CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Grünenthal GmbH/Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	
Name of Finished Product	To be determined	
Name of Active Ingredient(s)	CG5503/R331333	

Protocol No.: R331333-PAI-2003 (KF5503/22)

Title of Study: A randomized, double-blind, parallel-arm, placebo and active controlled dose-ranging study of the efficacy and safety of multiple doses of CG5503 IR for postoperative pain following bunionectomy surgery

Coordinating Investigator: Stephen E. Daniels, D.O. – 3200 Red River, Suite 300, Austin, Texas, 78705; USA

Publication (Reference): None

Study Period: 28 January 2005 to 19 August 2005 | **Phase of Development:** 2b

Objectives: The objective of this study was to evaluate the efficacy and safety of various oral multiple dose CG5503 immediate release (IR) regimens for the treatment of postoperative pain over a period of 12 hours on the first day following bunionectomy.

The primary objective was to demonstrate that the analgesic effect, as measured by the sum of total pain relief and sum of pain intensity difference over 12 hours ($SPRID_{12}$), of at least 1 of the treatment regimens of CG5503 IR is superior to placebo in the bunionectomy model, when studied in the first postoperative day.

Secondary objectives included evaluation of the following parameters across treatment regimens: a) dose-response relationships after the first dose of the study medication by determining any differences at 4 hours among values for total pain relief and sum of total pain intensity difference ($SPRID_4$), sum of pain intensity difference ($SPID_4$), and total pain relief ($TOTPAR_4$), b) differences in pain relief (PAR), categorical pain intensity difference (PID), PID according to visual analog scale (VAS) (VPID), time to first supplemental pain medication in the double-blind treatment period, and Subject Global Evaluation, c) onset and duration of effect of the first dose, d) differences at 8 and 12 hours in categorical SPID, SPID according to a visual analog scale (VSPID), and TOTPAR, e) tolerability and safety, and f) drug pharmacokinetics and pharmacodynamics.

Methodology: This was a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled dose study with multiple doses of CG5503 IR for post-operative pain following a bunionectomy. The study consisted of 4 phases: screening (2 to 28 days before surgery), surgical period (up to 30 hours, including a standardized first metatarsal bunionectomy and postsurgical analgesic procedures), baseline randomization followed by double-blind treatment for 12 hours, and posttreatment, including discharge evaluation and a final visit 5 to 9 days after surgery. Six treatment groups received study medications at 0, 4, and 8 hours with the following dosing regimen: 1) placebo, placebo, and placebo (placebo treatment group) 2) 93 mg, 93 mg, and 93 mg CG5503 IR (CG5503 IR 93 mg treatment group), 3) 140 mg, 140 mg, and 140 mg CG5503 IR (CG5503 IR 140 mg treatment group), 4) 140 mg, 70 mg, and 70 mg CG5503 IR (CG5503 IR 140/70 mg treatment group), 5) 186 mg, 93 mg, and 93 mg CG5503 IR (CG5503 IR 186/93 mg treatment group), and 6) 10 mg, 10 mg, and 10 mg oxycodone IR (oxycodone IR 10 mg treatment group).

Number of Subjects (planned and analyzed): Planned: 480 (80/group); analyzed for efficacy: intent-to-treat analysis set (ITT): 480 subjects; analyzed for safety (ITT): 480 subjects; analyzed for PK: 480 subjects**.** Four hundred, eighty subjects were randomized to the 6 treatment groups in a 1:1:1:1:1:1 ratio (79 subjects in placebo, 80 in CG5503 IR 93 mg, 79 in CG5503 IR 140 mg, 82 in CG5503 IR 140/70 mg, 79 in CG5503 IR 186/93 mg, and 81 in oxycodone IR 10 mg groups). Of the 480 subjects randomized, 185 subjects completed the study and 295 subjects withdrew from the study.

Diagnosis and Main Criteria for Inclusion: Study subjects were men and nonpregnant, nonlactating women at least 18 and no more than 75 years of age with moderate to severe pain intensity (categorical) and a pain intensity (VAS) ≥ 40 mm after at least 10 hours following the start of surgery and within 9 hours of discontinuation of a popliteal block or permitted systemic analgesics during postoperative surgical period.

Test Product, Dose and Mode of Administration, Batch No.: Size-0, elongated, blue capsules containing 70, 93, 140, or 186 mg CG5503 (HCl salt) corresponding to 60, 80, 120, and 160 mg free base, respectively. Batch numbers: 26120211-AAC-B-004, 26120211-AAC-B-003, 26120211-AAC-B-002, and 26120211-AAC-B-001, respectively. Capsules were orally administered.

SYNOPSIS (CONTINUED)

Reference Therapy, Dose and Mode of Administration, Batch No.: Two oxycodone tablets (5 mg) were over-encapsulated in size-0, elongated, blue capsules. Batch number: 80000-000-B-015Y. Placebo capsules matched CG5503 IR and oxycodone IR capsules. Batch number: 90000-000-B-030X. Both orally administered.

