Synopsis

Identifier: HM2007/00699/00 **Study Number**: CBA106191

Title: A double-blind, two-period, placebo controlled cross-over study of the effects of the CB2 agonist GW842166 on pain and sensitisation in patients with osteoarthritis

Investigator: Prof. [redacted]

Study Centre: [redacted] UK.

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

Study period:

Initiation Date:	29 May 2007
Completion Date:	Not applicable
Early Termination Date:	06 May 2008

Phase of Development: IIa

Objectives:

Primary:

- To investigate the effects of the CB2 agonist GW842166X on Pain Intensity and sensory endpoints in patients with painful osteoarthritis (OA) of one index knee
- To assess the value of experimental endpoints (capsaicin-evoked hyperalgesia, quantitative sensory testing, contact heat-evoked potentials and quantitative sensory tests) as markers of sensitisation in OA arthralgia and/or pharmacodynamic (PD) markers for CB2 agonists

Secondary:

- To evaluate the safety and tolerability of GW842166X in patients with OA

Methodology:

This was a double-blind, two-period, placebo-controlled, randomised, 2 way cross-over study using repeat doses of GW842166X.

The study consisted of screening, two 2-week treatment periods, and follow-up. The screening visit was carried out between 3-14 days prior to the first treatment visit. After completion of the baseline pain assessments on Day 1 of period 1, the patient was randomised into one of two treatment sequences. Pain and related assessments were performed at Day 1 (baseline) and Day 14 of periods 1 and 2 (the capsaicin tests were performed at Day 14 only). There was at least a 2 week washout between the treatment periods 1 and 2. The final follow-up visit was 7-14 days after the final dose of study medication.

Patients were to receive 100mg GW842166X once daily for 14 days in one treatment period and then receive placebo once daily for 14 days in the other treatment period. The order of treatment was randomised, whereby patients were assigned to one of two treatment sequences (AB or BA).

Number of subjects:

A sufficient number of subjects, 50-80 years of age, with ACR-defined OA of the knee were planned to be recruited to obtain a total of 36 evaluable datasets. Only one patient was successfully recruited to the study and she completed both treatment periods.

Subject Disposition and Demographics:

The demographic characteristics of the subject in this study are presented in the table below.

Diagnosis and main criteria for inclusion:

Male and female patients with OA on knee, aged 50 to 80 years.

A diagnosis of primary osteoarthritis of the knee at least 3 months in symptom duration prior to screen. For patients with OA in both knees, an index knee was specified.

The patient was required to meet the American College of Rheumatology (ACR) criteria for symptomatic osteoarthritis of the knee as defined by knee pain and radiographic evidence of osteophytes (Altman 1986).

The patient was required to meet Global functional status I, II or III according to ACR classification.

Patient was required to have a minimum of 40mm on the 100mm VAS (WOMAC pain subscale) at baseline / randomisation. In addition, baseline pain must have been stable for at least 72 hours prior to randomisation based on patient's assessment.

Patient was required to have a maximum of 80mm on the 100mm VAS (WOMAC pain subscale) at screening.

Treatment administration:

Each patient was planned to receive 100mg GW842166X once daily for 14 days and placebo dose once daily for 14 days. Patients were to be randomly assigned to one of two possible treatment sequences in accordance with the randomisation schedule, in a 1:1 ratio – A/B or B/A (see table below), where A = GW842166X (batch number: AK DP128685 PP142363) and B = matched placebo (batch number: ANH PB129818 PP142364).

Treatment sequences	Period 1		Period 2	
	Week 1	Week 2	Week 1	Week 2
A/B	GW842166 100mg	GW842166 100mg	Placebo	Placebo
B/A	Placebo	Placebo	GW842166 100mg	GW842166 100mg

[redacted] She received placebo in the first treatment period and GW842166 100mg in the second treatment period.

Criteria for evaluation:

Primary Clinical endpoint:

Change in Pain Intensity from baseline to the end of treatment using Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) pain subscore.

