Synopsis

Identifier: AH2007/00002/00 **Study Number:** CBA106809

Title: A multi-centre, randomised, single-blind, placebo-controlled, parallel group study to investigate the efficacy of single pre-emptive doses of GW842166X, a non-cannabinoid CB2 receptor agonist, on pain following third molar tooth extraction.

Investigators: Dr [redacted] (UK) Dr [redacted] (Italy) and Dr [redacted] (Germany)

Study centres: This study was carried out in 3 countries, United Kingdom, Italy and Germany. Each country had 1 clinical trial centre.

Publication(s): None

Study period:

12Oct2006 - 23Mar2007

Phase of development: IIa

Objectives:

Primary

- To evaluate the analgesic efficacy of pre-emptive doses of GW842166 (administered at two dose levels) following dental surgery

Secondary

- To further evaluate the safety and tolerability of GW842166
- To evaluate the duration of analgesic effect of GW842166
- To evaluate the pharmacokinetic (PK) and pharmacodynamic relationship between drug exposure and analgesic effect of GW842166
- To investigate the analgesic efficacy of GW842166 when dosed adjunctively with co-codamol.

Methodology:

A randomised, single-blind (double-blind for subject and investigator but the sponsor, GlaxoSmithKline, was unblinded), parallel group, placebo-controlled, single oral dose, multicentre study with a positive control arm. Ibuprofen was used as the comparator to validate the study. Due to the known differences in half-lives for GW842166 (t½~ 25-35 hours) and ibuprofen (t½~ 2 hours), the duration of action of ibuprofen was anticipated to be less than that of GW842166; therefore, it was planned that a second dose of ibuprofen would be administered (in a placebo-controlled fashion to maintain double-blind) in the post-operative period. Subjects were randomised to 4 possible treatment regimens as follows:

Regimen	Pre-Operative[a] (Dose 1)	Post-Operative (Dose 2)
Treatment arm (800 mg)	GW842166 800 mg	Placebo
Treatment arm (100 mg)	GW842166 100 mg	Placebo
Comparator arm	Ibuprofen 800 mg	Ibuprofen 400 mg
Placebo arm	Placebo	Placebo

a. Doses were administered 1 h pre-operatively

Subjects enrolled onto the study were required to attend the investigation site(s) on at least 4 separate occasions: screening, treatment and surgery day (when subjects were resident for 24 hour [h]), briefly at 48 h post-treatment and for a follow-up visit (Day 14-21).

Study procedures included the following

- Efficacy: visual analogues scales (VAS) and verbal rating scales (VRS) for assessment of pain up to 10h post surgery, duration of analgesic effect, patient global evaluation, completion of diary cards for rescue medications and other surgical assessments (surgical trauma rating scale, time of local anaesthetic, time of completion of last suture).
- Safety: adverse events (AEs), clinical laboratory evaluations (clinical chemistry, haematology, urinalysis), Holter ECG, lead-II ECG and 12-lead ECG monitoring and vital signs (blood pressure and heart rate).
- Pharmacokinetic: PK blood sampling up to 48 h for the analysis of GW842166 and paracetamol/morphine.

Number of subjects:

	Placebo	GW842166 100 mg	GW842166 800 mg	Ibuprofen
Number of Subjects Planned:	28	28	28	28
Number of Subjects Entered:	31	34	27	31
Number of Subjects included in safety analysis:	31	34	27	31
Number of Subjects included in PK analysis:	-	34	27	-
Number of Subjects Completed as Planned:	31	34	25	31
Number of Subjects Withdrawn (any reason):	0	0	2	0
Reasons for Subject Withdrawal				
Lost to follow-up	0	0	1	0
Protocol Violation	0	0	1	0

Diagnosis and main criteria for inclusion:

Healthy, female or male subjects aged 18 to 50, body weight ≥ 50 kg and body mass index (BMI) within the range 19 to 29.9 kg/m^2 and was scheduled for outpatient surgical removal of up to four third molar teeth under local anaesthesia. At least one molar tooth must have been a fully or partially impacted in the mandible requiring bone removal. Subjects agreed not to take analgesics other than protocol-defined rescue analgesics during treatment (up to 48 h post dose).

