Synopsis

Identifier: GM2007/00267/00 **Study Number:** MKI106209

Title: A randomised, double-blind, placebo-controlled parallel study to assess the safety, tolerability, pharmacodynamics and steadystate pharmacokinetics of repeated doses of GW856553 in patients with COPD.

Investigators: Prof. Dr. [redacted] Dr. [redacted] and Dr. [redacted]

Study centres: [redacted] Germany [redacted] Germany [redacted] and [redacted] Germany [redacted]

Publications: None at the time of this report.

Study period: 20 March 2006 – 20 December 2006

Phase of development: I

Objectives: Primary:

- To assess the safety and tolerability of GW856553 administered orally for 14 days in patients with chronic obstructive pulmonary disease (COPD).

Secondary:

- To assess the systemic anti-inflammatory activity of GW856553 administered orally for 14 days in patients with COPD as determined by changes in systemic biomarkers (whole blood).
- To assess the pharmacokinetics of GW856553 and GSK198602 (a known metabolite) in patients with COPD.

Methodology: This was a multi-centre, double-blind, randomised parallel group study in subjects diagnosed with moderate stable COPD. Following an initial Screening Visit (Visit 1), subjects were withdrawn from treatment with inhaled corticosteroids and other treatment for COPD and began a 14-day run-in period. Subjects were provided with short-acting bronchodilator therapy, comprising salbutamol for use on an 'as required' basis and, if considered necessary by the Investigator, stable treatment with ipratropium bromide at a standard dose from Visit 1 until study completion.

Following this there was a 14-day treatment period with GW856553 (7.5 mg twice-daily) or placebo twice-daily, followed by a 7-day follow-up period. After this subjects reverted to their usual treatment. During the treatment period safety assessments (not pulmonary function tests or electrocardiography [ECG]) were performed on days 1, 3, 6, 9, 12 and 14 of the treatment period. All pharmacodynamic assessments, as well as pulmonary function tests and ECG, were performed on days 1, 7 and 14 of the treatment period. Pharmacokinetic analyses were performed on days 1 and 14 of the treatment period.

Number of subjects:

Number of Subjects	Placebo twice-daily	7.5 mg GW856553 twice-daily
Planned, N	12	24
Randomised, N	12	24
Completed, n (%)	12 (100)	24 (100)
Total Withdrawn (any reason), n (%)	0	0
Withdrawn due to Serious Adverse Event, n (%)	0	0
Withdrawn due to Adverse Events, n (%)	0	0
Withdrawn due to other reason, n (%)	0	0

Diagnosis and main criteria for inclusion: Males and females aged between 40 and 75 years of age with an established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society. Subjects had a cigarette smoking history of ≥10 pack years (1 pack year = 20 cigarettes smoked per day for 1 year or the equivalent). Both current and former smokers were eligible to be enrolled. A former smoker was defined as a subject who had not smoked for ≥6 months at Visit 1.

Subjects were required to have a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio (FEV1: FVC) < 0.7 and a post-bronchodilator FEV1 ≥40% and <80% of predicted normal for height, age and sex at Visit 1. Subjects were assessed 30 (±5) minutes after receiving salbutamol 400 μg.

Treatment administration: Subjects were assigned to GW856553 (7.5 mg twice-daily) or placebo in a 2:1 ratio. Subjects received 7.5 mg twice-daily of GW856553 or matching placebo twice-daily for a total of 14 days.

Criteria for evaluation: Safety: adverse events (AEs), vital signs, clinical laboratory assessments (in particular, changes in liver function tests), ECG parameters, lung function (FVC and FEV1).

Pharmacodynamics: Inhibition of *ex vivo* sorbitol-induced phosphorylated heat shock protein 27 (pHSP27) and *ex vivo* lipopolysaccharide (LPS)-induced tumour necrosis factor-α (TNFα) in whole blood. Fluorocytometric quantification of resting and *ex vivo* LPS-stimulated CD11b surface expression on neutrophils in whole blood (at selected centres).

Pharmacokinetics: Population pharmacokinetics parameters of GW856553 and GSK198602 in COPD patients.

Statistical methods: Thirty-six subjects were randomised into the study. This sample size was based on feasibility and no formal statistical powering was carried out.

Safety data (AEs, vital signs, 12-lead ECG and clinical laboratory tests) were listed and summarised and a descriptive comparison made between active dose and placebo.

The pharmacodynamic endpoints, LPS-stimulated TNFα and sorbitol-stimulated pHSP-27, were summarised and analysed across serial time points using repeated measures modelling. Both inhibition relative to pre-dose on the relevant day and inhibition relative to baseline (i.e., pre-dose on Day 1) were investigated. Both LPS-stimulated TNFα and sorbitol-stimulated pHSP-27 inhibition ratio data were $\log_e$ transformed prior to statistical analysis using a mixed effects model.

To gain confidence that the model assumptions were reasonable, plots of residuals against their predicted values, as well as normal plots, were examined. CD11b data were listed and summarised and a descriptive comparison made between active dose and placebo. Where available plasma concentration data were listed and summarised.

