CLINICAL STUDY REPORT SYNOPSIS

Name of Sponsor/Company	Grünenthal GmbH; in codevelopment with /Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	to be determined	
Name of Active Ingredient(s)	CG5503/R1331333	

Protocol No.: KF5503/19 (R331333-PAI-2001) CR004183

Title of Study: A 4-week randomized, multicenter, double-blind, placebo- and active- controlled, parallel-group, forced-titration Phase 2b study comparing efficacy and safety of ascending doses of CG5503 prolonged release (PR) up to 233 mg twice daily (b.i.d.) and oxycodone prolonged release up to 20 mg b.i.d. to placebo in subjects with moderate to severe chronic pain due to osteoarthritis of the knee

Principal Investigator: Dr. Geoffrey Gladstein, M.D. - New England Research Associates, Trumball, CT; USA

Publication (Reference): none

Study Period: 14 July 2004 – 18 August 2005 | **Phase of Development:** 2b

Objectives: The primary objective was to assess the efficacy and safety of 2 titration regimens of orally administered CG5503 PR, up to 233 mg b.i.d. over 29 days, in comparison to placebo in subjects with moderate to severe chronic pain due to osteoarthritis of the knee.

The secondary objectives were

1 To generate data to be used to estimate the minimal effective dose of CG5503 PR,

2 To characterize and assess the pharmacokinetics of CG5503 PR, and

3 To generate data that will be used, in combination with data from other studies, to explore the population pharmacokinetic analysis and pharmacokinetic/pharmacodynamic analysis of CG5503 PR.

Methodology: This was a randomized, double-blind, parallel-group, forced-titration study that compared the efficacy and safety of 2 regimens of CG5503 PR (29 mg-58 mg-116 mg and 116 mg-175 mg-233 mg) b.i.d. and oxycodone CR 20 mg (controlled release, i.e., prolonged released) (10-10-20 mg) b.i.d. to placebo b.i.d. in subjects with moderate to severe chronic pain due to osteoarthritis of the knee. The study consisted of: screening period (duration up to 7 days), a washout period (duration 3 to 7 days; ending with Visit 2 and randomization), a double-blind active treatment period with titration [duration 14 days ending with Visit 4; subjects started with the lowest dose of the titration phase for the first 3 days and up-titrated to the intermediate dose on Day 4. Subjects were maintained at the intermediate dose for the next 11 days] and fixed-dose-maintenance [duration 14 days ending with Visit 6]. A follow-up visit occurred 2 to 5 days after Visit 6 or at the time of discontinuation. Rescue medication (paracetamol) was allowed during the washout period and during the active treatment period (maximum of 1000mg per day) except during the 24 hours preceding the assessment of pain intensity.

Number of Subjects (planned and analyzed): Planned: 568 subjects (142 per treatment group); randomized: 670 subjects; analyzed for safety (ITT): 665 subjects; analyzed for efficacy: full analysis set (ITT): 665 subjects; modified ITT analysis set: 647 subjects; and per-protocol analysis set: 544 subjects; and analyzed for PK: 460 subjects. A total of 461 subjects completed the study (placebo=127; CG5503 PR 116 mg=121; CG5503 PR 233 mg=101; and oxycodone 20 mg=112) and 204 discontinued (placebo=40; CG5503 PR 116 mg=41; CG5503 PR 233 mg=66; and oxycodone 20 mg=57). In the study, 102 subjects above the planned number were randomized. This was due to a number of centers initiated later in the study, and active recruitment efforts and advertisement. There were 102 subjects who were already screened at the sites at the time the decision to discontinue enrollment was made.

Diagnosis and Main Criteria for Inclusion: Subjects were men and women ≥40 years old with a clinical diagnosis of osteoarthritis of the knee based on American College of Rheumatology (ACR) criteria and functional capacity class of I to III with symptoms and/or radiographic criteria present for at least 3 months. Subjects had

unsatisfactory pain relief for 30 days prior to screening despite a dose regimen of nonsteroidal anti-inflammatory drugs (NSAIDS), cyclo-oxygenase 2 (COX 2)-inhibitors or acetaminophen as recommended in the product label. Subjects had OA of the knee with a pain intensity of ≥50 mm on the 100-mm visual analog scale (VAS) at the time of screening. Alternatively, subjects were included if they required regular treatments of opioids, including tramadol (i.e., on average >5 days/week), up to a maximum morphine equivalent dose of 50 mg per day during 3 months prior to screening. Subjects who previously used opioids were to have experienced a positive therapeutic benefit from these opioids and were to have a pain score ≤50 mm on a 100-mm VAS at the screening visit. In addition, subjects had OA of the knee that met the criteria for a flare state at the end of the washout period. Subjects in a flare state had an average pain intensity of ≥50 mm on a 100-mm VAS during the preceding 24 hours and an increase of ≥18 mm on the 100-mm VAS relative to the score at the start of the washout (Visit 1).

