Synopsis

Identifier: RM2007/00783/00 **Study Number:** CBA109389

Title: A Multicenter, Randomized, Double-Blind, Placebo and Naproxen (500 mg) BID controlled, Phase II Proof of Concept, Parallel Group Study to Assess the Efficacy and Safety of Oral GW842166 at Two Dose Levels Administered for 4 weeks in Adults with Osteoarthritis of the Knee

Investigators: Multicenter

Study centers: This study was conducted in 21 centers in 4 countries: Germany, Spain, Sweden, and Denmark.

Publications: None

Study Period: 04 Apr 2007 – 14 Aug 2007

Phase of Development: IIa

Objectives: The primary objective of this study was to evaluate the clinical efficacy of repeat doses of GW842166 versus placebo in the treatment of pain associated with osteoarthritis (OA) of the knee.

The secondary objectives were:

- To evaluate the safety and tolerability of GW842166 administered orally to subjects with OA of the knee.
- To evaluate the dose response of GW842166 (incorporating 2 dose levels) and placebo in the primary efficacy endpoint.
- To explore the clinical efficacy of GW842166 versus naproxen 500 mg BID in the treatment of pain associated with OA of the knee.
- To evaluate the pharmacokinetic (PK) parameters of GW842166 in subjects with OA of the knee.
- To characterise the relationship between plasma concentrations and analgesic effect of GW842166 (PK/PD).

Methodology: This study was a Phase IIa, multicenter, randomized, double-blind, placebo and active-controlled, parallel group study to evaluate the efficacy, safety and tolerability of repeat doses of GW842166 (two dose levels) compared to placebo and naproxen (500 mg bid) in subjects with symptomatic OA of the knee treated for a period of up to 28 days.

The study consisted of 4 distinct periods (Screen, Baseline, Treatment and Post-treatment Follow-up). The total duration of participation in the study should not have exceeded 50 days (7 weeks) including a maximum 14 day Screening, wash out period and 7 days post-treatment Follow-up period.

Number of subjects:

	Number (%) of Subjects			
	Placebo	GW842166 100mg OD	GW842166 350mg OD	Naproxen 500mg BID
Planned, N	88	88	88	44
Randomized, N	89	88	89	45
Completed, n (%)	79 (93)	73 (91)	76 (94)	35 (83)
Prematurely Withdrawn, n (%)	6 (7)	7 (9)	5 (6)	7 (17)
Primary Reason for Withdrawal, n (%)				
AE	3 (4)	4 (5)	2 (2)	6 (14)
Lost to Follow-up	0	1 (1)	0	0
Protocol Violation	1 (1)	0	0	0
Lack of Efficacy	0	2 (3)	2 (2)	0
Other	2 (2)	0	1 (1)	1 (2)

[redacted]

Diagnosis and main criteria for inclusion: Male or female subjects between the ages of ≥40 years having American College of Rheumatology (ACR) defined OA of the knee, and who required analgesic treatment for management of their knee OA on a regular basis. Subjects had a mean less than or equal to 80 mm on the 100 mm visual analogue scale (VAS) for the WOMAC pain subscale score at Screen and a mean minimum of 40 mm on the 100 mm visual analogue scale (VAS) for the WOMAC pain subscale score at Baseline *and* a minimum worsening between Screen and Baseline of at least 10 mm on the 100 mm VAS for the WOMAC pain subscale score.

Treatment administration: Subjects were randomly assigned to 1 of 4 treatment groups in a ratio of 2:2:2:1 (GW842166 350 mg: GW842166 100 mg: Placebo: Naproxen 500 mg BID). Subjects received study medication twice daily for a period of up to 28 days; subjects randomized to GW842166 took active drug once daily in the morning and placebo in the evening. Subjects randomized to the naproxen arm took naproxen 500 mg twice daily. The first dose of study medication was taken the day after randomization.

The following batch numbers for investigational product were provided: GW842166 100 mg: 071132992; GW842166 175 mg: 071133002; Placebo: 071133219; and Naproxen 500 mg: 071133004.

Criteria for evaluation: The primary efficacy endpoint was the change from Baseline to Day 28 Last Observation Carried Forward (LOCF) in Western Ontario and McMasters Universities OA Index (WOMAC) pain subscale score.

Secondary efficacy endpoints were:

- Change from Baseline in WOMAC pain subscale score at each scheduled visit.

