Synopsis

Document Number: RM2007/00010/00 **Study Number:** CXA30009

Title: A Phase III, 12-Week, Multicentre, Double-Blind, Randomised, Placebo- and Active Comparator-Controlled, Parallel Group Study to Investigate the Efficacy and Safety of GW406381, 5mg, 10mg, 25mg, and 50mg administered orally once daily, in Adults with Rheumatoid Arthritis

Investigators and study centers: The study was conducted in 228 centers in 31 countries.

Publication: None at the time of this report.

Study Period: 28 June 2005 to 14 September 2006

Phase of Development: III

Objectives: The primary objective was to evaluate the clinical efficacy of GW406381administered orally versus placebo in the treatment of the signs and symptoms of rheumatoid arthritis (RA). The secondary objectives were to evaluate the safety and tolerability of GW406381 administered orally to subjects with RA; to evaluate the optimal therapeutic dose(s) of GW406381 for further clinical investigations in RA; to explore the effect of GW406381 versus celecoxib on pain intensity and function in subjects with RA; to evaluate health outcomes data generated from subject-completed questionnaires; and to evaluate population pharmacokinetics (PK) /pharmacodynamics (PD) of GW406381 in subjects with RA.

> Note: The primary objective for this study was not met, therefore, results were reported using the GlaxoSmithKline format for an abbreviated clinical study report (ACSR).

Methodology: The study included a Screening Visit and Washout Phase (−1 to 14 days), a Baseline Visit (Day 1), a Double-Blind Treatment Phase (12 weeks), and a Post-Treatment Phase (7 days). Study visits were scheduled at screening, baseline, Weeks 2, 4, 8 and 12 (or early withdrawal), and follow-up. Total duration of subject participation in the study was up to 16 weeks. Eligible subjects underwent a washout of all non-steroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase-2 (COX-2) inhibitors for a period of at least 5 times the half-life of the relevant drug prior to baseline and randomized in equal numbers to 1 of 6 treatment groups: placebo, GW406381 5 mg, 10 mg, 25mg or 50 mg, or celecoxib 200mg twice daily (BID). Subjects received study drug on an outpatient basis for up to 12 weeks. Use of supplementary analgesic therapy (acetaminophen/paracetamol up to 3g/day) was permitted throughout the study.

Number of subjects:

Number of Subjects	Placebo	GW40638 15 mg	GW40638 110 mg	GW40638 125 mg	GW40638 150 mg	Celecoxib 200 mg BID
Number of subjects planned, N	368	368	368	368	368	368
Randomized, N	379	379	379	380	379	379
Completed, n (%)	262 (74)	287 (80)	297 (82)	277 (77)	265 (75)	281 (78)
Prematurely withdrawn, n (%)	92 (26)	73 (20)	66 (18)	81 (23)	88 (25)	80 (22)

Diagnosis and main criteria for inclusion: Male and female subjects with American College of Rheumatology (ACR)-defined RA, who required NSAID or COX-2 inhibitor treatment for management of their RA for 5 out of 7 days for each of the 4 weeks prior to screen, were screened for enrollment in the study. At baseline (post-washout), subjects were required to meet the following 'flare' criteria to be eligible for randomization:

i. a minimum of 6 tender/painful joints at baseline with an increase of ≥2 tender/painful joints (or 20% increase, whichever was greater) at baseline compared to screen;

ii. a minimum of 3 swollen joints at baseline with an increase of ≥2 swollen joints (or 20% increase, whichever was greater) at baseline compared to screen; and

iii. an assessment of pain (VAS) of ≥40mm at baseline with an increase of ≥10mm (or 20% increase, whichever was greater) at baseline relative to screen.

Treatment administration: GW406381 5mg (Batch 041059074P1), 10mg (Batch 041060400P1), 25mg (Batch 041060401P1), and 50mg (Batch 041060402P1) were supplied as hard gelatin capsules. Celecoxib 200mg (Batches 051062575 and 051063995) capsules were over-encapsulated for blinding. Matching placebo capsules (GW406381 placebo Batch 041032984P1, celecoxib placebo Batches 051062594 and 051065502) were supplied. Eligible subjects received up to 12 weeks of double-blind study drug per randomized assignment to 1 of 6 treatment groups as follows: placebo (placebo matching GW406381 capsules once daily [OD] + placebo matching celecoxib 200mg capsules BID); GW406381 5mg, 10mg, 25mg or 50mg (GW406381 capsule of appropriate dose + placebo matching celecoxib 200mg capsules BID); or celecoxib 200mg BID (placebo matching GW406381 capsule + celecoxib 200mg capsule BID).

