Synopsis

Identifier: GM2005/00545/00 **Study Number:** RA3103730

Title: A randomised, placebo-controlled, parallel group single dose study of GW856553 in patients with active RA to investigate the CRP dose response relationship.

Investigators: Multicentre study.

Study centres: Fifteen centres in five countries recruited subjects: four centres in Bulgaria, four in Germany, three in Spain, three in Ukraine, and one in Sweden.

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

Study period: 09 Nov 2005 – 18 Nov 2006 **Phase of development:** IIa

Objectives: Primary: to describe the single dose-response relationship of the dose range of 7.5 to 60 mg of GW856553 on circulating serum C-reactive protein (CRP) levels.

Secondary objectives:

- To describe the single dose-response relationship of GW856553 on circulating serum interleukin-6 (IL-6) levels.
- To describe the effect of GW856553 on circulating biomarker levels.
- To collect plasma drug concentration data to allow characterisation of the pharmacokinetics of GW856553 and GSK198602, a known metabolite of GW856553, following a single oral dose of GW856553 in rheumatoid arthritis (RA) subjects.
- To explore the relationship between plasma GW856553 concentration and CRP change.

Methodology: This was a double blind, parallel group study of GW856553 in subjects with active RA to investigate the CRP dose-response relationship after a single dose. Screening took place within 10 days prior to the first dose. Treatment arms comprised GW856553 7.5 mg, 20 mg, 60 mg or placebo. Treatment commenced between weekly doses of methotrexate. The 120-h post-dose visit constituted the follow-up visit. Therefore, subjects were in the study for less than 1 week in total.

Number of subjects: Subject disposition is summarised in the following table.

Number of Subjects	Placebo	GW856553 7.5 mg	GW856553 20 mg	GW856553 60 mg	Total [1]
Planned, N	12	12	12	12	48
Randomised, N	12	13	12	13	51
Completed, n (%)	12 (100)	13 (100)	12 (100)	13 (100)	50 (98)
Total Withdrawn (any reason), n (%)	0	0	0	0	1 (2)
Primary reason for withdrawal, n (%)					
Other [2]	0	0	0	0	1 (2)

1. Total column includes one subject who received unknown treatment.
2. Subject mistakenly took only one tablet instead of three.

Diagnosis and main criteria for inclusion: Male and female subjects aged ≥18 years, with diagnosis of RA according to revised 1987 American College of Rheumatology criteria; serum CRP ≥10 mg/L; and ≥3/66 swollen or ≥3/68 tender/painful joints; receiving stable weekly methotrexate (2.5 mg–25 mg).

Treatment administration: Each subject was randomised to a single oral dose of GW856553 7.5 mg, 20 mg, 60 mg or placebo, with each dose given as three tablets.

Investigational product	Dose/Form/Route	Batch Numbers
GW856553X	2.5 mg tablet oral	051096957, 061119859
GW856553X	5 mg tablet oral	051096955, 061119860
GW856553X	20 mg tablet oral	051096958, 061119858
Placebo	tablet oral	051096959, 061119838

Criteria for evaluation: The primary endpoint was serum CRP at 72 h post-dose. Secondary endpoints were: serum CRP at 24 and 48 h; IL-6; adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), laboratory assessments (including aspartate aminotransferase [AST] and alanine aminotransferase [ALT]; serum cytokines; blood cytokine messenger ribonucleic acid (mRNA) levels; GW856553 population pharmacokinetic parameters.

Statistical methods: The sample size of 12 evaluable subjects per group was based on estimates of between-subject variability of CRP in four previous GlaxoSmithKline studies. There was no formal analysis of safety data, which were summarised descriptively. Pharmacokinetic plasma drug concentrations were summarised and plotted.

The Modified Intent-to-Treat (MITT) population was used for all efficacy analyses. Following log-transformation, serum CRP and IL-6 concentrations were analysed using repeated measures analysis. The single dose-response relationship was tested using ordinal contrasts. Dose and time were treated as categorical variables. The estimate of the slope and the 95% confidence interval (CI) were not produced, but the p-value was reported as a valid test of trend. Baseline was fitted as a covariate. Supporting analyses included estimation of the slope of the single dose dose-response and analysis using a sequence of contrasts based on a logarithmic approach with displaced values for placebo. For each dose and time separately, point estimates and corresponding 95% CIs were constructed and back transformed and all pairwise treatment differences between doses of GW856553 and placebo presented accordingly.

A repeated measures model was used to assess the effect of treatment and time on biomarker mRNA, as measured by the change from baseline in gene expression. Pairwise comparisons were performed at each of the four time points. Predicted least squares means and associated 95% CIs were produced for each gene at all time points. A covariate was added that adjusted for between-sample variability in overall mRNA levels measured by the Taqman assay.

Summary: Demographic characteristics are summarised in the following table.

		Placebo	GW856553			Total [1]
			7.5 mg	20 mg	60 mg	
		N = 12	N = 13	N = 12	N = 13	N = 51
Age, years (Protocol age: ≥18 years)	Median	50.5	54.0	57.0	55.0	55.0
	Range	27–78	34–72	47–73	24–72	24–78
Body mass index, kg/m^2	Median	25.97	25.15	25.02	26.03	25.69
	Range	20.3–36.3	19.1–33.3	22.2–30.5	21.5–35.6	19.1–36.3
Sex, n (%)	Female	11 (92)	12 (92)	10 (83)	10 (77)	44 (86)
	Male	1 (8)	1 (8)	2 (17)	3 (23)	7 (14)
Ethnicity, n (%)	Hispanic or Latino	0	1 (8)	1 (8)	0	2 (4)
	Not Hispanic or Latino	12 (100)	12 (92)	11 (92)	13 (100)	49 (96)
Race, n (%)	White	12 (100)	13 (100)	12 (100)	13 (100)	51 (100)

1. Total column includes one subject who received unknown treatment.

Safety: There were no deaths, non-fatal serious adverse events (SAEs) or AEs leading to withdrawal. Adverse events are summarised in the following table.

