitors) had to be stable for at least 2 weeks prior to screening.

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

Treatment administration:

Patients were randomised to receive a single dose of one of the following:

Treatment	Formulation –Oral administration	Batch
Placebo	5 x Tablets to match SB-681323 +	031002312
	5 x Capsules to match prednisolone	051081156 031000243 E03B190
SB-681323 7.5mg	3 x 2.5mg SB-681323 tablets + 2 x placebo tablets + 5 x placebo capsules	041026485
SB-681323 15mg	3 x 5mg SB-681323 tablets + 2 x placebo tablets + 5 x placebo capsules	041026486
SB-681323 25mg	5 x 5mg SB-681323 tablets + 5 x placebo capsules	041026486
Prednisolone 10mg	1 x 10mg predniosolone capsules +4 x placebo capsules + 5 x placebo tablets	051112691 041061575
Prednisolone 20mg	2 x 10mg predniosolone capsules + 3 x placebo capsules + 5 x placebo tablets	051112691 041061575
Prednisolone 50mg	5 x 10mg predniosolone capsules + 5 x placebo tablets	051112691 041061575

Criteria for evaluation:

Endpoints:

The **primary** endpoint for this study was CRP levels 72 hours post-dose.

The secondary endpoints were:

- CRP levels 24 and 48 hours post-dose.
- Interleukin (IL)-6 levels post-dose.
- Safety and tolerability of oral SB-681323: adverse events (AE), vital signs, 12-lead ECGs and laboratory assessments (including liver function tests i.e. ALT, AST, ALP νGT and total, direct and indirect bilirubin).
- Serum cytokines: (chemokines and cytokines involved in the pathogenesis of RA).
- Whole blood messenger RNA levels of TNF-ζ, IL-8, IL-1η and COX-2 (and other genes implicated in the pathogenesis of RA or genes involved in the mode of action of the compounds administered).

IL-6 levels were measured 1, 3, 24 and 72 hours post-dose.

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.

The size of the treatment effect to be detected was based on consideration of CRP decrease in terms of mean ratio to baseline compared to placebo. Assuming a linear single dose dose-response relationship, a decrease of 30% in CRP for 7.5mg of SB-681323 compared to placebo corresponds to a slope of 0.048 decrease in log CRP per mg increase in dose. This implies a decrease of 51% and 70% in CRP for 15mg and 25mg of SB-681323 respectively, compared to placebo. It was estimated that 11 evaluable patients in each group were required to provide 90% power to detect the above decrease in log CRP based on a test of significance at the two-sided 5% level.

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

Following log-transformation, CRP andIL-6 levels were statistically analysed separately by Repeated Measure analysis. If applicable, the slope of the single dose dose-response was estimated and presented with the corresponding 95% confidence interval (CI). For each dose and time separately, point estimates and corresponding 95% CI were constructed and back transformed. Baseline was fitted as a covariate and Placebo treated as if it were a zero dose.

Summary:

Demographics:

	Total (N =77)
Age (years)	
Mean	56
Range	19-79
Sex, n(%)	
Female:	61 (79%)
Male:	16 (21%)
Ethnicity, n(%)	
Not Hispanic or Latino:	77 (100%)
Race, n(%)	
African American/African Heritage:	0
American Indian or Alaskan Native:	0
Asian – Japanese/East Asian/South East Asian Heritage:	0
Asian – Central/South Asian Heritage:	1(1%)
Native Hawaiian or Other Pacific Islander:	0
White – Arabic/North African Heritage	1(1%)
White – White/Caucasian/European Heritage	75 (97%)
Height, cm	
Mean	162.8
Range	138-186
Weight, kg	
Mean	74.21
Range	41-110

Data Source:Table 9.6 and 9.8

Patients enrolled into the study were experiencing RA signs and symptoms. The median level of disease activity was severe with a median DAS28 score of 5.61.

Safety:

Both SB-681323 and prednisolone were well tolerated in this study. There were few AEs and no withdrawals or SAEs. None of the AEs were serious.

		SB-681323			Prednisolone		
Number of Patients	Placebo (N=11)	7.5mg (N=12)	15mg (N=11)	25mg (N=11)	10mg (N=10)	20mg (N=11)	50mg (N=11)
Any Event	2 (18%)	4 (33%)	1 (9%)	1 (9%)	2 (20%)	5 (45%)	3 (27%)
Any Drug-Related Event	1 (9%)	3 (25%)	1 (9%)	1 (9%)	2 (20%)	4 (36%)	3 (27%)
Most Common AEs: (∅2 patients):							
Headache	0	1(8%)	1(9%)	0	1(10%)	1(9%)	0
Fatigue	0	1(8%)	0	1(9%)	0	0	0
Nausea	0	0	0	1(9%)	0	1(9%)	0
Feeling hot	0	0	1(9%)	0	1(10%)	0	0

Data Source Table 10.2 and 10.6

There were two patients with ALT levels considered to be of clinical concern (defined as greater than twice the upper limit of normal). [redacted] There were no AST values of clinical concern. There were no vital signs or ECG abnormailities which were considered of clinical significance.