Duration of Treatment: Study medication was administered at 0, 4, and 8 hours after randomization, which occurred within 9 hours of discontinuation of a popliteal block or permitted systemic analgesics during postoperative surgical period.

Criteria for Evaluation:

Pharmacokinetics: Venous blood samples were collected during the double-blind treatment (Day 1) 0, 1, 1.5, 4, 8, and 12 hours after administration of the first dose of study medication to determine serum CG5503 base, CG5503-glucuronide, and oxycodone concentrations. The pharmacokinetic samples for the 4 and 8 hour time points were taken before the administration of the second and third doses of study medication, respectively.

Efficacy: SPRID at 12 hours was the primary efficacy variable, which included the effects of drug exposure over the entire double-blind treatment period, integrating both cumulative PID and PAR. Secondary variables were used to assess the total effect, peak effect, onset of effect, duration of effects, and overall response to the proposed dosing regimens. Pain scale variables included the following: a) PID, VPID, PAR, and PRID at each observation time point (0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, and 12 hours after the first dose), b) total effect in terms of TOTPAR, SPID, and VSPID (4, 8, and 12 hours) and SPRID (4 and 8 hours), and c) peak effect in terms of peak PID, VPID, and PAR. Onset of effect was evaluated by measuring times to perceptible pain relief, meaningful pain relief, and confirmed perceptible pain relief. Duration of effect was determined based on time to rescue medication. A global assessment of the drug effect was conducted prior to discharge.

Safety: Safety and tolerability assessments were based on adverse events and changes in clinical laboratory tests, vital signs (heart rate, temperature, blood pressure, respiratory rate, and SpO_2), physical examination, and 12-lead ECG.

Pharmacokinetic/Pharmacodynamic Relationships: The relationship between efficacy parameters ($SPRID_4$, $SPRID_8$ and $SPRID_{12}$) and serum concentrations of CG5503 base at 4, 8, and 12 hours after administration were explored by graphical methods.

Pharmacogenomics: Deoxyribonucleic acid (DNA) samples were taken during the surgical period prior to administration of study medication to analyze genes associated with CG5503 or pain that may influence pharmacokinetics, efficacy, safety, or tolerability.

Statistical Methods:

Pharmacokinetics: Descriptive statistics of the serum concentration of CG5503 base, CG5503-O-glucuronide and oxycodone were used to assess pharmacokinetics.

Efficacy: The primary efficacy hypothesis was tested by comparing each of the 4 CG5503 IR regimens with placebo. The primary efficacy analysis on the primary variable ($SPRID_{12}$) was an analysis of variance (ANOVA) with the factors of treatment (excluding oxycodone IR 10 mg), center, and baseline PI (categorical). A many-to-one comparison according to Dunnett was applied to detect differences between each CG5503 IR group and the placebo group. The treatment effect was estimated by the least square means of the difference. This analysis was repeated for the 2 baseline PI groups (moderate and severe) separately without including baseline PI in the ANOVA model. Descriptive statistics (n, mean, standard deviation, median, and range) are provided for the primary efficacy variable for each of the following subgroups: sex, race, age group, and baseline PI (categorical). Assay sensitivity of the model was performed based on ANOVA including factors of treatment (all treatments included), center and baseline PI.

The intent-to-treat (ITT) analysis set included all randomized subjects who received at least 1 dose of study medication after randomization and was used for the efficacy analysis.

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

The intent-to-treat (ITT) analysis set included all randomized subjects who received at least 1 dose of study medication after randomization and was used for the safety analysis.

SYNOPSIS (CONTINUED)

Pharmacokinetic/Pharmacodynamic Relationships: The relationship between efficacy parameters ($SPRID_4$, $SPRID_8$ and $SPRID_{12}$) and serum concentrations of CG5503 base at 4, 8, and 12 hours after administration were explored by graphical methods.

Pharmacogenomics: No analysis or formal statistical tests were performed.

SUMMARY - CONCLUSIONS

DEMOGRAPHIC AND BASELINE CHARACTERISTICS: Most subjects were either white (66%) or Hispanic (25%). As would be expected for typical bunionectomy candidates, a majority of subjects across the treatment groups were female (87%) and <65 years of age. The remaining demographic and baseline characteristics were similar across the treatment groups.

PHARMACOKINETICS: Depending on the time of the observation, the intersubject variability for measured CG5503 base and CG5503-O-glucuronide serum concentrations was between 30 to 85%, and 25 to 76%, respectively, and for oxycodone between 38 to 75%. The time to maximum serum concentration for CG5503 base was between 1 and 1.5 hours after administration of 93 mg, 140 mg, and 186 mg. A dose proportional increase in serum concentration was observed. Twelve hours after the first dose administration, the mean serum concentration was comparable in both CG5503 IR 93 mg and CG5503 IR 186/93 mg treatment groups (i.e., with and without a loading dose of 186 mg).