Test Product, Dose and Mode of Administration, Batch No.: CG5503 prolonged release film-coated oral tablets containing 29 mg, 58 mg, 116 mg, 175 mg or 233 mg GC5503. Batch numbers: PD1192, PD1193, PD1194, PD1195, and PD1196, respectively.

Reference Therapy, Dose and Mode of Administration, Batch No.: OxyContin®: controlled release oral tablets containing 10 mg oxycodone HCl CR. One capsule containing 10 mg or 20 mg oxycodone HCl CR from over encapsulation of 1 or 2 OxyContin 10 mg tablets. Batch numbers: PD1245 (10 mg) and PD1146 (20 mg).

Placebo: Oral tablets to match CG5503 PR and oral capsules to match oxycodone HCL CR encapsulated tablets. Batch numbers: PD1202 (matching CG5503 PR) and PD1244 (matching oxycodone)

Rescue medication: paracetamol/acetaminophen 500 mg tablets.

Duration of Treatment: Study medication was administered twice daily; Active treatment (28 days) that included the titration phase (14 days) and fixed-dose/maintenance phase (14 days).

Criteria for Evaluation:

Pharmacokinetics: Blood samples were drawn in order to investigate population kinetics for CG5503 PR and its glucuronide metabolite and for the comparator (oxycodone) in the target population. Blood samples were taken at Visit 2 (1 sample), Visit 4 (2 samples), Visit 6 (2 samples), and Follow-up Visit. If the subject agreed, a further blood sample was taken during the time period of the first 2 doses of any new titration dose. In the event of a serious adverse event, an additional pharmacokinetic-sample was taken for pharmacokinetic analysis of inter-individual variability and efficacy/safety data.

Efficacy: The primary efficacy endpoint was the average pain intensity over the preceding 24 hours evaluated at the final visit on the 100-mm VAS with 0 indicating no pain to 100 indicating worst pain imaginable. The secondary efficacy endpoint was the Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC) pain subscale score evaluated at the final visit. Exploratory analyses of the primary efficacy variable; the percentage of responders based on average pain intensity during the prior 24 hours evaluated at the final visit on the 100-mm VAS; WOMAC total score and WOMAC stiffness and physical function subscale scores; the current pain intensity measured twice daily on an 11-point Numeric Rating Scale (NRS) on the 2 days preceding Visits 2, 3, 4, 5, and 6; Subject's and Physician's Global Assessment of the investigational drug; Subject's Global Impression of Change; Short Form 36® Health Survey (SF-36®); EuroQuol-5 Dimension Health Questionnaire (EQ-5D®); Hospital Anxiety and Depression Scale (HADS); Pittsburgh Sleep Quality Index Questionnaire (PSQI); and rescue medication use.

Safety: Safety assessment was based on reported adverse events, clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), Functional Living Index - Emesis (FLIE), and Clinical Opiate Withdrawal Scale (COWS).

Pharmacokinetic/Pharmacodynamic Relationships: Population kinetics explored drug exposure and associated covariates; exploratory analyses examined possible relationships between pharmacokinetic data, primary efficacy findings, and selected safety results. These analyses are reported separately.

Statistical Methods: Statistical Methods: Evaluation of efficacy was performed for 3 populations: full analysis set preserving intent-to-treat principle (ITT), modified ITT and per protocol set. The full analysis set consisted of all randomized subjects who received any amount of study medication, and is equal to the safety analysis set. The per protocol set consisted of all randomized subjects who received study medication regularly and were compliant with the protocol as defined in the Statistical Analysis Plan. The modified ITT set consisted of all randomized subjects who received any amount of study medication and had at least one post baseline pain assessment.