Criteria for evaluation: This study included efficacy, safety, health outcomes, and PK/PD endpoints. This ACSR presents results for all safety data and the primary efficacy endpoint only. Baseline disease characteristics were collected by history and included disease duration, American Rheumatism Association (ARA) functional status, tender/swollen joint count (T/SJC), and pain assessment (VAS) scores. Safety evaluations included continuous monitoring of adverse events (AEs), and changes from baseline to on-treatment and follow-up in clinical laboratory test results (including hematology, blood chemistry, C-reactive protein levels, and dipstick urinalysis), vital signs, weight, 12-lead electrocardiograms (ECGs), and pedal edema grades. A single fasting blood sample was taken to assess potential cardiovascular (CV) risk factors. Suspected

significant gastrointestinal (GI), CV or cerebrovascular events were reviewed by independent GI and CV adjudication boards to confirm diagnosis and categorization of events. Standard efficacy assessments for studies in RA were utilized in this study. The primary efficacy endpoint was the percentage of ACR20 Responders at the end of treatment (Week 12). A clinical response was defined according to ACR response criteria, i.e., at least 20% improvement relative to baseline in both tender and swollen joint counts, coupled with at least a 20% improvement relative to baseline in 3 of the following 5 parameters: pain assessment (VAS), Physician's (Patient's) Global Assessment of Arthritis Condition (VAS), Functional Disability Index (Health Assessment Questionnaire [HAQ]), and CRP level.

Statistical methods: Safety analyses were performed for the Safety Population which included all randomized subjects who received at least one dose of study drug. Safety data were summarized by treatment group using descriptive statistics. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA). Acceptable reference ranges for vital signs were 80mmHg (low) to 140mmHg (high) (systolic BP [SBP]); 50 to 90mmHg (diastolic BP [DBP]) and 50 to 120bpm (heart rate [HR]). Change from baseline to maximum on-treatment SBP also was analyzed adjusting for baseline SBP; adjusting for baseline SBP and age; and adjusting for baseline SBP, age and BMI. Changes from baseline to Week 12 LOCF and to average on-treatment SBP were also analyzed adjusting for baseline SBP value and age; and adjusting for treatment by covariate interaction.

The primary inference was based on the Intent-to-Treat (ITT) Population at Week 12. The ITT Population included subjects from the Safety Population with at least one post-baseline efficacy assessment. The analysis of the primary efficacy endpoint was performed using a logistic regression adjusting for treatment group, center group, baseline physician's global assessment, baseline functional disability index and baseline CRP. Adjusted odds ratios (ORs), 95% confidence intervals (CIs), and associated p-values were presented. A covariate significance table was also provided. The type I error rate was maintained at 5% using a hierarchical testing procedure to test each GW406381 dose versus placebo.

Summary:

Study population: Enrollment into the study was stopped after 1852 subjects enrolled to allow an unscheduled interim review of available safety data. The available data supported continuation of the study and enrollment was reinitiated; however, enrollment was not reinitiated at all participating countries/study sites. The result was 74 subjects (2% to 4% of subjects across treatment groups) who were prematurely discontinued from the study with the reason given as 'Sponsor-terminated study.' The majority of subjects discontinued for this reason were from a total of 4 sites in Peru (56 of 74 subjects) followed by 4 sites in Hungary (15 of 74 subjects) and 2 sites in India (3 of 74 subjects).

Subject demographics and baseline disease characteristics were comparable across treatment groups and consistent with the targeted population of subjects with active RA. The majority of subjects were female (range: 82% to 89%) and White (72% to 77%); mean age was 51.5 to 53.6 years; average disease duration was ~10 years; most subjects were ARA Functional Class II (56% to 62%) or I (20% to 27%); mean TJCs and SJCs

were ~16 and ~8, respectively; and average baseline pain scores were ~45 of 100mm. Symptom flare between screening and baseline was substantial across treatment groups and pain assessments; i.e., mean percentage degree of flare for each of the 3 flare criteria was 97.0% to 142.3%.