EFFICACY RESULTS: Primary efficacy variable: $SPRID_{12}$ showed statistically significantly improvement in pain for all CG5503 IR treatment groups compared to placebo (all p-values < 0.001, Dunnett's procedure). The mean $SPRID_{12}$ values were 38.4, 35.8, 33.6, and 32.3 in the CG5503 IR 140 mg, CG5503 IR 186/93 mg, CG5503 IR 140/70 mg, and CG5503 IR 93 mg groups, respectively, compared to 11.5 with placebo. Oxycodone IR 10 mg (mean $SPRID_{12}$: 26.4) also showed a statistically significant difference from placebo ($p<0.001$), thus validating the assay sensitivity of this study design.

Secondary efficacy variables: A statistically significant improvement in pain ($p<0.001$) was shown for all CG5503 IR groups compared to placebo for $SPRID_4$, $SPRID_8$, $SPID_4$, $SPID_8$, $SPID_{12}$, $TOTPAR_4$, $TOTPAR_8$, $TOTPAR_{12}$, time to meaningful pain relief, time to confirmed first perceptible pain relief, time to first rescue medication, and Subject's Global Evaluation of study medication. In addition, all CG5503 IR groups showed a numerical improvement in pain compared to placebo for the secondary efficacy variables of PID, VPID, PAR, PRID, peak PID, peak VPID, and peak PAR.

Exploratory efficacy analysis: The percentage of subjects who demonstrated ≤30% improvement in pain intensity (categorical or VAS) from baseline was numerically higher for all CG5503 IR treatment groups compared to placebo and oxycodone IR groups at both 4 and 12 hours.

Based on the values from the efficacy variables of $SPRID_4$, $SPID_4$, and $TOTPAR_4$, a positive dose response trend was observed during the first 4 hours following the first administration of study medication (i.e., 93 mg, 140 mg, and 186 mg CG5503 IR).

$SPID_{12}$ and PID over time showed improvement in pain for all CG5503 IR groups compared to placebo regardless of the imputation strategy used (LOCF or BOCF).

The robustness of CG5503 IR efficacy was not only demonstrated by consistency of outcome across efficacy variables but also based on efficacy regardless of the imputation used or subgroups analyzed.

Although statistical comparisons between oxycodone IR 10 mg and CG5503 IR were not performed, the CG5503 IR groups had a consistent trend of better qualitative outcome compared to oxycodone IR 10 mg on all efficacy variables with the exception of the times to perceptible pain relief, meaningful pain relief and confirmed perceptible pain relief.

SAFETY RESULTS: CG5503 IR was generally well tolerated with a safety profile typical for an opioid. All of the CG5503 IR groups, as well as, the oxycodone IR 10 mg group showed a similar overall incidence of treatment-emergent adverse events (TEAEs) that were higher than in the placebo group. The TEAEs reported in at least 5% of subjects in the CG5503 IR groups were typical opioid-related events of nausea, dizziness, vomiting, and somnolence. The incidence of opioid-related TEAEs of nausea, vomiting, and dizziness were similar between CG5503 IR 93 mg and oxycodone IR 10 mg groups, whereas the CG5503 IR 140 mg, CG5503 IR 140/70 mg, and CG5503 IR 186/93 mg groups showed a higher incidence compared to oxycodone IR 10 mg.

SYNOPSIS (CONTINUED)

No subjects died during the study or within 30 days of last treatment. Two subjects had serious adverse events within 30 days of the last treatment with study medication; both of which occurred more than 2 days after the last dose: 1 subject in the CG5503 IR 140/70 mg group had hypoaesthesia and 1 subject in the oxycodone IR 10 mg group had pyelonephritis and urosepsis.

There was a low percentage of subjects with TEAEs associated with discontinuation across the treatment groups (3% with CG5503 IR 140 mg, 2% with CG5503 IR 140/70 mg, and 3% with CG5503 IR 186/93 mg). Most of the TEAEs that led to treatment discontinuation were opioid-related including nausea, vomiting, dysphagia, somnolence, dizziness, and dysphasia.

Examination of individual values revealed no clear or consistent pattern of treatment-related changes in laboratory and urinalysis values, vital signs or ECG findings. The incidence of changes was low and there were no apparent dose-related associations with CG5503 IR administration.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS: There appeared to be no apparent relationship between serum concentrations of CG5503 base at 4, 8, and 12 hours after drug administration and SPRID values.

CONCLUSION: CG5503 IR, administered every 4 hours in a fixed- (CG5503 IR 93 mg or CG5503 IR 140 mg) or a loading-dose regimen (CG5503 IR 140/70 mg or CG5503 IR 186/93 mg), was effective in the treatment of moderate to severe acute pain during a 12-hour period on the day following a bunionectomy compared to placebo. Doses of 93 mg and 140 mg were efficacious with no apparent efficacy advantage above 140 mg within a 4 hour period, suggesting that the 140 mg dose may be approaching the upper end of the useful dose range in this model of acute pain. All CG5503 IR dosing regimens were well tolerated with a safety profile similar to other opioid analgesics.

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