Treatment administration:

Treatment group	Pre-operative dose (Dose 1)	Batch No	Post-operative (4 hour) dose (Dose 2)	Batch No
Placebo	4 × placebo capsules (size 000) 1 × placebo capsule (size 1)	061121129 051113430	1 × placebo capsule (size 000)	061121129
Active comparator (ibuprofen)	2 × 400 mg ibuprofen capsules (size 000) 2 x placebo (size 000) 1 × placebo capsule (size 1)	061121763 061121129 051113430	1 × 400 mg ibuprofen capsule (size 000)	061121763
GW842166 (100mg dose)	1 × 100 mg GW842166 capsule (size 1) 4 × placebo capsules (size 000)	051113217 061121129	1 × placebo capsule (size 000)	061121129
GW842166 (800mg dose)	4 × 200 mg GW842166 capsules (size 000) 1× placebo capsule (size 1)	061121121 051113430	1 × placebo capsule (size 000)	061121129

Criteria for evaluation:

Primary Efficacy:

- Weighted mean of the pain intensity over the 10 hours post-surgery as measured by the VAS (Visual Analogue Scale)

Secondary Efficacy:

- Weighted mean of the pain intensity over the 10 hours post-surgery as measured by the VRS (Verbal Rating Scale)
- VAS and VRS mean pain scores up to 10 hours post-surgery
- Elapsed time from study drug administration to rescue analgesic request
- Patient Global Evaluation prior to rescue medication use and at 10 and 24 hours post-dose
- VAS and VRS mean pain scores from the time of rescue up to 10 hours post-surgery
- Proportion of subjects requiring rescue medication
- Elapsed time from first rescue medication use to second rescue analgesic request

Safety:

The relationship between measures of systemic exposure to GW842166 efficacy and safety outcomes were investigated with the potential to use the following endpoints as required or as supported by study data:

- Plasma concentrations and other PK parameters for GW842166
- Primary or secondary efficacy endpoints (including time course measurements of pain intensity), and safety endpoints.

Statistical methods:

Efficacy variables, the weighted mean in pain intensity during the first 10 h post dose (both VAS and VRS) were compared using analysis of covariance where explanatory factors such as centre, age, sex, fear of pain (as measured by the fear of pain questionnaire) and number of teeth extracted were investigated as covariates in the model.

The weighted means of VAS and VRS were calculated using both the last observation carried forward (LOCF) and observed cases (OC) datasets. In the LOCF data set, missing values were estimated from the last observation prior to rescue, allowing estimates of treatment effect to be made with the complete study population. The observed case data set made no assumptions about the missing values, excluding them from any analyses. Patient global evaluation was analysed using Wilcoxon rank sum tests and 'time to' data was analysed using the log rank test.

Demographics

The groups were well matched for demographic characteristics although there was a greater proportion of females and lower mean weight in the ibuprofen group compared to other groups.

	Placebo	GW842166 100 mg	GW842166 800 mg	Ibuprofen
Age (yrs) mean, SD, range	26.5, 5.86 18-40	25.6, 4.48 19-37	24.9, 5.12 18-38	26.6, 5.20 19-39
Sex n (%)				
Female	13 (42%)	15 (44%)	15 (56%)	19 (61%)
Male	18 (58%)	19 (56%)	12 (44%)	12 (39%)
Ethnicity n (%)				
Hispanic or Latino	15 (48%)	17 (50%)	15 (56%)	15 (48%)
Not Hispanic or Latino	16 (52%)	17 (50%)	12 (44%)	16 (52%)
Race n (%)				
African American/African Heritage	1 (3%)	0	1 (4%)	0
Asian – Central / South Asian Heritage	0	1 (3%)	0	0
Asian – East Asian Heritage	0	1 (3%)	1 (4%)	0
Asian – South East Asian Heritage	0	1 (3%)	1 (4%)	0
White – Arabic/North African Heritage	0	1 (3%)	0	0
White – White/Caucasian/European Heritage	30 (97%)	30 (88%)	24 (89%)	31 (100%)
Weight (kg) mean, SD	74.8, 14.06	72.2, 10.26	69.2, 11.42	66.7, 13.23
BMI (kg/m^2) mean, SD	24.0, 2.75	24.2, 2.87	23.4, 2.35	23.1, 2.89

