A Randomized, Controlled Study to Investigate the Analgesic Efficacy of Single Doses of the Cannabinoid Receptor-2 Agonist GW842166, Ibuprofen or Placebo in Patients With Acute Pain Following Third Molar Tooth Extraction

Thor Ostenfeld, MBChB, PhD, Jeffrey Price, MSc,* Massimo Albanese, MD,† Jonathan Bullman, BSc,* Fiona Guillard, MSc,* Ingo Meyer, MD,‡ Rachel Leeson, PhD,§ Cristina Costantin, PharmD,‖ Luigi Ziviani, MD,‖ Pier Francesco Nocini, MD,† and Stefano Milleri, MD‖*

Objectives: To evaluate the postoperative analgesic efficacy of GW842166, a noncannabinoid CB2 agonist, in patients undergoing third molar tooth extraction.

Methods: This randomized, double-blind, placebo-controlled study compared the analgesic efficacy of single doses of GW842166 (100 or 800 mg) or ibuprofen with placebo in patients undergoing extraction of at least 1 fully or partially impacted third molar tooth. Eligible participants were dosed preoperatively within 1 hour of surgery. Participants allocated to active comparator received a second dose of ibuprofen (400 mg), 4 hours after the first 800 mg dose. Participants in the GW842166 and placebo groups received placebo at 4 hours. Procedures for the assessment of efficacy included a visual analog scale and verbal rating scale for scoring pain up to 10 hours postsurgery, duration of analgesia, patient global evaluation, proportion of patients requiring rescue medication, and elapsed time to rescue analgesia. Analysis of covariance was used to compare efficacy variables. Patient global evaluation was analyzed using Wilcoxon rank-sum tests and time to data was analyzed using the log-rank test.

Results: Ibuprofen was significantly more effective than placebo across all endpoints. Trends for an improvement in pain scores for GW842166 800 mg failed to be of either clinical or statistical significance. GW842166 100 mg showed little separation from placebo. There was no evidence for any beneficial adjunctive effect after coadministration of rescue analgesia with GW842166. All treatments were well tolerated.

Discussion: In comparison to ibuprofen, single doses of GW842166 (100 and 800 mg) failed to demonstrate clinically meaningful analgesia in the setting of acute dental pain.

Key Words: analgesia, selective CB2 agonist, GW842166, postoperative pain

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From the *Neurology Discovery Medicine Unit, GlaxoSmithKline R&D, Harlow; §UCL Analgesia Centre, London, UK; ‡Momentum Pharma Services, Hamburg, Germany; ‖Centro Ricerche Cliniche di Verona; and †Dentistry and Maxillofacial Surgery Section, University of Verona, Italy.

The authors declare no conflict of interest.

Reprints: Thor Ostenfeld, MBChB, PhD, GlaxoSmithKline R&D, Medicines Research Centre (1S202), Gunnels Wood Road, Stevenage SG1 2NY, United Kingdom (e-mail: thor.x.ostenfeld@gsk.com).

It is widely appreciated that activation of the G protein-coupled cannabinoid receptor subtypes, CB1 and CB2, will suppress nociceptive transmission in animal models of acute and chronic pain states.[1–5] As the undesirable psychotropic effects associated with nonselective cannabinoid agonists are largely mediated by activity at central CB1 receptors, the selective targeting of CB2 receptors may present an opportunity for the development of novel analgesics that are devoid of central nervous system side effects. Recent years have seen the disclosure of several different chemical classes of CB2-selective agonists; efficacy for these has been demonstrated in a variety of preclinical models of inflammatory and nerve injury-induced nociception (reviewed in Refs. 6–10). Against this background, there is a rationale for pursuing clinical studies to test the analgesic efficacy of selective CB2 agonists in patients with nociceptive, inflammatory and neuropathic pain.

We have previously reported on the lead optimization program, discovery, and candidate selection of GW842166 {2-[(2,4-dichlorophenyl) amino]-N-[(tetrahydro-2H-pyran-4-yl) methyl]-4-(trifluoromethyl)-5-pyrimidinecarboxamide}, a selective noncannabinoid CB2 agonist for the treatment of inflammatory pain.[11] In human CB1 and CB2 recombinant receptor assays, GW842166 was found to have moderate binding affinity for CB2 receptors (63 nM) and a high efficacy of 95% relative to the cannabinoid analog HU210.[11,12] No significant agonist activity was found for GW842166 in human CB1 recombinant assays at concentrations up to 30 μM. In the rat Freund's complete adjuvant model of inflammatory pain, GW842166 displayed extremely high potency with an oral ED_{50} of 0.1 mg/kg (blood concentration = 130 nM); full reversal of hyperalgesia, determined by a weight-bearing protocol, was achieved at 0.3 mg/kg (blood concentration = 370 nM).[11] The antihyperalgesic activity of GW842166 was reversed by administration of the CB2 selective antagonist AM630.[13]

