

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-304

MEDICAL REVIEW(S)



FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANALGESIA, ANESTHESIA, AND RHEUMATOLOGY PRODUCTS
10903 NEW HAMPSHIRE AVENUE, BLDG 22, SILVER SPRING, MARYLAND 20993

Memorandum: Labeling Addendum

DATE: November 20, 2008

RE: Labeling addendum

NDA: 22-304
Tapentadol

THROUGH: Sharon Hertz, M.D., Deputy Directory, DAARP

FROM: Robert Shibuya, M.D., Medical Team Leader, DAARP
Ellen Fields, M.D., MPH, Medical Team Leader, DAARP

This memorandum will summarize the resolution of three labeling issues for NDA 22-304, tapentadol tablets.

1. Serotonin syndrome
The clinical trial database was searched for the term "serotonin syndrome" and sign/symptom complexes suspicious for serotonin syndrome, and no cases were identified. The pharmacology of tapentadol reflects primarily selective norepinephrine reuptake inhibition and mu opioid agonism, however there is serotonin reuptake inhibition as well, albeit to a lesser extent. Taken in concert with the potential level of morbidity and mortality associated with serotonin syndrome, we felt that appropriate language regarding serotonin syndrome should be placed into the Warnings and Precautions section of the labeling.
2. Contraindication for concomitant use of monoamine oxidase inhibitors
Although patients receiving MAOIs were not included in the clinical trials of tapentadol, because of the pharmacology of tapentadol and the applicant's concerns about this risk, this contraindication was included in the product labeling.

3. Medication Guide

In their review of the abuse liability data, the Controlled Substance Staff noted that studies with tapentadol had findings consistent with a very high abuse liability (similar to hydromorphone). Despite the fact that tapentadol is likely to be classified in Schedule II by the Drug Enforcement Administration, additional patient education is considered prudent and necessary to mitigate abuse. Hence, a Medication Guide (and subsequently a REMS) has been added to the labeling for tapentadol.

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/s/

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11/20/2008 01:36:24 PM
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CLINICAL REVIEW N 22-304 Tapentadol



**Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology
Products, HFD-170
10903 New Hampshire Avenue, Silver Spring, MD 20993**

Medical Officer Review

Date of Submission: January 23, 2008

Type of Submission: New Drug Application

Product: Tapentadol™

Sponsor: Johnson & Johnson

Review Date: September 18, 2008

PDUFA Date: November 23, 2008

Reviewer: Ellen W. Fields, M.D., M.P.H.
Clinical Team Leader

Project Manager: Matthew Sullivan

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1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

I recommend approval for tapentadol HCL IR for the management of acute moderate-to-severe pain in adults. Efficacy was demonstrated at doses of 50mg, 75mg, and 100mg, using a dosing interval of every 4 to 6 hours in two adequate and well-controlled clinical trials. These trials examined subjects with moderate-to-severe pain following a bunionectomy or due to end-stage degenerative joint disease. Efficacy was supported by the improvement of pain compared to placebo across several standard pain assessments and by using different imputation methods.

The safety profile of tapentadol HCL IR was demonstrated in over 3500 treated subjects. The adverse event profile appeared acceptable across the intended marketed dosage range in both inpatients and outpatients. The profile of adverse events is consistent with a centrally acting compound with mu-opioid agonist activity.

The dosing recommendations are acceptable based on data from Phase 2 and 3 studies. No dosing adjustments are recommended for the elderly, or patients with hepatic or renal impairment; however tapentadol IR is not recommended for patients with severe renal or hepatic impairment. Details regarding dosing are located in Section 4.4.

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1.2 Risk Benefit Analysis

The efficacy of tapentadol IR was demonstrated at doses of 50mg, 75mg, and 100mg, using a dosing interval of every 4 to 6 hours in two adequate and well-controlled clinical trials. These trials were carried out in two distinct patient populations; an inpatient post-operative population who experienced moderate-to-severe acute pain following bunionectomy procedures, and an outpatient population with end-stage osteoarthritis of the hip or knee (awaiting joint replacement) who also had moderate-to severe pain, although chronic in nature.