	Placebo	GW856553		
		7.5 mg	20 mg	60 mg
	N = 12	N = 13	N = 12	N = 13
Any adverse event, n (%)	0	2 (15)	1 (8)	3 (23)
Any adverse event possibly related to investigational product, n (%)	0	0	1 (8)	2 (15)
All adverse events				
Abdominal pain upper [1]	0	0	0	1 (8)
Arthralgia	0	0	0	1 (8)
Aspartate aminotransferase increased [1]	0	0	1 (8)	0
Chest discomfort	0	1 (8)	0	0
Headache	0	1 (8)	0	0
Hepatic enzyme increased [1]	0	0	0	1 (8)
Tachycardia	0	1 (8)	0	0

1. Considered possibly related to the investigational product by the Investigator.

The possibly drug-related AEs of increased AST and hepatic enzyme were associated with AST and ALT values >3x the upper limit of normal (ULN). No other subjects had treatment-emergent chemistry values of potential clinical concern. Median haematology and clinical chemistry values did not show any differences among treatment groups.

Average vital signs values did not show any notable differences among treatment groups. There were no clinically significant abnormal ECG findings. Abnormal, but not significant, ECG traces were reported in a small proportion of subjects at any given time (up to 3 subjects, 23%), but no differences among treatment groups were apparent. Average ECG interval values over time (PR, QRS, RR, QT, QTc (Bazett) and QTc (Fridericia)) did not show any notable differences among treatment groups.

Pharmacokinetics: A trend towards higher systemic exposure to GW856553 and GSK198602 was observed with increasing dose. This increase was less than dose-proportional between the 20 and 60 mg doses. There was no major difference in the time course of systemic exposure to GW856553 between healthy subjects (in a previous study) and subjects with RA (in this study), but there appeared to be a tendency for higher

exposure to GW856553 in subjects with RA, compared with healthy subjects. These observations will be investigated and evaluated by population pharmacokinetic analyses.

Efficacy (surrogate markers): There was no evidence of a relationship between increasing doses of GW856553 and CRP levels at 24, 48 and 72 h post-dose. GW856553 did not have a significant effect on CRP levels 24, 48 or 72 h post-dose when compared with placebo, although the study was not powered for this comparison. Serum amyloid A was measured in only a small number of subjects and no conclusions could be drawn.

Biomarkers: Serum IL-6: There was a significant reduction in serum IL-6 at 3 h post-dose for all doses of GW856553 compared with placebo, however the differences were similar across all of the doses. No significant differences between GW856553 and placebo were observed at the other time points (1 h, 24 h and 72 h post-dose).

Treatment group	IL-6 adjusted ratio to baseline	95% CI	IL-6 adjusted ratio to placebo	95% CI
Placebo	0.92	0.60, 1.41	Not applicable	Not applicable
GW856553 7.5 mg	0.41	0.26, 0.63	0.45	0.24, 0.82
GW856553 20 mg	0.43	0.27, 0.68	0.47	0.25, 0.88
GW856553 60 mg	0.38	0.25, 0.57	0.41	0.23, 0.75

CI = confidence interval.

Biomarker mRNA: There was an increase in tumour necrosis factor-alpha (TNF-α) mRNA following GW856553 60 mg at 3 h post-dose compared with placebo, but this was not statistically significant (treatment ratio 1.939; 95% confidence interval: 0.969, 3.881; p=0.061) and no dose-response effect was observed. There was no evidence of an effect of single doses of GW856553 on other biomarker mRNA levels (IL-6, cyclo-oxygenase-2 [COX-2], IL-8, IL-1β, matrix metalloprotease-9 [MMP-9] or inducible nitric oxide synthase [iNOS]).

Conclusions:

- There was no evidence of a dose-response relationship between single doses of GW856553 and serum CRP concentrations.
- There was a significant reduction in serum IL-6 at 3 h post-dose for all doses of GW856553 compared with placebo, however the differences were similar across all of the doses. No significant differences between GW856553 and placebo were observed at the other time points (1 h, 24 h and 72 h post-dose).
- Single oral doses of GW856553 7.5 mg, 20 mg and 60 mg were well tolerated in subjects with RA.
- There were no deaths, non-fatal SAEs or AEs leading to withdrawal.
- Two subjects, one with GW856553 20 mg and one with 60 mg, had AEs associated with liver function tests, which were judged by the Investigator to be possibly related to the investigational product. Both subjects had ALT values >3 x ULN.
- Higher systemic exposure to GW856553 and GSK198602 was observed with increasing GW856553 dose, but this increase was less than dose-proportional between the 20 and 60 mg doses.

- There was no major difference in the time course of systemic exposure to GW856553 between healthy subjects and subjects with RA, but there appeared to be a tendency towards higher exposure to GW856553 in the RA subjects compared with healthy subjects. These observations will be investigated and evaluated by population pharmacokinetic analyses.
- There was evidence of an increase in TNF-α mRNA following GW856553 60 mg at 3 h post-dose compared with placebo, but this was not significant (p=0.061). There was no evidence of changes in mRNA levels for markers IL-8, IL-1β, COX-2, IL-6, MMP-9 and iNOS.

Date of Report: May 2007