Here we report the results of the first exploratory clinical efficacy study undertaken with GW842166, in which we sought to evaluate the postoperative analgesic efficacy of the compound at 2 dose levels (100 and 800 mg) in patients undergoing third molar tooth extraction. Single oral doses were administered preoperatively and benchmarked against ibuprofen and placebo. The utility of this clinical population has been widely established in clinical pharmacology studies for the preliminary investigation of

efficacy for novel analgesic compounds including those with anti-inflammatory properties.[14–18]

MATERIALS AND METHODS

Study Design

This study was undertaken as a randomized, double-blind, placebo-controlled study incorporating 4 parallel groups, in which the treatment arms comprised preoperative single doses of GW842166 100 mg, GW842166 800 mg, ibuprofen 800 mg (+400 mg postoperative), and placebo. It was conducted in 3 member states of the European Union (United Kingdom, Italy, and Germany) from October 2006 to March 2007. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki, and had the approval of country-specific Regulatory Authorities and Local Research Ethics Committees (GSK protocol: CBA106809; Clinical Trials Identifier: NCT00444769; EUDRACT Number: 2006-002691-18). All participating individuals provided written, informed consent before their participation in the study.

Participants entered a screening phase of up to 21 days to determine eligibility and to allow washout from any prohibited medications. Baseline assessments were undertaken either the night before or on the morning of the day of surgery, and the timing of these was consistent across all participants for any individual trial site. After baseline assessments and a light breakfast, patients were randomized to 1 of 4 possible treatment regimens: GW842166 800 mg preoperative and placebo postoperative; GW842166 100 mg preoperative and placebo postoperative; Ibuprofen 800 mg preoperative and Ibuprofen 400 mg postoperative; Placebo preoperative and Placebo postoperative. For all treatments, the first dose was administered (as a premedicant) within 1 hour of the dental surgery taking place. At least 90 minutes elapsed between consumption of a light breakfast and the administration of preoperative treatments.

It was anticipated that the duration of the dental surgery could last up to 1 hour, depending on the number of teeth being extracted. Surgery was performed under local anesthetic using 2% lidocaine (with 1:80,000 epinephrine). Nitrous oxide in conjunction with the local anesthetic was permitted. Postoperative treatments were to be administered 4 hours after the preoperative dose. After the surgery, patients remained resident for a 24 hours (postdose) follow-up period. A rescue analgesic (co-codamol 15/500: paracetamol 500 mg, codeine phosphate 15 mg) was available if pain became intolerable. Patients were not permitted to receive other analgesics or anti-inflammatory drugs. Similarly, psychoactive drugs such as tranquillizers, hypnotics, and sedatives were not permitted within 48 hours before, or 5 half-lives before, the start of surgery and for 48 hours postdose. Caffeine-containing beverages or foods were not permitted from midnight of the evening before surgery through the entire study period. Patients were asked to wait at least 90 minutes after completion of surgery before requesting rescue analgesia. Poststudy follow-up visits occurred approximately 48 hours postdose and at 14 to 21 days postdose.

Participants

Male or female participants were recruited if aged 18 to 50 years, in general good health, and scheduled for surgical extraction of up to 4 third molar teeth under local anesthesia, at least 1 of which was required to be fully or partially impacted in the mandible requiring bone removal. Key exclusion criteria were previous allergic reactions to drugs or foods, presence of significant organ disease or mental illness, pregnant or lactating women, or women of childbearing potential who were not using adequate contraception as defined by the protocol, previous exposure to either non-steroidal antiinflammatory drugs or COX 2 inhibitors within 48 hours or 5 half-lives before the start of surgery, intolerance of paracetamol or opioid-based rescue medication, concomitant use of other drugs, history of either drug or alcohol abuse or positive prestudy drug/alcohol screen.

Study Assessments

Pain intensity was recorded predose, at 1 hour, every 15 minutes from 2 to 4 hours, and at 5, 6, 7, 8, 9, and 10 hours postsurgery using 2 scales: a 0 to 100 mm ungraded Visual Analog Scale (VAS) (0 = no pain, 100 = worst pain imaginable) and a 4-point categorical (0 = none, 1 = mild, 2 = moderate, 3 = severe) Verbal Rating Scale (VRS). Duration of analgesic effect (defined as the median time to first rescue analgesic) was determined by recording the time of dosing with rescue medication. The pain intensity was also rated at this time using VAS and VRS scores. A patient global evaluation of the study medication was determined from patient-derived subjective assessments of the treatment using a 4-point categorical scale (excellent, good, fair, and poor) undertaken at 10 and 24 hours postdose. Supplementary analgesics (rescue medication) taken during the in-patient stay were recorded. Use of rescue medication was also recorded by the patients in a diary after discharge. A short form of the Fear of Pain Questionnaire (FPQ)[19] was completed by all the patients before entering the study. This score was used as covariate in the pain intensity analysis. A 4-point surgical trauma rating scale was used by the surgeon to rate the degree of difficulty of the surgical procedure for each tooth removed. The number of teeth extracted was used as covariate in the pain intensity analysis.

Safety assessments were undertaken up to 48 hours postdose and included safety laboratory parameters (clinical chemistry, hematology, and urinalysis), 12-lead electrocardiograms (ECG), vital signs, 24 hours Holter ECG monitoring, adverse events (AEs), and continuous lead-II ECG monitoring. Blood samples for the determination of plasma levels of GSK842166 and subsequent pharmacokinetic (PK) analysis were taken predose, and then at 15 to 30, 60, 90 minutes, hourly from 2 to 10, 24, and 48 hours postdose.