The endpoints for both studies were based on the summed pain intensity difference (SPID) from baseline to endpoint, 48 hours in the bunionectomy study and 5 days in the OA study. SPIDs are used frequently and are acceptable for the analysis of analgesic efficacy for acute pain. The analyses showed significance at the $p < 0.001$ level for the two studies using imputation methods that included last observation carried forward (LOCF), baseline observation carried forward (BOCF), and worst observation carried forward (WOCF).

In the bunionectomy study, there was a trend of increasing efficacy with increasing tapentadol dose (50mg, 75mg, 100mg). In addition, between 65% and 79% of the

tapentadol-treated subjects experienced at least a 30% improvement in pain intensity at 48 hours compared to 40% of the placebo treated patients, which further supports the finding of efficacy. In the OA study, there was not a dose related increase in efficacy from 50mg to 75mg. The proportion of subjects who showed at least 30% improvement in pain intensity at Day 5 was 30% in the placebo group, and 43% and 41% in the tapentadol IR 50 mg and 75 mg groups, respectively. The subjects in the OA study had a high rate of concomitant non-opioid analgesic use, which may have affected the results of the study and the less impressive treatment effect. Nonetheless, tapentadol was found to be efficacious in both populations.

In terms of safety, the premarketing exposure to tapentadol IR (>3500 subjects) appears adequate. There were no deaths attributable to tapentadol IR, and no unexpected or unusual adverse events of interest.

Tapentadol IR was found to have a safety profile very similar to that of other immediate-release opioid analgesics and tramadol to which it tapentadol is structurally related. Common adverse events included nausea, dizziness, vomiting, somnolence, headache, constipation, pruritis, and asthenic conditions. As expected, the incidence of treatment emergent adverse events appeared to be dose-related. There were no important laboratory or ECG related adverse events, and the only vital sign seemingly affected by tapentadol was oxygen saturation as measured by pulse oximetry. A thorough QT study was negative.

In a Phase 1 study, tapentadol IR was found to have an abuse liability similar to hydromorphone. In addition, when subjects in a Phase 3 study abruptly discontinued treatment with tapentadol IR, 17% experienced at least one withdrawal symptom, and 1% experienced a withdrawal syndrome. There were no reports of overdose during the development program.

The risk/benefit analysis for tapentadol IR is similar to that of other opioid analgesics and Tramadol. Tapentadol IR appears to be effective in the treatment of acute moderate-to-severe pain as studied in two distinct populations. Given its safety profile, the risks of tapentadol IR appear manageable by standard pharmacovigilance approaches and the proposed DEA Schedule II status.

As there were no issues identified related to CMC, Pharmacology/toxicology, or Biopharmaceutics that would affect the approvability of tapentadol, and given the clinical risk/benefit analysis, I recommend approval for tapentadol IR for the treatment of moderate-to-severe acute pain.

1.3 Recommendations for Postmarketing Risk Management Activities

A "Tapentadol IR Safety Surveillance Plan" was submitted by the Applicant with this NDA, which was reviewed by the Division of Drug Risk Management (DRISK, June 26, 2008).

The Applicant identified important and potential risks associated with tapentadol IR as follows:

Table 1: Summary of Safety Concerns

Safety Concerns
Important identified risks:
Potential for abuse
Seizure
Important potential risks:
Overdose
Off-label use, incl. pediatric patients
Potential for medication errors (inappropriate prescribing, inappropriate dosing, inappropriate use) and patient misuse
Accidental exposure
Diversion
Important missing information:
Use in pediatrics

Source: Tapentadol IR Safety Surveillance Plan

A plan was proposed that will include routine and product specific pharmacovigilance.