Summary:

Demographics

		Placebo (N=12)	GW856553 7.5 mg bid (N=24)
Sex, n (%)	Males	8 (67)	19 (79)
	Females	4 (33)	5 (21)
Age, years	Mean	59.9	55.5
	Range	41–73	42–74
Race, n (%)	White/Caucasian/European Heritage	12 (100)	24 (100)
Height, cm	Mean	169.4	174.2
	Range	157–178	160–187
Weight, kg	Mean	84.3	82.7
	Range	58–111	52–116
Body mass index, kg/m^2	Mean	29.2	26.9
	Range	23.5–35.5	19.8–33.5
Percent oxygen in blood	Mean	96.1	96.5
	Range	93–100	93–99
Ethnicity, n (%)	Hispanic or Latino	0	0
	Not Hispanic or Latino	12 (100)	24 (100)

Safety

Most Frequent Adverse Events	Placebo N=12	GW856553 7.5 mg bid N=24
	n (%)	n (%)
Any AE	9 (75)	13 (54)
Any AE related to investigational product	5 (42)	7 (29)
Most Frequent AEs (reported by at least one subject in each group):		
Anaemia	3 (25)	2 (8)
Nasopharyngitis	2 (17)	3 (13)
Blood creatine phosphokinase increased	1 (8)	2 (8)
Urinary tract infection	0	2 (8)
Tachycardia	1 (8)	1 (4)
Chronic obstructive pulmonary disease	1 (8)	1 (4)

Pharmacodynamics: There was evidence of LPS-stimulated TNFα inhibition following repeat dosing with 7.5 mg GW856553 compared with placebo when adjusted for pre-dose levels on Day 1. Results for the treatment ratios relative to placebo indicated that 7.5 mg GW856553 twice-daily demonstrated a statistically significant increase in inhibition of LPS-stimulated TNFα at 2 h post-dose on Day 1, at pre- and 2 h post-dose on Day 7, and pre-, 2 h and 6 h post-dose on Day 14 (particularly at 2 h post-dose on each of the days). There was a clear reduction in pre-dose LPS-stimulated TNFα on days 7 and 14 compared with Day 1 following GW856553, suggesting that levels of LPS-stimulated TNFα on days 7 and 14 did not return to the baseline levels seen on Day 1.

There was some indication (although no statistical evidence) of sorbitol-stimulated pHSP-27 inhibition following repeat dosing with 7.5 mg GW856553 compared with placebo, when adjusted for pre-dose levels on Day 1. No reduction in pre-dose sorbitol-stimulated pHSP-27 levels on days 7 or 14 compared with Day 1 were observed in the active treatment arm. However, in the placebo group, pre-dose sorbitol-stimulated pHSP-27 levels on Day 14 were considerably higher than on Day 1.

Flouorocytometric quantitation of resting *ex-vivo* LPS-stimulated CD11b was conducted at one site on eight subjects only. Two subjects on placebo were assessed and six subjects on investigational product. On Day 14 only four patients in the GW856553 group had CD11b data. Two hours post-treatment with 7.5 mg GW856553 a reduction in CD11b levels was observed. However, it should be noted that in the two subjects who received placebo, one subject also showed decreased levels of CD11b at this time point.

Pharmacokinetics: There appeared to be an increase in systemic exposure after repeat dosing of GW856553, largely due to the twice-daily dosing regimen. The plasma concentration at trough (pre-dose on corresponding day) demonstrated that steady state was reached and was maintained during the 14 days of the study.

Conclusions:

- GW856553 was generally well tolerated following repeat dosing of 7.5 mg twice-daily in COPD patients. No subjects were withdrawn from the study.
- One subject in the active treatment group had an increase in alanine aminotransferase levels (≥1 x but <2 x upper limit of normal).
- Two subjects in the placebo group and three subjects in the active treatment group had increases in aspartate aminotransferase levels (≥1 x ULN but ≤2 x ULN).
- Two clinically significant ECG abnormalities (first degree AV block and ectopic supraventricular rhythm) were reported by two subjects pre-GW856553 dose on Day 14. Both were reported as AEs by the Investigator. Neither subject was withdrawn from the study due to these ECG findings.
- Changes in baseline in mean vital signs and 12-lead ECG intervals appeared comparable across treatments.
- There was evidence of LPS-stimulated TNFα inhibition following repeat dosing with 7.5 mg GW856553 compared with placebo, when adjusted for pre-dose levels on Day 1. Results for the treatment ratios relative to placebo indicated that 7.5 mg GW856553 twice-daily demonstrated a statistically significant increase in inhibition of LPS-stimulated TNFα at 2 h post-dose on Day 1, at pre- and 2 h post-dose on Day 7, and pre-, 2 h and 6 h post-dose on Day 14 (particularly at 2 h post-dose on each of the days).
- There was a clear reduction in pre-dose LPS-stimulated TNFα on days 7 and 14 compared with Day 1 following GW856553, suggesting that levels of LPS-stimulated TNFα on days 7 and 14 did not return to the baseline levels seen on Day 1.
- There was some indication (although no statistical evidence) of sorbitol-stimulated pHSP-27 inhibition following repeat dosing with 7.5 mg GW856553 compared with placebo, when adjusted for pre-dose levels on Day 1.
- No reduction in pre-dose sorbitol-stimulated pHSP-27 levels on days 7 or 14 compared with Day 1 were observed in the active treatment arm. However, in the placebo group, pre-dose sorbitol-stimulated pHSP-27 levels on Day 14 were considerably higher than on Day 1.
- There appeared to be an increase in systemic exposure after repeat dosing of GW856553, largely due to the twice-daily dosing regimen. The plasma concentration at trough (pre-dose on corresponding day) demonstrated that steady state was reached and was maintained during the 14 days of the study.

Date of Report: June 2007