- Change from Baseline in WOMAC pain subscale score question 1 (pain walking on a flat surface) score at each scheduled visit.
- Change from Baseline in WOMAC stiffness subscale score at each scheduled visit.
- Change from Baseline in WOMAC physical function subscale score at each scheduled visit.
- Change from Baseline in patient's global assessment of arthritis condition at each scheduled visit.
- Change from Baseline in physician's global assessment of arthritis condition at each scheduled visit.
- Discontinuation due to lack of efficacy.

Exploratory endpoints were:

- Percentage of responders as measured by the Osteoarthritis Research Society International (OARSI) responder index (using the OMERACT:OARSI definition) at each scheduled visit.
- GW842166 versus Naproxen comparisons:
  - Change from Baseline in WOMAC pain subscale score at each scheduled visit.
  - Change from Baseline in WOMAC pain subscale question 1 (pain walking on a flat surface) score at each scheduled visit.
- Use of rescue medication in all randomized subjects.
- Assessment of pain catastrophising in all randomized subjects.

Safety endpoints were:

- Changes from Pre-treatment to On-treatment and post-treatment Follow-up in vital signs (blood pressure and heart rate), 12-lead electrocardiogram (ECG), clinical chemistry, hematology, and urinalysis.
- Adverse events (AEs) reported from obtaining informed patient consent until post-treatment Follow-up.

Statistical methods: Analysis of covariance (ANCOVA), adjusting for statistically significant pre-specified covariates, was used to test the null hypotheses of no treatment difference between GW842166 and placebo for the WOMAC pain subscale score, with the alternative hypotheses being that there was a treatment difference. The results of the analysis of the change from Baseline were presented as a point estimate, a 95% confidence interval (CI) and an associated p-value for the adjusted mean difference between each dose level of GW842166 and placebo at Day 28 LOCF and Day 28 OC for the ITT population for the mean WOMAC pain subscale score.

Treatment by covariate interactions was investigated for the secondary efficacy variables only if a significant and meaningful interaction was observed for the primary efficacy variable.

In order to assess the efficacy of GW842166 compared to naproxen, analyses were run comparing GW842166 to naproxen for the primary endpoint, the WOMAC pain subscale score question 1, WOMAC physical function subscore and patient global assessment of arthritis condition. The analyses were run using parametric ANCOVA.

The proportion of subjects who took rescue medication at any time during the treatment period was analyzed using logistic regression. Results were presented as an odds ratio, 95% CI and p-value for the treatment effect.

A sample size of 78 evaluable subjects per GW842166 and placebo treatment groups was estimated to be sufficient to detect a treatment difference of at least 10 mm between treatments using a 2-sided test, with 80% power, and a 5% significance level, assuming an underlying standard deviation (SD) of 22.2 mm for the primary endpoint, using the 100mm VAS. This sample size was estimated to be sufficient to detect a treatment difference of 12 mm in the WOMAC pain sub-scale score at Day 28 between GW842166 and placebo with 90% power (assuming the same SD).

Four populations were evaluated: the Randomized population (all subjects who were randomized to treatment), the Safety population (all subjects who were randomized and took at least 1 dose of study medication), the Intent-to-treat (ITT) population (all subjects randomized to treatment, who took ≥1 dose of study medication and who had ≥1 post Baseline efficacy assessment), and the Per-Protocol (PP) population (those members of the ITT population who had no major protocol deviations).

Summary:

Demographics:

		PBO	GW842166 100mg OD	GW842166 350mg OD	Naproxen 500mg BID
N (ITT)		85	80	81	42
Females: Males		56:29	53:27	40:41	29:13
Mean Age, years (SD)		64.9 (9.78)	64.0 (8.82)	65.3 (10.23)	61.0 (9.44)
Ethnicity n (%)	Hispanic/Latino	8 (9)	10 (13)	13 (16)	3 (7)
	Not Hispanic/Latino	77 (91)	70 (88)	68 (84)	39 (93)
Race n (%)	Asian- East Asian Heritage	1 (1)	0	0	0
	White	84 (99)	80 (100)	81 (100)	42 (100)

Primary Efficacy Results: Analysis of Change from Baseline for WOMAC Pain Subscale Score (LOCF: ITT Population)

At Day 28 LOCF, the adjusted mean change from Baseline for WOMAC Pain Subscale score was similar between the GW842166 treatment groups and placebo.