Safety: Between 33% to 42% of subjects across treatment groups reported at least one treatment phase-emergent AE and 3% to 6% of subjects reported at least one follow-up phase-emergent AE. There were no consistent differences between active treatments and placebo or dose-related trends seen for the overall incidence of these events. Treatment phase-emergent AEs reported for ≥2% of subjects in any treatment group during the study are summarized below:

	Number (%) of Subjects					
	Placebo	GW406381 5mg	GW406381 10mg	GW406381 25mg	GW406381 50mg	Celecoxib 200mg BID
Preferred Term	N=369	N=372	N=374	N=376	N=373	N=372
Any treatment phase-emergent AE	132 (36)	152 (41)	123 (33)	147 (39)	156 (42)	140 (38)
Diarrhea	5 (1)	10 (3)	8 (2)	7 (2)	13 (3)	11 (3)
Nausea	7 (2)	9 (2)	8 (2)	6 (2)	9 (2)	7 (2)
Dyspepsia	4 (1)	11 (3)	6 (2)	6 (2)	9 (2)	7 (2)
Abdominal pain upper	8 (2)	10 (3)	3 (<1)	3 (<1)	7 (2)	7 (2)
Vomiting	2 (<1)	2 (<1)	2 (<1)	1 (<1)	4 (1)	7 (2)
Nasopharyngitis	8 (2)	14 (4)	2 (<1)	1 (<1)	5 (1)	9 (2)
Sinusitis	1 (<1)	2 (<1)	1 (<1)	4 (1)	6 (2)	2 (<1)
Bronchitis acute	3 (<1)	0	2 (<1)	6 (2)	2 (<1)	1 (<1)
CRP increased	8 (2)	6 (2)	3 (<1)	10 (3)	12 (3)	7 (2)
Headache	10 (3)	16 (4)	8 (2)	9 (2)	10 (3)	7 (2)
Back pain	6 (2)	4 (1)	1 (<1)	1 (<1)	4 (1)	3 (<1)
Edema peripheral	1 (<1)	3 (<1)	2 (<1)	12 (3)	10 (3)	6 (2)
Hypertension	3 (<1)	6 (2)	9 (2)	14 (4)	12 (3)	6 (2)

Headache, hypertension and nasopharyngitis were the only treatment phase-emergent AEs reported for at least 4% of subjects in an active treatment group. The incidence of treatment phase-emergent AEs was comparable for the active treatments and placebo with the exception of hypertension (2% to 4% [active treatments] vs. <1% [placebo]), diarrhea (2% to 3% vs. 1%, respectively), and dyspepsia (2% to 3% vs. 1%, respectively). There were no dose-related trends for the incidence of treatment phase-emergent AEs.

Treatment-emergent vascular disorders reported for more than one subject in any treatment group were hypertension (2% to 4% [active treatments] vs. <1% [placebo]), hot flush (no subject to <1% vs. no subject, respectively), and hypotension (no subject to <1% vs. no subject, respectively).

Treatment phase-emergent AEs reported as severe for more than 1 subject in any treatment group were dyspepsia (3 GW406381 5mg subjects); arthralgia (2 GW406381 25mg subjects); back pain (2 GW406381 50mg subjects); and tooth abscess (2 celecoxib 200mg BID subjects).

Approximately one-third of all treatment phase-emergent AEs were considered by the investigator to be drug-related for all but the GW406381 50mg group where the incidence was 50%. Peripheral edema was the only drug-related treatment-phase emergent AE reported for at least 2% of subjects in any treatment group and reported more often for active treatments (<1% to 2%) relative to placebo (no subject). No dose-related trends were seen for drug-related, treatment phase-emergent AEs.

A total of 37 SAEs, including 3 fatal events were reported for 31 subjects during the study. The incidence of SAEs was low (≤2%) across treatment groups. Nephrolithiasis was the only SAE reported for more than 1 subject in any treatment group and this event was reported for 2 (<1%) GW406381 10mg-treated subjects.

The percentage of subjects with AEs leading to premature discontinuation of study drug was low and comparable across treatment groups (range: 2% to 5%). There were no consistent differences between the active treatments and placebo and no dose-related trends seen for the incidence of these events. Hypertension was the only AE leading to premature discontinuation of study drug for ≥1% of subjects in any treatment group.

Four AEs for the GW406381 groups were confirmed as CV events following adjudication: myocardial infarction and paroxysmal atrial fibrillation (5mg), and tachycardia and atrial fibrillation (10mg). One confirmed CV event occurred in the placebo group: angina pectoris. The myocardial infarction was fatal and the angina pectoris, paroxysmal atrial fibrillation were SAEs leading to premature discontinuation of study drug. Two confirmed GI events occurred in the GW406381 25mg group: bowel obstruction and intestinal pneumatosis. Both GI events were SAEs leading to premature discontinuation of study drug.