Safety

Overall, GW842166 was well tolerated throughout the study following single 100 mg or 800 mg doses. A summary of the most common treatment emergent AEs (TEAEs) is provided as follows:

Treatment Emergent Adverse Event n %	Placebo N=31	GW842166 100 mg N=34	GW842166 800 mg N=27	Ibuprofen N=31
Any AE	19 (61%)	24 (71%)	18 (67%)	22 (71%)
Any related AE	3 (10%)	2 (6%)	2 (7%)	2 (6%)
AEs reported in 5% or more in any treatment group				
Headache	10 (32%)	12 (35%)	4 (15%)	12 (39%)
Nausea	2 (6%)	3 (9%)	3 (11%)	3 (10%)
Pyrexia	3 (10%)	2 (6%)	3 (11%)	1 (3%)
Syncope	0	1 (3%)	2 (7%)	0
Diarrhoea	1 (3%)	2 (6%)	1 (4%)	0
Odynophagia	1 (3%)	1 (3%)	1 (4%)	2 (6%)
Vomiting	2 (6%)	2 (6%)	1 (4%)	3 (10%)
Pharyngolaryngeal Pain	1 (3%)	3 (9%)	0	3 (10%)
Dysmenorrhoea	0	2 (6%)	0	2 (6%)
Dysphagia	0	2 (6%)	0	1 (3%)
Influenza-like Illness	0	2 (6%)	0	1 (3%)
Dyskinesia	2 (6%)	1 (3%)	0	1 (3%)
Dizziness	1 (3%)	0	0	2 (6%)

Few of these AEs (one or less subjects for any AE reported) were considered drug-related and the majority were mild to moderate in intensity. No subject died or withdrew due to an AE.

Non-fatal SAEs were reported for 2 subjects, but neither of these events was judged to be causally related to exposure to GW842166:

One subject (female, 23 years) in the GW842166 800 mg group, was diagnosed with a submandibular abscess (of moderate intensity) that was judged to be a complication of the dental extraction. Symptoms and signs started around 24 hours post-dose and the subject was admitted to hospital for treatment with intravenous antibiotics. She made a full recovery. This event was judged unrelated to study medication.

Another subject (female, 26 years), in the ibuprofen group, had a SAE of intestinal obstruction. Symptoms started on the day of dosing with ibuprofen. She was admitted to hospital and underwent surgery for division of intra-abdominal adhesions (adhesiotomy). The subject underwent an uncomplicated post-operative course and made a full recovery. This event was judged to be unrelated to the study medication.

Overall evaluation of the summary data for clinical laboratory safety tests (haematology, clinical chemistry) revealed no obvious patterns or trends to indicate drug-related effects. Pre-defined values of potential clinical concern (PCC) were reported and the incidence of these values (excluding subjects who had PCC values at screening) was slightly higher with placebo than with the active treatment groups (placebo (4 subjects, 13%),

GW842166 100 mg (3 subjects, 9%), GW842166 800 mg (2 subjects, 7%) and ibuprofen (2 subjects, 6%). None of the values were considered to be of medical importance.

Two subjects in the placebo group had liver function test values of PCC [relating to ALT/AST and ALT/bilirubin] and the changes were also reported as AEs. No other AEs related to laboratory evaluations were reported.

Values of PCC were reported for urinalysis data across all treatment groups [placebo, (35%), GW842166 100mg (44%), GW842166 800mg (56%), ibuprofen (55%)], but none were considered to be of medical importance and there was no overall evidence to suggest that any were drug-related.