	PBO	GW842166 100mg OD	GW842166 350mg OD	Naproxen 500mg BID
n	85	80	81	42
Baseline Mean (SD)	66.19 (10.096)	65.37 (10.983)	65.41 (11.389)	66.74 (12.251)
Day 28 LOCF Mean (SD)	41.14 (23.533)	40.74 (21.139)	40.61 (21.681)	36.00 (20.871)
Day 28 LOCF				
n	85	80	81	42
Mean Change (SD)	-25.05 (23.487)	-24.64 (21.735)	-24.80 (21.193)	-30.74 (22.367)
n	84	79	79	42
Adjusted Mean (SE) [a]	-24.3 (2.22)	-23.3 (2.31)	-22.6 (2.30)	-29.9 (3.12)
Difference vs Placebo (95% CI)	-	1.0 (-5.1, 7.1)	1.6 (-4.5, 7.8)	-5.7 (-13.1, 1.7)
p-value	-	0.754	0.596	0.132

a. Adjusted for WOMAC pain subscale score flare and center group

Secondary Outcome Variables: ITT Population

The secondary endpoints supported the findings from the primary endpoint.

Day 28 LOCF	PBO	GW842166 100mg OD	GW842166 350mg OD	Naproxen 500mg BID
WOMAC Pain Subscale Question 1: Change from Baseline				
n	84	79	79	42
Adjusted Mean (SE)	-21.1 (2.36)	-21.2 (2.45)	-19.1 (2.45)	-29.3 (3.32)
Difference vs Placebo	-	-0.0	2.0	-8.2
95% CI for Treatment Difference	-	-6.5, 6.4	-4.5, 8.5	-16.0, -0.3
WOMAC Stiffness Subscale Score: Change from Baseline				
n	84	79	79	42
Adjusted Mean (SE)	-25.7 (2.48)	-26.5 (2.57)	-24.0 (2.57)	-26.8 (3.48)
Difference vs Placebo	-	-0.7	1.8	-1.1
95% CI for Treatment Difference	-	-7.5, 6.1	-5.0, 8.6	-9.3, 7.2
WOMAC Physical Function Subscale Score: Change from Baseline				
n	84	79	79	42
Adjusted Mean (SE)	-21.0 (2.30)	-20.2 (2.39)	-19.3 (2.39)	-26.6 (3.24)
Difference vs Placebo	-	0.8	1.7	-5.6

Day 28 LOCF	PBO	GW842166 100mg OD	GW842166 350mg OD	Naproxen 500mg BID
95% CI for Treatment Difference	-	-5.5, 7.1	-4.6, 8.0	-13.3, 2.1
Patient's Global Assessment of Arthritis Condition: Change from Baseline				
n	82	79	79	42
Adjusted Mean (SE)	-15.7 (2.49)	-21.7 (2.57)	-18.1 (2.56)	-29.2 (3.48)
Difference vs Placebo	-	-6.0	-2.5	-13.5
95% CI for Treatment Difference	-	-12.8, 0.8	-9.3, 4.4	-21.8, -5.3
Physician's Global Assessment of Arthritis Condition: Change from Baseline				
n	80	79	79	42
Adjusted Mean (SE)	-15.6 (2.29)	-18.1 (2.32)	-17.3 (2.31)	-27.0 (3.14)
Difference vs Placebo	-	-2.4	-1.7	-11.3
95% CI for Treatment Difference	-	-8.6, 3.8	-7.9, 4.6	-18.8, -3.9
Discontinuation from Study Due to Lack of Efficacy				
Completed	79 (93)	73 (91)	76 (94)	35 (83)
Prematurely Withdrawn	6 (7)	7 (9)	5 (6)	7 (17)
Withdrawn Due to Lack of Efficacy During the Treatment Phase	0	1 (1)	0	0
Withdrawn Due to Lack of Efficacy Outside the Treatment Phase	0	1 (1)	2 (2)	0
Withdrawn for Other Reasons	6 (7)	5 (6)	3 (4)	7 (17)

Pharmacokinetic and Pharmacodynamic Results: PK-PD analysis revealed no evidence for a relationship between GW842166 concentrations and changes from Baseline in WOMAC pain sub-score over time.

Safety Results: An on therapy treatment emergent AE was defined as an AE that emerged during treatment having been absent Pre-treatment, or worsened relative to the Pre-treatment state. An on therapy SAE was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication.

