Synopsis

Identifier: GM2006/00105/00 **Study Number:** CXA30007

Title: A Phase III, 12-week, Multicentre, Double-blind, Double-dummy, Randomised, Placebo- and Active Comparator-Controlled, Parallel Group Study to Investigate the Efficacy and Safety of GW406381 1mg, 5mg, 10mg, 25mg and 50mg Administered Orally Once Daily, in Adults with Osteoarthritis of the Knee.

Investigator(s): This was a multicentre study conducted by 187 investigators

Study center(s): This study was conducted at 187 centres in 16 countries

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

Study Period: 19 May 2005 - 5 Dec 2005

Phase of Development: III

Objectives: The primary objective of the study was to evaluate the clinical efficacy of GW406381 versus placebo in the treatment of the signs and symptoms of osteoarthritis of the knee. Secondary objectives were: to evaluate the safety and tolerability of GW406381 administered orally to subjects with osteoarthritis of the knee; to evaluate the optimal therapeutic dose(s) of GW406381 for further clinical investigations in osteoarthritis; to explore the clinical efficacy of GW406381 versus celecoxib in the treatment of the signs and symptoms of osteoarthritis of the knee; to evaluate health outcomes data generated from subject-completed questionnaires and to evaluate population pharmacokinetics (PK) of GW406381 in subjects with osteoarthritis of the knee.

Methodology: This was a multicentre, randomised, double-blind, double-dummy, placebo-controlled, parallel group study. Following the initial Screening Visit, eligible subjects entered a non-steroidal anti-inflammatory (NSAID)/analgesic Washout period (up to 2 weeks). At the Baseline Visit (Day 1), subjects who continued to meet eligibility criteria (including meeting the pre-defined symptom flare criteria) were randomised to receive one of 7 double-blind treatments (placebo, celecoxib 200mg, GW406381 50mg, 25mg, 10mg, 5mg or 1mg) for 12 weeks. Clinic visits to assess efficacy and safety were scheduled during the Treatment period at Weeks 2, 4, 8 and 12. A post-treatment Follow-up Visit was scheduled for 7 days post-last dose. For the follow-up visit there was a visit window of -2 to +7 days, therefore the total duration in the study could be up to 16 weeks including washout, treatment and follow-up.

Number of subjects:

	Number (%) of subjects						
	Placebo	**Celecoxib 200mg OD**	**GW406381 1mg OD**	**GW406381 5mg OD**	**GW406381 10mg OD**	**GW406381 25mg OD**	**GW406381 50mg OD**
Planned	159	159	159	159	159	159	159
Randomised, N	189	190	189	191	192	190	190
Safety Population	188	189	189	189	192	189	190
ITT population	186	185	188	187	188	189	186
Completed[1]	146 (78)	156 (84)	146 (78)	140 (75)	145 (77)	155 (82)	150 (81)
Withdrawn	40 (22)	29 (16)	42 (22)	47 (25)	43 (23)	34 (18)	36 (19)
Reason for withdrawal							
Due to AE	8 (4)	6 (3)	5 (3)	7 (4)	19 (10)	13 (7)	12 (6)
Lack of efficacy	17 (9)	8 (4)	18 (10)	21 (11)	13 (7)	7 (4)	7 (4)
Lost to follow-up	2 (1)	3 (2)	4 (2)	2 (1)	1 (<1)	1 (<1)	1 (<1)
Protocol violation	5 (3)	4 (2)	0	5 (3)	1 (<1)	2 (1)	6 (3)
Consent withdrawn	6 (3)	5 (3)	12 (6)	7 (4)	7 (4)	7 (4)	4 (2)
Sponsor terminated	1 (<1)	0	0	0	0	0	0
Investigator decision	0	1 (<1)	1 (<1)	2 (1)	0	0	1 (<1)
Other	1 (<1)	2 (1)	2 (1)	3 (2)	2 (1)	4 (2)	5 (3)