There were consistent, but not clinically relevant increases in mean serum creatinine seen for the GW406381 25mg and 50mg group relative to decreases seen for the celecoxib 200mg BID, GW406381 10mg and to a lesser extent for the placebo group. Otherwise, there were no clinically meaningful changes in laboratory values with GW406381.

Mean SBP was modestly increased at Week 12 at the highest GW406381 dose (50mg) (1.8mmHg) and celecoxib 200mg BID group (1.5mmHg) compared to placebo (−0.4mmHg). The finding was similar at follow-up for the GW406381 50mg group only. In contrast, mean changes from baseline in SBP were small and comparable to those seen with placebo at both Week 12 and follow-up for the GW406381 5mg, 10mg and 25mg groups.

Shifts to ‘to high’ in SBP were most common for the GW406381 50mg group relative to all other treatment groups including celecoxib 200mg BID at each visit with the exception of Week 4. In contrast, shifts to ‘to high’ in DBP were comparable over time, including follow-up, across treatment groups and comparable for active treatments relative to placebo over time, including follow-up.

SBP increases above the reference range were dose-related at the end of treatment (Week 12) (10%, 14%, 15% and 18% for GW406381 5mg, 10mg, 25mg and 50mg, respectively) and dose-related trends were also seen at Weeks 2, 4 and 8, and follow-up. In contrast,

mean changes in DBP, HR and weight were small and comparable across treatment groups.

The percentage of subjects with SBP increases of concern was consistently higher for the active treatment groups relative to placebo for each category of clinical concern. The greatest differences were seen for the GW406381 50mg group relative to placebo for each category of concern; i.e., >140mmHg; ≥20mmHg increase (10% vs. 4%, respectively), >140mmHg; ≥30mmHg increase (5% vs. 1%, respectively), and >140mmHg; ≥40mmHg increase (2% vs. no subject, respectively). A comparable percentage of subjects across treatment groups had DBP increases of concern. No dose related trends were seen across the GW406381 groups for vital sign measurements of concern.

Statistically significant treatment differences relative to placebo were seen for change from baseline to maximum on-treatment SBP for GW406381 10mg, 25mg and 50mg and celecoxib 200mg BID ($p \leq 0.037$), and for change to Week 12 LOCF and average on-treatment SBP for the GW406381 50mg group only ($p < 0.001$).

Subject pedal edema and ECG data showed no clinically meaningful changes associated with the use of GW406381.

Efficacy: The analysis of ACR20 responders at Week 12 using the non-responders dataset and excluding data from Investigator #[redacted] is summarized below:

	Placebo	GW406381 5mg	GW406381 10mg	GW406381 25mg	GW406381 50mg	Celecoxib 200mg BID
	N=354	N=360	N=363	N=358	N=353	N=361
Week 12 LOCF, n (%)	157 (44)	170 (47)	182 (50)	175 (49)	174 (49)	180 (50)
Odds ratio[1] (95% CI)	-	1.12 (0.80, 1.57)	1.36 (0.97, 1.93)	1.18 (0.84, 1.65)	1.21 (0.86, 1.71)	1.27 (0.90, 1.79)
p-value	-	0.520	0.077	0.345	0.279	0.167

The percentages of ACR20 responders at Week 12 (ITT; non-responders) were not statistically significantly different between any GW406381 dose and to placebo or for celecoxib 200mg BID relative to placebo. The percentages of responders were numerically higher for each active treatment group (47% to 50%) relative to placebo (44%). No dose-related trend was seen. Results were similar for the additional sensitivity analyses conducted to test the robustness of the primary analysis.

Conclusions:

- This study failed to detect a treatment effect of GW406381 (5mg, 10mg, 25mg and 50mg) and celecoxib 200mg BID compared to placebo on the primary endpoint, percentage of ACR20 responders.
- Headache, hypertension and nasopharyngitis were the only treatment phase-emergent AEs reported for at least 4% of subjects in an active treatment group with GW406381.
- The profile with GW406381 appeared to be less favorable for the highest doses of 25mg and 50mg relative to the 5mg and 10mg doses in terms of increases in SBP.
- GW406381 at 5mg to 50mg given for up to 12 weeks showed an overall safety profile consistent to that seen with celecoxib 200mg BID and consistent with NSAID therapy in general.
- Overall, the nature and frequency of AE reporting were consistent with published data on COX-2 inhibitor treatment in an RA population.

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