Secondary Clinical endpoints

- Change in Pain Intensity from baseline to the end of treatment in WOMAC pain subscore of question 1 (pain walking on a flat surface)
- Change from baseline to the end of treatment in WOMAC stiffness subscore

- Change from baseline to the end of treatment in WOMAC physical function subscore
- Change from baseline to the end of treatment in WOMAC composite score
- Change from baseline to the end of treatment in Patient's Global assessment of arthritis condition
- Change from baseline to the end of treatment in Physician's Global assessment of arthritis condition
- Time and pain intensity (100mm Visual Analogue Scale, VAS) from the 40m self-paced walk test (optional)
- Time and pain intensity (100mm VAS) from the 11 step stair climb test (optional)
- Percentage of patients discontinuing due to lack of efficacy
- Average total daily use of rescue medication

Psychophysical and electrophysiological endpoints:

- Rating of intensity of pain evoked by joint movement (100mm VAS)
- Quantitative Sensory Testing (QST)
- Contact heat-evoked potentials (CHEPs, optional)
- Rating of intensity of pain evoked by capsaicin application (100mm VAS, optional)
- Cutaneous hyperalgesia at the site of application of capsaicin (optional)
- Rating of intensity of pain evoked by suprathreshold heat stimuli (100mm VAS, optional)

Pharmacokinetic endpoints:

- Plasma concentrations of GW842166 at the end of the treatment period

Safety endpoints:

- Safety and tolerability of GW842166X: reported adverse events, blood pressure, heart rate, 12-Lead ECG, Holter monitoring and clinical laboratory evaluations

Statistical methods:

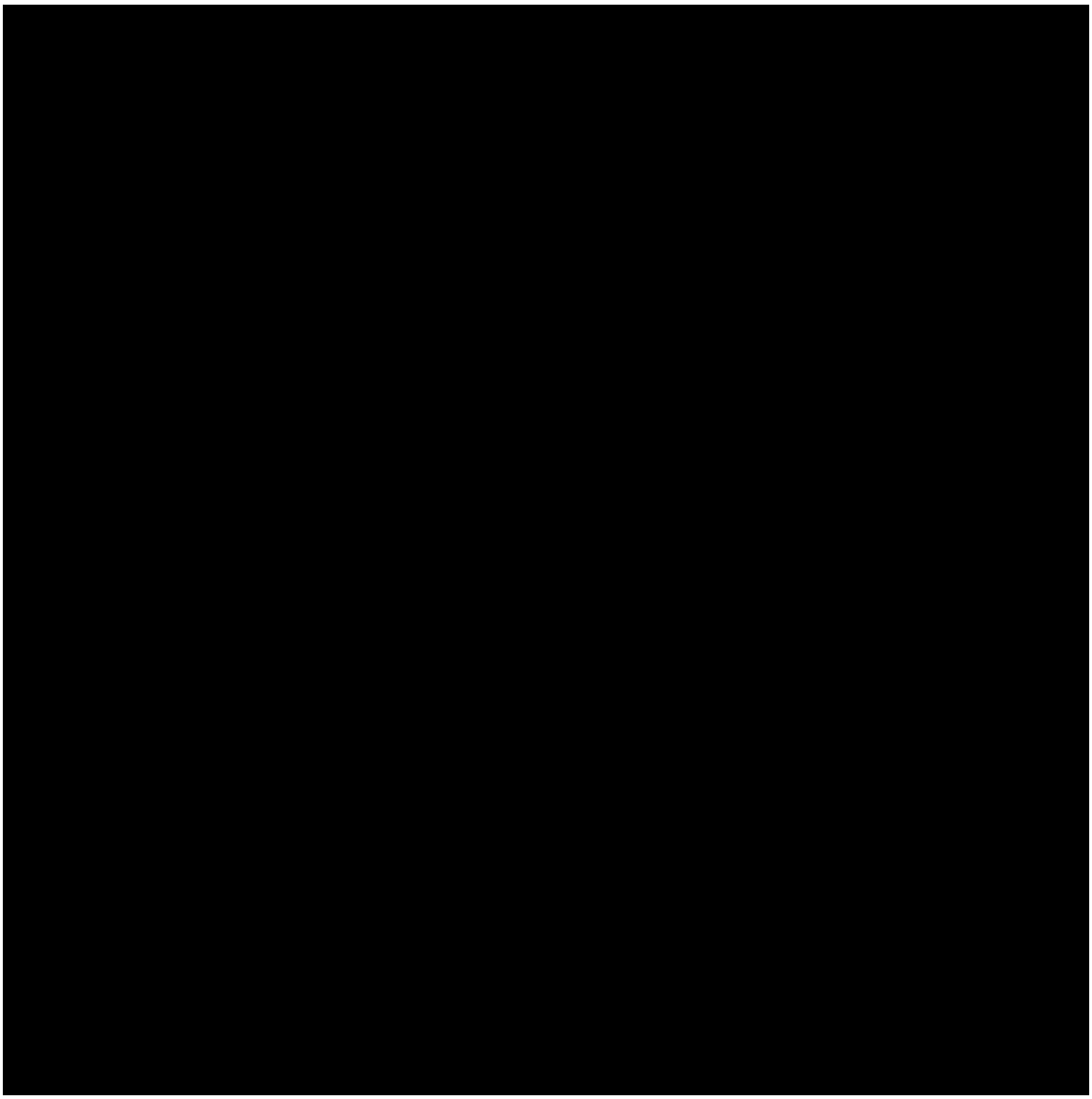
Due to the early termination of this study, no formal statistical analysis was performed. Following database release, Excel .CSV data listings, directly exported from the inform eCRF system, were provided.