1. Percentages based on ITT population.
Data Source: DST 6.01; DST 6.02

Diagnosis and main criteria for inclusion: Male and female (non-child bearing potential or using adequate contraception) subjects aged 40 to 80 years and with a diagnosis of primary OA of the knee for at least 3 months in symptom duration prior to screening were eligible. Subjects were required to have a maximum of 80mm at Screen on the 100mm visual analogue scale (VAS) for pain walking on flat surface (Western Ontario and McMasters Universities Osteoarthritis Index [WOMAC] question 1). Following the washout of NSAID/analgesic therapy, subjects were required to meet the following criteria to be eligible for study participation: a Baseline WOMAC pain subscale question 1 score of ≥50mm with a worsening of ≥15mm between Screen and Baseline; increase of ≥1 point on the patient global assessment of arthritis condition (5-pt Likert scale). One knee, the index knee (defined as the knee with the greatest pain), was studied. Subjects were required to have anteroposterior radiographic evidence of tibio-femoral OA within past 12 months (grade 2 or 3 according to the Kellgren & Lawrence scale).

Treatment administration: Treatment was administered orally, once daily. Due to the nature of the double-dummy blinding method, subjects took 2 capsules, once daily. GW406381 50mg, 25mg, 10mg, 5mg and 1mg was supplied as hard gelatin capsules. All GW406381 capsules were Size 2, Swedish Orange, and opaque. Visually matching placebo capsules were supplied.

Celecoxib was administered orally as a 200mg Celebrex capsule over encapsulated into a Size 0 Swedish Orange opaque hard gelatin capsule shell with a powder backfill.

Size 0 placebo capsules that visually matched the over encapsulated Celebrex capsules were supplied.

Criteria for evaluation: Efficacy was measured by the WOMAC index, Patient's Global Assessment of Arthritis Condition question, Physician's Global Assessment of Arthritis Condition question, Osteoarthritis Research Society International (OARSI) responder index, discontinuations due to lack of efficacy, and supplementary analgesic therapy use. The co-primary efficacy endpoints utilised the pain and function subscales of the WOMAC and the Patient's Global Assessment question. The other efficacy measures were utilised in secondary endpoint analyses. Safety evaluations comprised adverse events, clinical laboratory tests, pedal oedema assessment, vital signs and 12-lead ECG. Blood samples were also collected for pharmacokinetic/pharmacodynamic assessment, to assess H. Pylori status, to assess potential blood protein biomarkers and to test for potential CV risk factors. If the subject provided consent, an additional blood sample was obtained for pharmacogenetics research.

Statistical methods: The co-primary efficacy variables were the change from baseline in WOMAC pain subscale score, the change from baseline in WOMAC physical function subscale score and the change from baseline in patient's global assessment of arthritis condition. The primary inferential dataset was week 12 last observation carried forward (LOCF) and the primary population was the Intent-to-Treat (ITT) population.

A sample size of 143 evaluable subjects per treatment group was expected to provide 90% overall power to detect a difference between GW406381 and placebo of at least 10mm in the change from baseline in the WOMAC pain subscale score (5 questions) and the WOMAC physical function subscale score (17 questions), and a difference of at least 0.5 in the change from baseline in the patient's global assessment of arthritis condition using a two-sided test with a 5% significance level.

A hierarchical testing procedure was used; hence no adjustment to the significance level was required.

The results of the analyses are presented as point estimates, 95% confidence intervals (CI) and associated p-values for the adjusted mean difference between each dose level of GW406381 and placebo.

The primary analyses were repeated for the week 12 observed cases (OC) and baseline observation carried forward (BOCF) datasets and for the Per Protocol (PP) population. A Mixed-effects Model Repeated-Measures (MMRM) analysis was also performed for each co-primary variable. These analyses were considered supportive of the week 12 LOCF ITT population analyses.