Statistical Analysis

The sample size for this study was based on estimates of the variability and treatment difference observed for the weighted mean of the change from baseline in pain intensity over 8 hours postdose in a previous study in which the underlying standard deviation, estimated from an analysis of covariance was 25 mm on a 0 to 100 mm VAS. A sample size of 28 patients per group was deemed appropriate to detect a difference on the VAS of 20 mm with 90% power and a 10% significance level. It was therefore intended that sufficient patients were to be recruited to enable 112 evaluable datasets.

Efficacy analyses were performed on the intent-to-treat population and included all randomized patients, who took

at least 1 dose of study medication and who had at least 1 postdose assessment. The primary efficacy measure of pain intensity was based on the VAS. The primary efficacy variable was the weighted mean of the pain intensity during the first 10 hours postsurgery, and the primary comparison of interest was the difference in the weighted mean pain intensity for each dose level of GW842166 from placebo. Comparisons between the treatments were made using analysis of covariance in which exploratory factors such as center, age, sex, fear of pain (as measured by the FPQ), and number of teeth extracted was investigated as covariates in the model. The secondary efficacy variables were the weighted mean of pain intensity over the 10 hours postsurgery based on the VRS, VAS, and VRS mean pain scores up to 10 hours postsurgery, patient global evaluation before rescue medication use and at 10 and 24 hours postdose, elapsed time from study drug administration to use of first rescue analgesia, and the proportion of patients requiring rescue medication. 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 before rescue, allowing estimates of treatment effect to be made with the complete study population. The OC dataset made no assumptions about the missing values, excluding them from any analyses. Patient global evaluation was analyzed using Wilcoxon rank-sum tests and time to data was analyzed using the log-rank test.

The safety population comprised all randomized patients who received at least 1 dose of study medication. Clinical monitoring and laboratory data were reviewed by the study physician and were not formally analyzed. ECG, vitals, and safety laboratory data were flagged against normal ranges and ranges of potential clinical concern.

PK analysis was conducted using plasma GW842166 concentration-time data and a noncompartmental model for extravascular administration. Actual elapsed time from dosing was used to estimate all individual plasma PK parameters for evaluable patients. The following parameters were estimated: the time before the first measurable GW842166 concentration (t_{lag}), the maximum observed plasma GW842166 concentration (C_{max}), and the time to reach C_{max} (t_{max}), the area under the plasma GW842166 concentration-time curve (AUC) from time 0 to 10 hours postdose [$AUC_{(0\text{-}10)}$], from time 0 to 24 hours postdose [$AUC_{(0\text{-}24)}$], and from time 0 to t_{last} [$AUC_{(0-t)}$].

RESULTS

A total of 123 patients were recruited in the study; 31 received placebo, 34 received GW842166 100 mg, 27 received GW842166 800 mg, and 31 received ibuprofen. One hundred twenty-one patients completed the study as planned, with 2 patients withdrawing after dosing with GW842166 800 mg. One patient was withdrawn after dosing due to a protocol violation (tooth not removed from the mandible) and was excluded from the statistical analysis. Another patient was lost to follow-up. One hundred twenty-one patients were included in the intent-to-treat population that was used for all efficacy outputs. All 61 patients, who received GW842166 (100 or 800 mg), had at least 1 PK sample analyzed and were included in the PK analysis. The baseline demographic characteristics (age, ethnicity, race, and body mass index) were similar among groups although there was a greater proportion of female participants than male participants and a lower mean weight in the ibuprofen group than for the other treatment groups (Table 1). Across the 4 treatment groups, 42% to 61% of the patients were female and 88% to 100% were white. The mean age ranged from 24.9 to 26.6 years, the mean weight ranged from 66.7 to 74.8 Kg, and the mean body mass index ranged from 23.1 to 24.2 Kg/m^2. All patients had moderate–to-severe pain after surgical extraction.

Efficacy

The adjusted means and 95% confidence interval for the weighted means of the pain intensity measured by VAS (primary endpoint, LOCF) are shown in Figure 1. Summary statistics for the primary comparisons of interest are shown in Table 2. On average, the weighted mean of the pain intensity (VAS) for the LOCF dataset was similar for both GW842166 100 mg and placebo, but was 8.12 mm lower for GW842166 800 mg relative to placebo. However, for ibuprofen the weighted mean of the pain intensity VAS was, on average, 31.79 mm lower relative to placebo. Although there was a small tendency for GW842166 800 mg to show reduced pain relative to placebo, neither the 100 mg nor 800 mg doses showed a statistical significant or clinically meaningful improvement relative to placebo;

TABLE 1. Baseline Demographic Characteristics

No. Patients (N)	Placebo	GW842166 100 mg	GW842166 800 mg	Ibuprofen
Planned N	28	28	28	28
Entered (dosed) N	31	34	27	31
Completed N	31	34	25	31
Withdrawn N	0	0	2	0
Efficacy analysis (ITT) N	31	34	26	31
Safety analysis N	31	34	27	31
PK analysis N	—	34	27	—
Demographics				
Age (y) 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: males	13:18	15:19	15:12	19:12
White/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

BMI indicates body mass index; ITT, intention-to-treat.