Overall evaluation of summary statistics for 12-lead ECG data and vital signs revealed no obvious patterns or trends to indicate drug-related effects. Values of PCC for ECG parameters were reported but only one 12-lead ECG (showing non-specific intraventricular conduction delay, following dosing with placebo) was reported as clinically significant.

For one subject (male, 38 years), an episode of asymptomatic non-sustained ventricular tachycardia was captured on 24-hour Holter ECG around 15 hours after dosing. The subject had been dosed with ibuprofen and the event is therefore not related to GW842166.

Pharmacokinetics:

Following oral administration of GW842166, systemic concentrations of GW842166 were detected at around 30 mins after dosing and peak concentrations generally observed 3 to 3.5 h after dosing. All subjects apart from one, displayed tmax within 8 h post dose. GW842166 Cmax and AUC at 100 mg and 800 mg were not proportional to dose. For the 8-fold increase in dose, an approximate 2.5-fold increase in Cmax and AUC was observed.

The relationship between GW842166 systemic exposure and VAS pain scores were investigated. There was little evidence of a relationship between higher average GW842166 concentration and lower VAS pain scores. There was no evidence of a relationship between slower GW842166 absorption or lower GW842166 exposure and the need to rescue.

Efficacy:

The primary efficacy variable was the weighted mean of the pain intensity over 10 h post-surgery as measured by the VAS (Visual Analogue Scale) and data are presented below for the LOCF dataset.

Comparison	Test LSMean	Ref LSMean	Estimate	90% CI
GW842166 100mg-Placebo	55.80	53.98	1.82	(-9.42, 13.07)
GW842166 800mg-Placebo	45.86	53.98	-8.12	(-20.87, 4.62)
Ibuprofen-Placebo	22.19	53.98	-31.79	(-44.2, -19.4)

Although there was a small tendency for GW842166 800 mg to show reduced pain relative to placebo, neither of the GW842166 dose levels showed a statistical significant or clinically meaningful improvement relative to placebo. This was in contrast to ibuprofen which showed both a clinically and statistically significant improvement. Similar results were found with the OC dataset. There was no difference in the pain intensity profile following administration of rescue medication for subjects receiving GW842166 relative to those receiving placebo or ibuprofen; this suggests that there is no beneficial adjunctive effect of dosing co-codamol (rescue medication) with GW842166.

The secondary efficacy variable, pain intensity as measured using VRS, yielded similar results to the VAS assessments; GW842166 100 mg showed little difference relative to placebo, larger differences were apparent for GW842166 800 mg but the largest difference achieving statistical significance was for ibuprofen.

These findings were also consistent with data achieved on other secondary endpoints that included elapsed time from study drug administration to rescue medication, proportion of patients requiring efficacy medication and patient global evaluation at 10 hours post-dose. Although a statistically significant effect was detected specifically for GW842166 800 mg at 24 h for patient global evaluation this isolated result should be interpreted with caution given that it is inconsistent with the principle pain assessment data undertaken using VAS and VRS and the number of endpoints studied.

Conclusions:

- Ibuprofen was consistently better than placebo for all endpoints, indicating that the sample size was appropriate and that the study methodology was sufficiently sensitive to detect an effect of an established analgesic following pre-emptive dosing. Although there was a tendency for an improvement in pain scores following dental surgery in the GW842166 800 mg treatment group, all of the remaining endpoints failed to be of either clinical or statistical significance. GW842166 100 mg showed very little difference from placebo for all study endpoints.
- There was no difference in pain intensity profile following administration of rescue medication to subjects receiving GW842166 relative to those receiving placebo or ibuprofen, indicating that there was no beneficial effect of adjunctive dosing with co-codamol (rescue medication).
- There was little evidence of a relationship between higher average GW842166 concentration and lower VAS pain score and no evidence of a relationship between slower GW842166 absorption or lower GW842166 exposure and the need for rescue medication.

- GW842166, administered as either 100 mg or 800 mg single doses, was well tolerated and the study did not reveal any safety concerns that would prevent further evaluation in humans.

Date of Report: November 2007