The secondary efficacy variables WOMAC pain subscale question 1, WOMAC stiffness subscale and physician's global assessment were analysed using analysis of covariance and the statistical model used and presentation of results was as for the co-primary endpoints. The secondary efficacy endpoints, proportion of OARSI responders, discontinuation due to lack of efficacy and proportion of subjects who took a least one dose of supplementary analgesic therapy were analysed using logistic

regression. Results were presented as an odds ratio, 95% confidence interval and p-value for the treatment effect.

A number of statistical analyses were performed on the change from baseline in systolic blood pressure (SBP). The endpoints analysed using analysis of covariance were change from baseline to maximum on treatment SBP, change from baseline to average on treatment SBP and change from baseline to Week 12 LOCF SBP. Covariate significance and treatment by covariate interaction significance tables were produced for each analysis.

Adverse events, clinical laboratory evaluations, other vital signs data, ECG and pedal oedema data were summarised by treatment group; no formal testing was performed. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary.

The number and percentage of subjects with each score within each category of the EQ-5D was summarised. Summary statistics for the thermometer and utility scores were produced. EQ-5D thermometer and utility scores were analysed using analysis of covariance and the results were presented as point estimates, 95% confidence intervals and associated p-values for the adjusted mean differences between each dose of GW406381 and placebo.

Summary statistics were produced for the SF-36 v2 domain scores, component scores and reported health transition score, as were change from baseline summaries. Change from baseline to week 12 and week 12 LOCF for the domain and component scores were analysed using analysis of covariance.

Summary. Efficacy: Baseline demographic characteristics were generally balanced across treatment groups and consistent with the OA population studied. No dose of GW406381 was statistically superior to placebo on any of the 3 co-primary endpoints: WOMAC pain, WOMAC function or patient global assessment. Celecoxib was statistically superior to placebo on all 3 co-primary endpoints. A summary of analysis of the change from Baseline to Week 12 LOCF for WOMAC pain subscale scores is presented.

WOMAC pain subscale score[1]	Number (%) subjects						
	Placebo N=186	Celecoxib 200mg N=185	GW406381 1mg N=188	GW406381 5mg N=187	GW406381 10mg N=188	GW406381 25mg N=189	GW406381 50mg N=186
Baseline n	186	185	188	187	188	188	186
Mean (SD)	65.8 (16.9)	66.0 (17.0)	64.0 (18.8)	66.6 (16.5)	65.0 (15.6)	64.2 (16,7)	65.4 (17.2)
Wk 12 LOCF n	178	178	182	177	181	187	182
Mean (SD)	44.0 (25.7)	39.0 (26.9)	46.2 (27.2)	48.4 (25.6)	38.8 (24.8)	37.5 (25.3)	38.8 (26.5)
Mean change from Baseline (SD)	-21.8 (24.7)	-27.1 (26.4)	-17.6 (23.6)	-18.1 (21.3)	-26.2 (24.9)	-26.7 (23.1)	-26.3 (24.5)
Analysis - n	168	165	172	166	173	163	174
Adjusted[2] mean change (SE)	-21.5 (1.8)	-27.8 (1.9)	-18.1 (1.8)	-17.2 (1.9)	-26.4 (1.8)	-26.1 (1.9)	-25.2 (1.8)
Difference vs. placebo	-	-6.4	3.4	4.2	-4.9	-4.6	-3.7
95% CI	-	-11.4, -1.3	-1.6, 8.4	-0.8, 9.3	-9.9, 0.1	-9.7, 0.4	-8.6, 1.3
p-value	-	0.014	0.184	0.100	0.053	0.074	0.149

1. WOMAC scale pain score: 0 = no pain to 100 = extreme pain
2. Adjusted for Baseline score, WOMAC Q 1 flare, Patient Global Assessment flare and centre group

For the GW406381 treatment groups, no consistent dose ordering was observed for the efficacy endpoints. Secondary endpoints showed similar results, supporting the primary endpoint findings.

Safety: Overall, the percentages of subjects reporting at least one treatment-emergent AE ranged from 43% to 54% across treatment groups. The incidence of AEs relative to placebo was slightly higher for the GW406381 50mg group (54% vs. 43%) and similar for GW406381 25mg, 10mg, 5mg, 1mg and celecoxib 200mg. A summary of treatment-emergent AEs reported in ≥5% of subjects in any treatment group during the treatment phase of the study is presented.