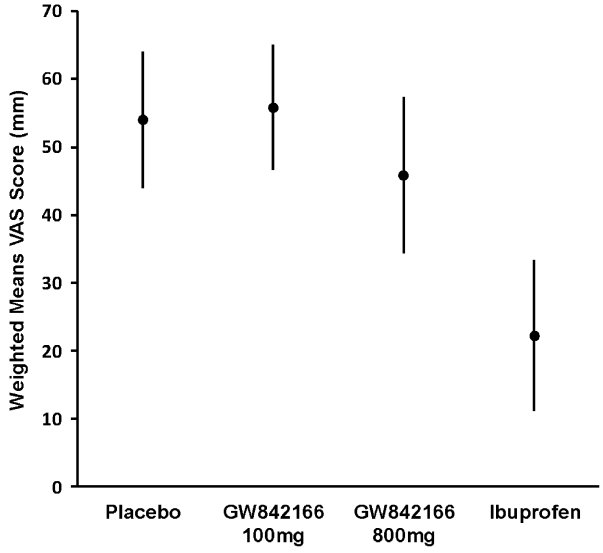

FIGURE 1. Weighted means of the pain intensity measured by VAS (primary endpoint, LOCF) over the 10 hours postsurgery across the different treatment regimens (placebo, GW842166 100 or 800 mg, ibuprofen). Data are the adjusted means and 95% CI for each of the 4 treatment regimens.

this was in contrast to ibuprofen which showed both a clinically and statistically significant improvement over placebo.

Summary statistics for comparisons of interest using the weighted means of the pain intensity measured by the VRS are shown for the LOCF population in Table 3. On average, the weighted mean of the pain intensity (VRS) for the LOCF dataset was similar for both GW842166 100 mg and placebo, but was lower for GW842166 800 mg relative to placebo (−0.31). However, this difference was not as large as the decrease in the weighted mean of the VRS score for ibuprofen relative to placebo (−0.92).

The FPQ was statistically significant at the 5% level as a covariate (data not shown). Center, age, sex, and number of teeth extracted were not significant. A positive relationship between the total fear of pain score and the weighted mean for the VAS may have been driven by some of the more extreme values.

At the 10 and 24 hours time-points, the scores for patient global evaluation showed a statistically significant improvement for ibuprofen over placebo (Table 4). This was also true for GW842166 800 mg at 24 hours postdose. However, this latter result should be interpreted with caution. Although ibuprofen was recognized as consistently better than placebo across the efficacy endpoints, the significant effect of GW842166 800 mg on patient global evaluation was an isolated result.

An analysis of the time to first dose of rescue medication relative to the first dose of study medication is shown in Table 5. Patients receiving ibuprofen tended to request rescue medication later than patients receiving GW842166, relative to placebo. The likelihood of patients needing rescue medication was significantly lower for ibuprofen relative to placebo than for GW842166. There was little evidence of any separation between placebo and the 2 doses of GW842166 in terms of time to rescue.

TABLE 2. Comparisons of Interest for Weighted Means of the Pain Intensity Measured by VAS (Intention-to-treat Population, Last Observation Carried Forward)

Comparison	Test LS Mean	Placebo LS Mean	Point Estimate	90% CI
GW842166 100 mg-Placebo	55.80	53.98	1.82	(−9.42, 13.07)
GW842166 800 mg-Placebo	45.86	53.98	−8.12	(−20.87, 4.62)
Ibuprofen-Placebo	22.19	53.98	−31.79	(−44.16, −19.43)

CI indicates confidence interval; LS, least squares.

TABLE 3. Comparisons of Interest for Weighted Means of the Pain Intensity Measured by VRS (Intention-to-treat Population, Last Observation Carried Forward)

Comparison of Interest	Test LS Mean	Reference LS Mean	Point Estimate	95% CI
GW842166 100 mg-Placebo	2.16	2.17	−0.01	(−0.34, 0.32)
GW842166 800 mg-Placebo	1.86	2.17	−0.31	(−0.68, 0.07)
Ibuprofen-Placebo	1.25	2.17	−0.92	(−1.28, −0.56)

CI indicates confidence interval; LS, least squares.

Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Relationship

After oral administration, GW842166 was found to be rapidly absorbed with detectable systemic concentrations appearing around 30 minutes after dosing and peak concentrations being observed on average from 3 to 3.5 hours postdose (Table 6). All patients apart from 1, displayed t_{max} within 8 hours postdose. GW842166 C_{max} and AUC at 100 and 800 mg were not proportional to dose.

TABLE 4. Summary of Analysis of Patient Global Evaluation by Time (ITT)

	Placebo	GW842166 100 mg	GW842166 800 mg	Ibuprofen
10 h				
n	24	30	24	26
Median	1.0	2.0	2.0	3.0
Median difference		0.0	0.0	2.0
95% CI		0.0, 1.0	0.0, 1.0	1.0, 2.0
P		0.5487	0.2165	< 0.0001
24 h				
n	29	34	25	31
Median	1.0	2.0	2.0	3.0
Median difference		0.0	1.0	1.0
95% CI		0.0, 1.0	0.0, 1.0	1.0, 2.0
P		0.0932	0.0194	< 0.0001

CI indicates confidence interval.