The Division agrees with DRISK's review of the plan. The risks associated with the use of tapentadol HCL IR are similar to the risks of other immediate-release opiate products indicated for the treatment of pain with potency similar to morphine IR and oxycodone IR. It is appropriate to manage the risks of tapentadol HCL IR with labeling and routine pharmacovigilance. At this time, the establishment of a risk evaluation and mitigation strategy (REMS) for this product is not recommended.

1.4 Recommendation for other Postmarketing Study Commitments

In order to comply with Pediatric Research Equity Act of 2007 (PREA), the Applicant submitted a Pediatric Plan and staged deferral request with this NDA. They propose to begin clinical studies in the oldest age group ([] years of age) approximately ([]) following approval of the adult indications in acute pain, to take advantage of available safety information from both the preclinical juvenile program and the adult postmarketing database. Trials will be conducted in a step-wise manner to gather adequate pharmacokinetic, safety and efficacy information in the older children before exposing younger age groups. This staged deferral proposal will expose the minimum number of children and will allow the ability to perform the necessary clinical studies that will support information on dosing tapentadol in the pediatric population.

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The Pediatric Plan and deferral request will be reviewed by PERC on October 8, 2008.

No additional postmarketing study commitments are recommended at this time.

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

Tapentadol HCl is a novel centrally-active antinociceptive agent being developed in an immediate-release (IR) tablet formulation for the relief of moderate-to-severe acute pain.

It appears to have a dual mode of action, being both a μ -opioid receptor (MOR) agonist and an inhibitor of norepinephrine (NE) (re)uptake. Both mechanisms are likely to contribute to the analgesic effects of the compound.

- Description of the product: Immediate-release oral tablet; 50, 75, and 100mg doses
- Established name and proposed trade name: Tapentadol HCL (no proposed tradename at this writing)
- Chemical class: New molecular entity
- Pharmacological class: Centrally acting analgesic (opioid plus SNRI)
- Applicant's proposed indications, dosing regimens, age groups: Relief of moderate-to-severe acute pain in adults; 50mg, 75mg, or 100mg every 4 to 6 hours as needed

2.2 Table(s) of Currently Available Treatment(s) for Proposed Indication(s)

Multiple products are available for the treatment of moderate-to-severe acute pain, including immediate-release opioids, prescription strength NSAIDs, and tramadol.

2.3 Availability of Proposed Active Ingredient in the United States

This product is not marketed in or outside the United States.

2.4 Important Issues with Consideration to Related Drugs

Tapentadol is a centrally-acting synthetic analgesic combining opioid and non-opioid activity, similar to Tramadol. Both drugs appear to have mu-receptor agonist activity combined with inhibition of norepinephrine reuptake. Consequently, both drugs have adverse events common to other mu-receptor agonists and SNRIs.

A serious risk associated with Tramadol is the occurrence of seizures, which have been reported in patients receiving Tramadol within the recommended dosage range. Spontaneous post-marketing reports indicate that seizure risk is increased with doses of Tramadol HCL above the recommended range, and the risk of seizure is increased in patients taking SSRIs, tricyclic antidepressants, or other opioids. Administration of tramadol may enhance the seizure risk in patients taking MAO inhibitors, neuroleptics, or other drugs that reduce the seizure threshold.

Concomitant use of Tramadol with MAO inhibitors and SSRIs also may increase the risk of serotonin syndrome.

Tramadol and other opioid analgesics are associated with known and potentially serious adverse events of respiratory depression, withdrawal, physical dependence and abuse, and the risk of overdose. Labels include warnings regarding concomitant use with CNS depressants such as alcohol, opioids, anesthetic agents, narcotics, phenothiazines, tranquilizers or sedative hypnotics.

The common adverse event ($\geq 5\%$ incidence) profile for Tramadol includes dizziness, nausea, constipation, headache, somnolence, vomiting, pruritus, CNS stimulation, asthenia, sweating dyspepsia, dry mouth and diarrhea. These are also seen commonly with other opioid analgesics.