The primary efficacy analysis was based on the full analysis set. Missing pain intensity values were replaced by carrying the last valid value (i.e., not assessed during the use of rescue medication) forward (last observation carried forward; LOCF). Evaluation of the primary endpoint was done by an analysis of covariance (ANCOVA) with the center and treatment factors and baseline as covariates. Dunnett's method for adjustment for multiple comparisons was used for the primary efficacy analysis. Exploratory subgroup analyses were performed for the

primary endpoint.

The secondary efficacy endpoint was analyzed using an ANCOVA with the factors treatment and center, and baseline as covariate. The secondary efficacy analysis was based on the full analysis set. The oxycodone CR 20 mg group was excluded from the analysis. If the analysis of the primary efficacy endpoint detected differences between the 2 CG5503 PR groups and placebo, then a many-to-one comparison according to Dunnett's method was applied to detect differences between the 2 CG5503 PR groups and placebo with respect to the secondary efficacy endpoint. If only 1 group of CG5503 PR differentiated from placebo with respect to the primary endpoint, then only for this group a pair-wise treatment comparison for the secondary efficacy endpoint was performed using Fisher's least significant difference (LSD). This method properly controls the type-I error rate on the secondary analysis.

Summary descriptive statistics and exploratory analyses are provided for the exploratory efficacy endpoints (WOMAC total score and WOMAC stiffness and physical function subscale scores, daily pain intensity, rescue medication usage, SF-36, EQ-5D, PSQI, and HADS); some comparison tests, Cochran-Mantel-Haenszel for Responder Analysis, Subject/Physician Global Assessments, and Subject Global Impression of Change; and ANCOVA and Fishers LSD for WOMAC total score and WOMAC stiffness and physical function subscale scores,

In order to evaluate the sensitivity of missing data imputation, Baseline Observation Carried Forward (BOCF) and Worst Observation Carried Forward (WOCF) were performed as exploratory analysis for the primary endpoint.

Descriptive statistics and frequency analysis (percentage of subjects) were used to assess safety.

Pharmacokinetic analysis of inter-individual variability was performed.

SUMMARY - CONCLUSIONS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS: A majority of subjects were female (62%), white (83%), and younger than 65 years of age (78%). In addition, most subjects did not have opioid treatment prior to the study (82%).

PHARMACOKINETICS: The mean serum concentrations of CG5503 base at all CG5503 PR dose levels were the highest during 0–4 hours after dosing. CG5503 serum and CG5503-O-glucuronide levels increased proportionally to CG5503 PR dose in the range of 29 mg b.i.d. to 233 mg b.i.d.

EFFICACY RESULTS: For the primary efficacy variable ('average pain intensity during the prior 24 hours' at endpoint based on the 100-mm VAS), the CG5503 PR 233 mg treatment group (40.0 mm) was clinically and statistically superior to placebo (49.0 mm) (p=0.021) as demonstrated on the VAS pain intensity scale. There was a numerical decrease indicating improvement in the CG5503 PR 116 mg and oxycodone 20 mg groups, but the decrease did not reach statistical significance in either group when compared with the placebo group.

A higher percentage of subjects in the placebo (77%), CG5503 PR 116 mg (75%), and oxycodone CR 20 mg (76%) groups than in the CG5503 PR 233 mg group (66%) took rescue medication during the double-blind treatment period. The median time to first rescue medication was 3.6 and 3.7 days in the CG5503 PR 116 mg and CG5503 PR 233 mg groups, respectively, compared with 2.5 days in the placebo group.

Overall, the SF-36 Health Survey findings suggested that CG5503 PR 233 mg has a more positive effect in short term health status than placebo in the domains expected to be affected in OA (i.e., physical functioning and bodily pain). Positive effects on these domains were not observed in the comparison of oxycodone CR 20 mg and placebo. A small, but statistically significant negative effect on mental health was observed for both CG5503 PR 233 mg and oxycodone CR only at endpoint. It is also of interest that negative effects were observed in the domains of vitality and social functioning for oxycodone CR at Day 29 and endpoint (last available assessment) and not with the CG5503 PR treatment groups. The reason for these differences is not readily apparent.