TABLE 5. Analysis of Data for Time to First Dose of Rescue Medication Relative to First Dose of Study Medication

Summary of Analysis of Time to First Dose of Rescue Medication (ITT)	Placebo	GW842166 100 mg	GW842166 800 mg	Ibuprofen
N	31	34	26	31
Rescued	25	28	23	25
Censored	6	6	3	6
Kaplan-Meier estimate—median time to rescue (h)	4.75	4.74	4.83	11.47
Hazard ratio*		0.95	0.95	0.77
95% CI		0.55, 1.63	0.71, 1.26	0.63, 0.93
Log-rank *P*		0.8482	0.7023	0.0054

*The Hazard Ratio represents the likelihood of receiving rescue medication with active treatment relative to that with placebo.
CI indicates confidence interval.

For the 8-fold increase in dose, an approximate 2.5-fold increase in C_{max} and AUC was observed.

In exploratory pharmacokinetic-pharmacodynamic analyses, the relationship between GW842166 systemic exposure and VAS pain scores was investigated. Analyses focused on VAS pain scores using weighted mean observed data, in which data postrescue was set to missing, and the average GW842166 concentration up to the time of rescue. Regression analysis was used to generate 95% confidence and prediction intervals. The average GW842166 concentration versus VAS weighted means up to the time of rescue (OC dataset) is shown in Figure 2. There was little evidence of a relationship between higher average GW842166 concentrations and lower VAS scores. Differences in the PKs of GW842166 between patients who received rescue medication and those who did not take rescue medication were investigated by visual inspection of plots of t_{lag}, t_{max}, C_{max}, and $AUC_{(0\text{-}10)}$ for each group. There was no evidence of a relationship between slower GW842166 absorption or lower GW842166 exposure and the need of rescue medication.

Safety

The frequency of AEs being reported was high (61% to 71% across treatment groups), which is not unexpected for patients in the postoperative period, and was found to be similar across all the active treatment groups (approximately 70%), although slightly less in the placebo group (61%). The most common treatment emergent AE was headache in all groups (15% to 39%) followed by nausea, pyrexia, and syncope in the GW842166 800 mg group; nausea and pharyngolaryngeal pain in the GW842166 100 mg group; nausea, vomiting, and pharyngolaryngeal pain in the ibuprofen group; and pyrexia in the placebo group (Table 7).

Few of these AEs (1 or less patients for any AE reported as drug-related) were considered to be drug-related. The majority of AEs were considered to be of mild or moderate intensity across all treatment groups. A few events were reported as severe as follows (number and percentage of patients with AEs of severe intensity is given in brackets): Placebo group: headache [3 (10%)], myalgia [1 (3%)], postprocedural swelling [1 (3%)], procedural pain [1 (3%)]; GW842166 100 mg group: headache [4 (12%)], dysphagia [1 (3%)], pharyngolaryngeal pain [1 (3%)]; GW842166 800 mg group: no severe AEs were reported in this group; Ibuprofen group: dizziness [1 (3%)], dyspepsia [1 (3%)], stomach discomfort [1 (3%)], incision site hemorrhage [1 (3%)], intestinal obstruction [1 (3%)]. There were no AEs leading to patient withdrawl. Two nonfatal serious AEs were reported by 2 patients as follows: Patient 113 (female; 23 y), in the GW842166 800 mg group, was diagnosed with a submandibular abscess that required treatment with intravenous antibiotics. Patient 170 (female, 26 y), in the ibuprofen group, had a serious AE of intestinal obstruction (intra-abdominal adhesions requiring adhesiotomy). Both patients made a full recovery and neither event was judged to be related to study medication. Evaluation of summary statistics for hematology, clinical chemistry, and 12-lead ECG parameters revealed no obvious patterns or trends to indicated drug-related adverse effects.

DISCUSSION

Typically, in the absence of any systemic analgesia being administered, patients undergoing third molar tooth extraction can be expected to report maximum pain intensity levels at around 2 to 3 hours after surgery,[20,21] and this has been the generally accepted pain baseline for many acute studies in which patients are randomized to receive investigational medicinal products in the postoperative period. In this study, however, we proposed to investigate the analgesic efficacy of GW842166 administered as an oral premedication for the relief of postoperative pain in

TABLE 6. Pharmacokinetic Analysis of GW842166

GW842166 Dose	t_{lag}(h) Median (Range)	t_{max}(h) Median (Range)	C_{max}(μg/mL) Geometric Mean (CVb%)	AUC(0-10) (μg.h/mL) Geometric Mean (CVb%)	AUC(0-24) (μg.h/mL) Geometric Mean (CVb%)
100 mg	0.26 (0.00-1.82)	3.50 (1.00-24.25)	0.285 (45.1)	1.68 (36.3)	3.57 (36.9)
800 mg	0.25 (0.00-0.50)	3.00 (1.75-6.27)	0.714 (35.2)	4.56 (32.8)	9.01 (27.1)

Plasma samples were analyzed for GW842166 using a validated analytical method based on protein precipitation, followed by high pressure liquid chromatography/tandem mass spectrometry analysis. The lower limit of quantitation for GW842166 was 2 ng/mL using a 50 μL aliquot of human EDTA plasma.
CVb indicates Coefficient of variation between patients.