Summary of Common (>=5% incidence in any treatment group) Treatment-emergent Adverse Events	PBO N=89 n (%)	GW842166 100 mg OD N=88 n (%)	GW842166 350 mg OD N=88 n (%)	Naproxen 500 mg BID N=45 n (%)
Subjects with Any AEs	33 (37)	23 (26)	26 (30)	18 (40)
Headache	4 (4)	3 (3)	6 (7)	1 (2)
Fatigue	6 (7)	2 (2)	4 (5)	1 (2)
Dyspepsia	2 (2)	1 (1)	1 (1)	3 (7)
Osteoarthritis	0	3 (3)	1 (1)	3 (7)
Abdominal Pain Upper	1 (1)	0	0	3 (7)
Hypotension	1 (1)	0	0	3 (7)

Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	PBO N=89 n (%) [related]	GW842166 100 mg OD N=88 n (%) [related]	GW842166 350 mg OD N=88 n (%) [related]	Naproxen 500 mg BID N=45 n (%) [related]
Subjects with non-fatal SAEs	0	0	0	1 (2) [0]
Cystitis	0	0	0	1 (2) [0]
Subjects with fatal SAEs, n (%)	0	0	0	0

The incidence of AEs that were judged to be drug-related was highest in the naproxen group (24%) when compared to the other treatment groups (placebo: 18%, GW842166 100mg: 10%, GW842166 350mg: 14%) and the majority were mild to moderate in intensity.

There was no evidence of any clinically significant or medically important changes in any of the clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs or 12-lead ECG parameters either within the treatment groups or between the different groups.

Conclusions:

- The demographic characteristics of the study population were as expected and comparable across the different treatment groups. The average [osteoarthritis] disease duration was 8 years.
- For the primary endpoint (change from Baseline for WOMAC pain subscale score at Day 28 [LOCF]), there was no statistically significant treatment difference between placebo and the two doses of GW842166.
- Although there was no statistically significant separation between placebo and naproxen on the primary endpoint, there was a trend for an improvement in the mean WOMAC pain subscale scores at Day 21 and Day 28 of the study for the naproxen group, although the magnitude observed was lower than expected.

- For the secondary outcome variables, there was no statistical separation between placebo and either of the GW842166 treatment groups at Day 28 (LOCF). Similarly there was no evidence for any difference between placebo and the GW842166 treatments at any of the other time-points.
- With the exception of the WOMAC Stiffness Subscale Score, there was a trend for an improvement for the naproxen group across all the secondary endpoints when compared to placebo. The difference between naproxen and placebo was statistically significant for both the Patient's and Physician's Global Assessment of Arthritis Condition at day 28 (LOCF).
- Analysis of exploratory endpoints revealed a clear trend for a higher percentage of responders in the naproxen group (compared to the other treatment groups) measured by the Osteoarthritis Research Society International (OARSI) Index at each scheduled visit. There was no evidence for any differences between placebo and the GW842166 treatment groups.
- At all time periods examined, the proportion of subjects receiving rescue medication was similar across the placebo and the GW842166 treatment groups. However, there was a clear trend for a reduction in the proportion of subjects receiving rescue medication in the naproxen treatment group. Similarly, the mean and median total daily usage of rescue medication was less in the naproxen group than in the other treatment groups.
- The PP results differed from the ITT in that there was no difference from placebo observed in any treatment arm. Therefore the trend seen in the naproxen treated patients was lost.
- Exposure of GW842166 increased in a less than dose-proportional fashion, such that between doses of 100 mg and 350 mg GW842166, a 3.5 fold increase in dose, resulted in only an approximate 2 fold increase in GW842166 systemic exposure.
- PK-PD analysis revealed no evidence for a relationship between GW842166 concentrations and changes from Baseline in WOMAC pain sub-score over time.
- Overall, the data failed to identify any substantial difference between placebo and GW842166 (at either of the two dose levels studied) on any of the efficacy endpoints in this study. In contrast, although at a lower magnitude than expected, there were trends for superior efficacy in the naproxen group when compared to placebo across nearly all of the efficacy endpoints, suggesting that the trial methodology was successful.
- The incidence of treatment phase emergent AEs was higher in the placebo (37%) and naproxen (40%) groups than in the GW842166 treatment groups (100 mg [26%], 350 mg [30%]). There were no trends to indicate an increased incidence in any drug-related AEs in the GW842166 treatment groups.
- There was no evidence of any clinically significant or medically important changes in any of the clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs or 12-lead ECG parameters either within the treatment groups or between the different groups.

- GW842166, administered as either 100 mg or 350mg repeat doses for 28 days, was well tolerated and the study did not reveal any safety concerns.

Date of Report: July 2008