Efficacy Results:

CRP:

There was no evidence of a dose-response relationship between increasing doses of SB-681323 and levels of CRP at 24, 48 and 72 hours post-dose. SB-681323 did not have a significant effect on CRP levels 24, 48 or 72 hours post-dose when compared with placebo, although the study was not powered for this comparison.

There was no evidence of a dose-response between increasing doses of prednisolone and CRP levels 72h post-dose. Following prednisolone, there was a significant reduction in CRP levels 72 hours post-dose only at the 10mg dose when compared with placebo. However, single doses of prednisolone significantly reduced serum CRP levels 48h post-dose when compared with placebo and there was evidence for a dose-response relationship between increasing doses of prednisolone and CRP levels, although this trend did not quite achieve statistical significance (p=0.070).

Analysis of Serum CRP at 48h following Prednisolone or Placebo

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to Placebo	95% CI
Placebo	0.90	0.68, 1.20		
Prednisolone 10mg	0.53	0.39, 0.72	0.59	0.38, 0.89
Prednisolone 20mg	0.61	0.46, 0.80	0.67	0.45, 1.00
Prednisolone 50mg	0.55	0.41, 0.72	0.61	0.41, 0.90

Data Source: Table 11.3 and 11.7

IL-6:

There was no evidence of a dose-response relationship between SB-681232 and IL-6 at any time point. There was no significant effect on IL-6 levels following any dose of SB-681323 at the 1h, 24h and 72h post-dose when compared with placebo. However, at 3h post-dose following a single 15mg dose of SB-681323 there was a significant reduction in IL-6 levels compared with placebo.

Analysis of Serum IL-6 at 3h following SB-681323 or Placebo

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to Placebo	95% CI
Placebo	0.58	0.36, 0.93		
SB-681323 7.5mg	0.72	0.44, 1.17	1.24	0.63, 2.44
SB-681323 15mg	0.27	0.16, 0.44	0.46	0.23, 0.92
SB-681323 25mg	0.43	0.28, 0.68	0.75	0.39, 1.43

Data Source: Table 11.21 and 11.24

There was a significant dose-response relationship between increasing doses of prednisolone and IL-6 levels at 3h (p=0.04) and 24h (p=0.03) post-dose. This appeared to be influenced by a substantial reduction in IL-6 levels when compared with placebo following the 50mg dose, which was statistically significant at the 3h time point.

Analysis of Serum IL-6 at 3h following Prednisolone or Placebo

Treatment group	Adjusted ratio to baseline	95% CI	Adjusted ratio to Placebo	95% CI
Placebo	0.58	0.36, 0.93		
Prednisolone 10mg	0.35	0.19, 0.62	0.60	0.28, 1.27
Prednisolone 20mg	0.51	0.31, 0.86	0.89	0.44, 1.78
Prednisolone 50mg	0.27	0.18, 0.41	0.47	0.25, 0.88

Data Source: Table 11.21 and 11.27

mRNA:

There was no evidence of an effect of single doses of SB-681323 on the biomarker mRNA levels measured. Single doses of prednisolone significantly up regulated GILZ, DUSP1, IL-2R, TXNIP, DDIT4 and ZNF145 mRNA levels and significantly inhibited mRNA levels of IL-1η, TNF-ζ and IFI30.

Conclusions:

- There was no evidence of a significant dose-response relationship between single doses of SB-681323 and serum CRP levels in RA patients when measured 24, 48 and 72 hours post-dose.
- There was evidence for a single dose-response relationship between prednisolone and serum CRP levels when measured 48h post-dose, although this did not achieve statistical significance in this study.
- There was no evidence of a significant dose-response relationship between single doses of SB-681323 and serum IL-6 levels when measured 1, 3, 24 and 72 hours post-dose. A significant decrease in IL-6 was observed 3 hours post dosing with 15mg SB-681323 compared with placebo.
- There was a significant single dose-response relationship between prednisolone and serum IL-6 levels when measured 3h and 24h post-dose. This appeared to be

influenced by a substantial reduction in IL-6 levels when compared with placebo following the 50mg dose.

- The reduction in serum IL-6 levels 3 and 24h post prednisolone may be associated with a reduction in serum CRP levels 48h post-dose.
- There was no evidence of a significant dose-response relationship between a single dose of SB681323 and IL-6, TNF-ζ, COX-2, IL-8 or IL-1η mRNA levels.
- A single dose of either 20mg or 50mg prednisolone significantly up regulated GILZ, DUSP1, IL-1R2, TXNIP, DDIT4 and ZNF145 mRNA levels and significantly inhibited mRNA levels of IL-1η, TNF-ζ and IFI30.
- SB-681323 and prednisolone were well tolerated in this population. There was no evidence of phototoxicity or adverse effects on liver function. There were no SAEs or clinically significant AEs reported.

Date of Report:

April 2007