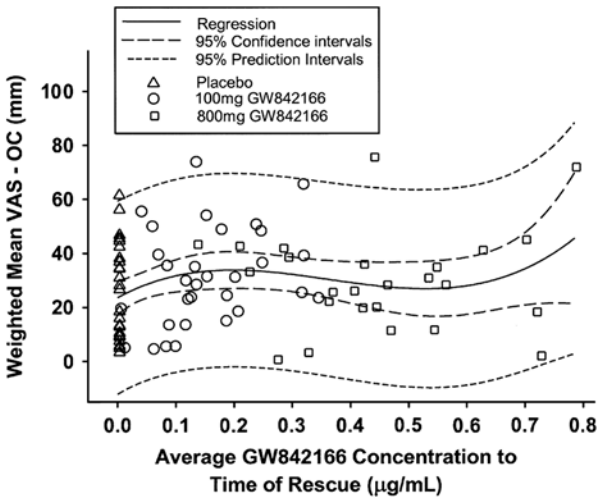

FIGURE 2. Average GW842166 concentration up to time of rescue versus VAS weighted means of the pain intensity (OC dataset).

patients undergoing third molar tooth extraction. We had previously established in phase 1 investigations that the time to reach C_{max} (t_{max}) for GW842166 in the fasted state to be approximately 2 hours and, in the fed state to be approximately 3 hours. Therefore, to allow the treatment, sufficient time to provide analgesic benefit before patients were likely to request rescue analgesia, patients were administered treatments pre-emptively (as a premedicant) within 1 hour of surgery taking place. The pre-emptive timing for drug administration was expected to accommodate the known t_{max} for orally administered GW842166 within a time-window relevant to the emergence of postoperative peak pain intensity.

Ibuprofen was chosen as the active comparator to validate the study model and for benchmarking the analgesic efficacy of GW842166 in keeping with similar studies that have been conducted with this NSAID.[22–29] Although it has been recognized that systemic ibuprofen exposure after a single pre-emptive dose was likely to be relatively short [ibuprofen elimination half-life ($t_{1/2}$) is approximately 2 h] in comparison to that of GW842166 (elimination $t_{1/2}$ is approximately 25 to 35 h), and to optimize the chances of the active comparator remaining efficacious for the full duration of the postoperative pain intensity assessments, patients allocated to the active comparator group received a second dose of ibuprofen (400 mg), 4 hours after the first pre-emptive dose of 800 mg. The remaining patients in the treatment and placebo groups received placebo at the 4 hours postdose time-point.

Patients were requested to abstain from taking paracetamol and codeine as rescue medication until at least 90 minutes after surgery, and all patients complied with this. To account for missing data resulting from patients' use of rescue medication, our statistical approach elected to use the LOCF technique. Owing to the preoperative timing of the dosing regimen, the absence of a predose pain baseline value precluded consideration of the baseline observation carried forward method for the imputation of missing data. Although single imputation using linear regression also provides a widely used approach to the handling of missing data, the validity of the methodology applied to this study might otherwise have been limited by the large number of missing values after early rescue in the postoperative period.

The 100 mg dose of GW842166 was chosen, because earlier exploratory pharmacodynamic data achieved in a phase 1 repeat dose study (unpublished data; Clinical Study Identifier GW842166/902; Eudract No. 2004-003911-22) suggested that this dose level was associated with an antinociceptive effect on the basis of an observed increase in heat pain threshold measured in healthy volunteers after dosing to steady state (100 mg, once daily). A comparison between the groups [GW842166 100 mg (n = 8) versus placebo (n = 14)] for this effect provided a treatment estimate of 2.26°C (95% confidence interval: 0.58, 3.95). Such an effect size compares favorably to that reported

TABLE 7. Number (%) of Patients With Common Treatment Emergent AEs (Reported for at Least 5% Patients in Any Group) (Safety Population)

Treatment Emergent AEs* n (%)	Placebo N = 31	GW842166 100 mg N = 34	GW842166 800 mg N = 27	Ibuprofen N = 31
No. patients with AEs n (%)	19 (61)	24 (71)	18 (67)	22 (71)
AEs: (most frequent 5 AEs 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
Diarrhea	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%)
Dysmenorrhea	0	2 (6%)	0	2 (6%)
Dysphagia	0	2 (6%)	0	1 (3%)
Influenza-like illness	0	2 (6%)	0	0
Dyskinesia	2 (6%)	1 (3%)	0	1 (3%)
Dizziness	1 (3%)	0	0	2 (6%)

*Only treatment emergent AEs are listed in this table and are reported in decreasing frequency for GW842166 800 mg followed by GW842166 100 mg followed by ibuprofen.

after administration of intravenous opioids to healthy volunteers.[30,31]

The 800 mg dose was chosen because this was the highest dose of GW842166 that had been shown previously to be well tolerated in healthy human volunteer studies (unpublished data; Clinical Study Identifier GW842166/901). Doses higher than 800 mg (up to 1600 mg) were also well tolerated in that study; PK data, however, have shown that it is not possible to achieve higher systemic exposures with doses above 800 mg and that a plateauing in the exposures is observed over the 800 to 1600 mg dose range. This is despite the development of a capsule formulation incorporating wet bead milled drug material in an attempt to compensate for the known poor aqueous solubility of GW842166 (< 1 μg/mL) and to improve oral bioavailability.