Comparison between CG5503 PR 233 mg and oxycodone CR 20 mg showed a positive effect for CG5503 PR 233 mg in physical functioning (Day 15 and endpoint), bodily pain (Day 15, Day 29 and endpoint [last available assessment]), and general health (Day 29 and endpoint). While these differences are small and cover a brief time period, they suggest that CG5503 PR 233 mg may have beneficial effects over oxycodone CR 20 mg in the areas of high concern to subjects with OA. These outcomes should be explored in more detail in future studies.

For the EQ-5D Sum of Index, a statistically significant (nominal p=0.018) difference between the CG5503 PR 233 mg group and the placebo group was observed at Day 29. There were no differences between the CG5503 PR 116 mg group and the placebo group. For the individual dimensions, small but significant differences favoring CG5503 PR 233 mg compared to placebo were observed in 'mobility' at Day 15 and for 'pain/discomfort' at Day 15, Day 29, and endpoint (last available assessment). There were no differences between the CG5503 PR 116 mg group and the placebo group for the Sum of Index score or any of the individual dimension scores.

There were no differences in the mean changes from baseline in the component or global score for the Pittsburgh Sleep Quality Index Questionnaire among the 4 treatment groups. At endpoint, the percentage of subjects that had a global score >5 (suggesting significant sleep disturbance) were similar among the 3 active treatment groups (52%, 53%, and 57% in the CG5503 116 mg, CG5503 PR 233 mg, and oxycodone CR 20 mg groups, respectively), and each was higher than in the placebo group (41%). However, the findings were difficult to interpret. The subject responses were qualitative, and there was a 1-month recall period that made it difficult for subjects to accurately record the quality of sleep. The findings suggest that the PSQI may not be an appropriate instrument to measure sleep quality in this setting.

No significant differences in mean changes from baseline to endpoint in either of the CG5503 PR groups compared with placebo were noted for any of the HADS scores.

SAFETY RESULTS: One subject in the placebo group died. Seven subjects had serious adverse events: 2 subjects in the placebo group and 2 subjects in the oxycodone CR 20 mg group and no subjects in the CG5503 PR groups had serious TEAEs; 3 subjects had serious adverse events that began prior to the first dose of study medication (i.e., non TEAEs). None of the serious TEAEs were considered by the investigator or the sponsor to be related to study medication.

The overall incidence of TEAEs associated with discontinuation was higher in the CG5503 PR 233 mg (23%) and oxycodone CR 20 mg (23%) groups compared to the CG5503 PR 116 mg (6%) and the placebo (6%) groups. The most common TEAEs that led to study discontinuation were nausea, vomiting, somnolence, and dizziness, with a similar distribution pattern in the CG5503 PR 233 mg and oxycodone CR 20 mg groups. The incidence of constipation in the CG5503 PR 233 mg group (10%) was substantially lower compared to the oxycodone CR 20 mg group (20%).

There were no clinically important treatment-related changes in laboratory values, vital signs, or ECG findings. There was no dose-related association with CG5503 PR administration on these parameters.

Based on the FLIE results, the gastrointestinal profile (nausea and vomiting) for CG5503 PR 233 mg group had a comparable profile to the oxycodone CR 20 mg group. The COWS score indicated that a low percentage of subjects in the CG5503 PR groups had mild withdrawal (CG5503 PR 116 mg: 1% and CG5503 PR 233 mg: 7%), with an indication of possible dose-effect relationship. No subject treated with CG5503 PR had moderate withdrawal when treatment was discontinued. The CG5503 PR 233 mg and oxycodone CR 20 mg groups were similar in their response to withdrawal of treatment.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: The full pharmacokinetic-pharmacodynamic relationships are provided in a separate report.

CONCLUSION: CG5503 PR 233 mg was effective when administered in a fixed-dose design for up to 4 weeks in subjects with moderate to severe chronic pain due to osteoarthritis. The results of this study suggest a dose-response relationship with efficacy demonstrated at doses as low as CG5503 PR 175 mg b.i.d. The safety profile of CG5503 PR is consistent with the profile expected for an opioid but with reduced incidence of constipation, which can be an important benefit for the overall tolerability of CG5503 PR. No clinically important safety signals were evident with CG5503 PR compared with placebo. These observations indicate that the analgesic effect of CG5503 has been demonstrated with a favorable tolerability profile in subjects with moderate to severe chronic pain due to osteoarthritis. These findings need to be confirmed in larger Phase 3 studies.

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