Adverse Event Preferred term	Number (%) subjects						
	Placebo N=188	Celecoxib 200mg OD N=189	GW406381 1mg OD N=189	GW406381 5mg OD N=189	GW406381 10mg OD N=192	GW406381 25mg OD N=189	GW406381 50mg OD N=190
Any event	80 (43)	84 (44)	81 (43)	82 (43)	89 (46)	83 (44)	102 (54)
Headache	13 (7)	5 (3)	6 (3)	4 (2)	8 (4)	10 (5)	8 (4)
Diarrhoea	9 (5)	6 (3)	7 (4)	6 (3)	7 (4)	5 (3)	7 (4)
Nasopharyngitis	4 (2)	6 (3)	8 (4)	5 (3)	7 (4)	5 (3)	9 (5)
Arthralgia	6 (3)	1 (<1)	9 (5)	8 (4)	7 (4)	5 (3)	4 (2)

There were 72/1326 (5%) subjects who reported AEs that led to permanent discontinuation of investigational product. There was no clear pattern to the reporting of events and there were three events reported in at least 1% of subjects in any treatment group: arthralgia, hypertension and dyspepsia.

A total of 18 subjects reported 22 Serious Adverse Events (SAEs) one of which was fatal (acute myocardial infarction in a subject on GW406381 25mg). The remaining 21 non-fatal SAEs occurred in 14 subjects receiving GW406381, one subject

receiving celecoxib and two subjects receiving placebo. Of these SAEs five (cardiac arrest, advanced heart block, congestive cardiac failure, arrhythmia and sick sinus syndrome) reported in subjects receiving GW406381, were considered by investigators as possibly related to use of the study medication.

Dose-related increases in mean systolic blood pressure (SBP) were observed for GW406381. Mean SBP increases (change from Baseline to Week 12) were 0.8, 3.0 and 5.2 mmHg for the GW406381 10mg, 25mg and 50mg groups respectively; a mean increase of 1.0 mmHg was observed in the celecoxib group and a mean change of -2.5 mmHg in the placebo group.

Increases in mean weight were observed in subjects treated with GW406381 25mg (0.66kg) and 50mg (0.62kg); the increase in mean weight in the celecoxib and placebo treatment groups was 0.39kg and 0.20kg respectively.

The frequency of subjects with a serum creatinine value above the upper limit of normal (124µmol/L) for GW406381 25mg and 50mg treatment groups was 3% and 4%, respectively, compared with 0% in the placebo and celecoxib groups.

Conclusions:

- GW406381 (50mg, 25mg, 10mg, 5mg and 1mg) failed to demonstrate efficacy on the 3 co-primary endpoints: change from baseline to Week 12 LOCF in the WOMAC Pain and Physical Function Subscale Scores and the change from baseline to Week 12 LOCF in the Patient's Global Assessment of Arthritis Condition
- Celecoxib 200mg was statistically superior to placebo on all three co-primary endpoints. These results validate the assay sensitivity in this study
- No clear dose response relationship was established between GW406381 and the co-primary endpoints precluding selection of an optimal therapeutic dose for further investigation
- Overall, the nature and frequency of adverse event reporting were consistent with published data on COX-2 inhibitor treatment in an OA population
- Findings for mean SBP, mean diastolic BP (DBP) and mean weight indicate a dose-related effect of GW406381 with the greatest increases from baseline observed in the 25mg and 50mg treatment groups
- GW406381 showed an overall safety profile that is consistent with NSAID therapy in general but at doses of 25 and 50mg, appeared less favourable (in terms of blood pressure, weight and serum creatinine changes) to that of celecoxib administered at a dose of 200mg once-daily
- There is no consistent evidence to support an improvement in patient quality of life with either of the active treatments in this short term study.

Date of Report: Aug 2006