The PK data achieved in this study confirmed our previous findings in healthy volunteers. Thus, after oral administration of GW842166, systemic concentrations of GW842166 were detected at around 30 minutes after dosing and peak concentrations were generally observed 3 to 3.5 hours after dosing. The t_{max}, therefore, correlated well with the emergence of pain in the immediate postoperative period. All patients apart from 1 displayed t_{max} within 8 hours postdose. As predicted, the exposures (in terms of C_{max} and AUC) achieved at the 100 and 800 mg dose levels were reasonably well differentiated, albeit not dose proportional.

The primary efficacy variable was a measure of pain intensity based on the VAS and was the weighted mean in pain intensity during the first 10 hours postsurgery. On average, the weighted mean of the pain intensity for the LOCF dataset was 1.82 mm higher for GW842166 100 mg relative to placebo, and 8.12 mm lower for GW842166 800 mg relative to placebo. However, for ibuprofen, the weighted mean of the pain intensity VAS was, on average, 31.79 mm lower relative to placebo representing both a clinically and statistically significant improvement. Similar results were found with the OC dataset (not shown). There was no discernible difference in the pain intensity profile after administration of rescue medication to patients receiving GW842166 relative to those receiving placebo or ibuprofen, suggesting the absence of any adjunctive benefits of co-codamol coadministration with GW842166. The secondary efficacy variable, pain intensity as measured using VRS, yielded similar results and showed that there was little difference between GW842166 and placebo; larger differences for this endpoint were apparent for GW842166 800 mg, but the largest difference, achieving both statistical and clinical significance, was for ibuprofen.

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

Overall, the efficacy data from this study showed that ibuprofen was consistently better than placebo across almost all the endpoints, indicating that the study methodology and sample size enabled sufficient sensitivity to detect a difference from placebo. Although there was a slight tendency for an improvement in pain with the higher dose of GW842166 (800 mg), this failed to be of either clinical or statistical significance. The relationship between GW842166 systemic exposure and VAS pain scores was also investigated in this study. There was little evidence of a relationship between higher than average GW842166 plasma concentration and lower VAS pain scores. Similarly, there was no evidence of a relationship between slower GW842166 absorption or lower GW842166 exposure and the need for rescue medication. Overall, then, it is not possible to explain the distribution of VAS pain scores in terms of the systemic exposures to GW842166.

The fear of pain score was found to be a significant covariate as a predictor of pain outcome score. Other studies have similarly found strong association between anxiety levels, fear of dental pain, and pain outcome score after third molar extraction.[32,33] In terms of safety assessments, the data from this study suggest that GW842166 has an acceptable safety profile and is well tolerated in single doses over the range 100 to 800 mg; this is consistent with the findings of earlier single and repeat dose studies conducted in healthy volunteers.

There are several plausible reasons that may help to explain why, in contrast to ibuprofen, it was not possible to demonstrate efficacy with GW842166 in this study. The most likely explanation is that the freely available biophase concentrations achieved at the 100 and 800 mg dose levels in humans were inappropriate or otherwise suboptimal. The known high plasma protein-binding (> 99%) of GW842166 for both rat and human, raises the possibility that the unbound systemic concentrations were insufficient to fully test the CB2 agonist mechanism in vivo. Although it has been reported previously that single doses of GW842166 (0.3 mg/Kg) produced full reversal of hyperalgesia in the rat Freund's complete adjuvant model, at blood concentrations (370 nM) in excess of the EC_{50} (91 nM) at recombinant rat CB2 receptors in vitro, the demonstration of efficacy in that in vivo model is nevertheless difficult to reconcile in terms of a free fraction of GW842166 that is < 1% (< 3.7 nM). Similar considerations may also apply to this clinical study in which the mean C_{max} (714 ng/mL; 1.6 μM) achieved after the 800 mg dose of GW842166 would equate to a free concentration (16 nM) below the cited EC_{50} (63 nM) at recombinant human receptors in vitro.