Summary:

Pharmacodynamics:

The patient completed the pain assessments (except for the optional ones in the protocol) which included WOMAC index; Patient's Global Assessment of Arthritis Condition; Physician's Global Assessment of Arthritis Condition; Rating of intensity of pain evoked by joint movement; Quantiative Sensory Testing and Pain rating in diary card. Summaries of the results are presented in the tables below:

WOMAC index questionnaire results:



[redacted] Overall though, it is not possible to draw any conclusions from this data, given that it was achieved in only one subject.

Quantitative Sensory Test results:

[redacted]

1. Day 1 pre-dose
2. Day 14 after 2-4 hours dose

The daily Pain ratings are presented at the table below for the patient.

[redacted]

Pain rating (0 – 10)* results

Safety:

A total of three AEs were recorded during the study for the patient, these were considered by the investigator not to be drug related and have been listed in the table below.

The subject did not experience any serious adverse event (SAE) during the study.

Most Frequent Adverse Events	Treatment A N=1	Treatment B N=1
	n (%)	n (%)
Any AE	0	1 (100%)
Any AE related to investigational product	0	0
All AEs:		
1. Mild shortness of breath		1 (100%)
2. Insomnia		1 (100%)
3. Sore throat		1 (100%)

No serious Adverse Events occurred during the study

There were no medically important changes or abnormalities in haematology, clinical chemistry, vital signs or 12-lead ECG values which were judged to be clinically significant during the study. Overall, there was no evidence that GW842166X caused any clinically relevant or important changes in these safety parameters in this study for the subject who participated.

Pharmacokinetics:

[redacted] No pharmacokinetic or statistical analyses were performed on the data. Samples collected following placebo were not assayed.

[redacted]

NA = Not assayed

Conclusions:

The objectives of this study were not met due to the early termination of the study. Only one subject was recruited who completed all treatment periods (BA) and no conclusions can be drawn from the data achieved in this subject. No safety concerns were raised. The decision to terminate the study early was primarily based on the results of a recently completed Phase II exploratory efficacy study (CBA109389 – in reporting), which showed no evidence of analgesic efficacy for GW842166 in patients with osteoarthritis of the knee treated with either 100mg or 350mg doses (administered once daily for 28 days). As such, there was little rationale for undertaking further exposure of osteoarthritis patients to GW842166 in this study.

Date of Report: May 2008