Considerable uncertainty surrounds both the mechanism of action of CB2-mediated analgesia in animal models and the precise location(s) of the CB2 receptors that mediate antinociception. This poses significant challenges for the development (and choice) of relevant human native tissue assays that could be used to facilitate clinical dose predictions for CB2 selective candidates. Anand et al[34] have demonstrated that CB2 and CB1 receptors are coexpressed along with the capsaicin transient receptor potential vanilloid receptor 1 receptor on human dorsal root ganglion (DRG) sensory neurons. In primary cultures of human DRG, selective activation of CB2 receptors was shown to block capsaicin-activated whole-cell currents and GW842166 was shown to produce a CB2-mediated attenuation of capsaicin-mediated calcium influx; interestingly, the concentration range over which GW842166 operates in this preparation (100 nM to 5 μM; EC_{50} ~1 μM) further calls into question the therapeutic relevance of the plasma concentrations achieved in this clinical study. On the other hand, models based on DRG-responsiveness to capsaicin are widely appreciated to be more relevant to chronic

neuropathic pain and, arguably, may bear little translational value for a postoperative pain study.

Another possibility for the lack of demonstrable efficacy with GW842166 in this clinical study relates to the duration of drug exposure and occupancy of the CB2 receptor. From the earlier human clinical investigations, the kinetics of absorption and distribution for GW842166 are known to be relatively slow [median t_{max} in these patients after the single 800 mg dose was 3.0 hours (range, 1.75 to 6.27)]. The timing of dosing in this study was chosen to ensure that the C_{max} was achieved at the expected time of emergence of the postoperative dental pain. As described above, this expectation was met. However, it is possible that a more sustained exposure and occupancy at the CB2 receptor would have been achieved with a longer period of preoperative dosing. If this had been feasible in the context of a dental pain study, then effective drug disposition might have been enabled. Such a repeat dosing regimen would be more appropriate in a different clinical surgical context, such as postbunionectomy pain, in which the period of need for postoperative analgesia is more prolonged.[16,35–37] The bunionectomy model has been widely applied in the clinical pharmacology setting and also carries the added advantage of allowing an objective assessment of the opioid-sparing effects of novel analgesics for up to a week postoperatively. Alternatively, clinical models based on an assessment of CB2-mediated analgesia and associated immunomodulatory actions in rheumatology patients with chronic pain may also be appropriate.

Despite the widespread interest in CB2 as a therapeutic target for pain, no clinical studies with CB2-selective agonists have been reported in the literature. The Pharmos Corporation have provided an internet communication on 2 phase II investigations undertaken with their CB2 agonist Cannabinor.[38] In the first study, a single dose of intravenous Cannabinor failed to attenuate capsaicin-induced allodynia and hyperalgesia when compared with placebo; however, a statistically significant effect on pressure-induced pain and thermal pain was noted. An unexpected pattern of results was reported by Pharmos in a second clinical study undertaken in patients undergoing third molar tooth extraction, in which intravenous Cannabinor was found to have a postoperative antinociceptive effect at the 12 mg dose level, but not at the higher 24 and 48 mg dose levels.[38] Glenmark is also planning to undertake phase II investigations in patients with neuropathic pain, osteoarthritis, and other inflammatory indications with their CB2 agonist GRC10693[39]; however, the pharmacodynamic data from phase I studies undertaken with this compound have yet to be disclosed.

Although there is mounting evidence to suggest a therapeutic role for cannabinoids in chronic pain, in the context of this study, it is interesting to note that several studies have been undertaken with nonselective cannabinoids in the acute postoperative setting. Using Δ^9-tetrahydrocannabinol, no analgesic benefits have been reported across 3 postoperative pain trials.[40–42] Although the cannabinoid levonantradol was shown to provide analgesic effects in postoperative or trauma pain, these were independent of dose.[43] On the other hand, a study with the cannabis plant extract Cannador was able to demonstrate dose-related benefits in terms of reduced requirements for rescue analgesia in the postoperative period.[44] Given the somewhat conflicting evidence to suggest that nonselective cannabinoids might have acute analgesic effects, what then are the key drivers for the continued investigation of CB2-selective agonists in this clinical setting? These would seem to be underpinned by the observed expression of CB2 receptors on (largely peripheral) immune cells and primary sensory neurons, coupled with evidence for CB2-mediated suppression of inflammatory nociception in a variety of behavioral, electrophysiological, and neurochemical investigations, along with supporting data from CB2 receptor knockout animals (reviewed in[7,8,10]). Evidence of "cross-talk" between the endocannabinoid and the opioid systems also raises the possibility of synergy between cannabinoids and opioids. As such, it is possible that CB2 agonists, devoid of CB1-mediated psychotropic effects, might be usefully developed in combination with other analgesics and endocannabinoid modulators.[10]

In summary, we provide the first literature report of a clinical trial undertaken to assess the postoperative analgesic efficacy of an orally dosed CB2-selective agonist in patients undergoing dental extraction. Ibuprofen was found to provide statistically and clinically significant better analgesia than placebo, thus supporting the validity of the trial methodology. A single 100 mg preoperative dose of GW842166 was noted to have a similar effect to placebo. GW842166 800 mg provided, on average, improved analgesia over placebo for both VAS and VRS pain ratings, but this difference was not significant. The profile for use of rescue medication was found to be similar across the placebo and GW842166 groups. Patients tended to take rescue medication later for ibuprofen. There was no evidence of an exposure-response (pharmocokinetic-pharmacodynamic) relationship for GW842166. Data from a completed 28-day repeat-dose study to explore the analgesic efficacy of GW842166 in patients with osteoarthritis will be reported elsewhere.

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