Drug abuse, dependence, overdosage and withdrawal are important safety concerns associated with Tramadol and other Schedule II opioid analgesics.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

Important aspects of the presubmission regulatory activity for this NDA are described below.

Pre-IND Meeting, November 17, 2000

- Efficacy must be addressed in multiple-dose studies.
- CMC requirements outlined
- Pharmacokinetic study requirements outlined
- CSS requirement outlined, including binding studies to identify site of action in the brain, effect of route of administration of product on behavior and bioavailability, assessment of abusability of formulation, studies in subjects with a history of drug abuse to assess drug discrimination, self-administration, and drug abuse liability.

Response to Applicant's Questions in Writing, March 28, 2005

- The highest and lowest doses to be marketed, as well as dosing regimen, must be demonstrated to be safe and effective in a clinical trial. Modeling and simulation may suffice for intermediate doses.

Type C Meeting, December 16, 2005

- Division agreed that a bioequivalence study bridging the capsule and tablet formulation to be used in the Phase 3 program is adequate.
- The information provided to the Division suggested that 46mg CG5503 IR could be the minimum target dose for Phase 3, as it was approximately the minimal efficacious dose found in bunionectomy patients.
- The choice of 93mg of CG5503 IR appeared reasonable as a maximum target dose for Phase 3; however the Applicant could consider exploring a slightly higher dose.
- Division agreed that a flexible dosing interval of Q4 to 6 hours would be acceptable in a Phase 3 study as long as the timing of doses was carefully captured and analyzed.
- Labeling instructions to patients to take a second "reloading" dose as soon as one hour after initiating treatment (for insufficient analgesia) is acceptable as long as it was studied in that manner and the data support the benefit and safety of such use.
- In general the use of rescue medication in analgesic trials is encouraged, and when used should be accounted for in the efficacy analysis.

- A minimum of three to five days of treatment is recommended to support a finding of efficacy.
- Onset of action should be defined using the double stopwatch method
- To support proposed dosing interval, median time to remedication should be determined
- More than one patient population should be studied to support a finding of efficacy for acute pain since this product is an NME.
- The proposed endpoint for the pivotal Phase 3 trials, SPI-12, is not acceptable. The endpoint should be modified to address the effect of study drug on pain intensity over three to five days (e.g., SPID48).
- LOCF is not adequate as the method for imputing missing data in the primary efficacy analysis. The method of imputation should assign a bad score to patients who drop out of the study early regardless of reason, such as BOCF. Another approach is use of a continuous responder analysis.

Pre-NDA Meeting, June 5, 2007

- The Sponsor's non-clinical package appears adequate for the NDA submission
- The types of clinical pharmacology studies conducted appear adequate.
- The Division agreed with the Applicant's proposed PK/PD/AE analysis.

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- Study population and primary endpoint for study KF5503/33 are acceptable.
- Studies KF5503/32 and KF5503/33 appear to be sufficient to support filing an application for treatment of moderate to severe acute pain.
- Regarding the SAP, as stated during the December 16, 2005 meeting, LOCF is not adequate as the method for imputing missing data in the primary efficacy analysis. A conservative strategy should be used, such as BOCF. The Applicant stated they wished to retain LOCF as the primary analysis, but would conduct BOCF as a sensitivity analysis. The Division stated that a positive study using LOCF that fails more conservative imputation methods will not be considered adequate demonstration of efficacy and will not support approval.

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- A summary of safety from studies of the ER formulation must be provided.

- A proposal for scheduling must be provided with justification.
- All information and data related to abuse liability must be provided.
- A formal RiskMAP is not required for tapentadol IR, however a careful pharmacovigilance program should be formulated.

2.6 Other Relevant Background Information

This product is not approved or marketed outside the United States.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

This submission appeared to be of good quality. It was well organized and easily navigated. A number of information requests were sent to the Applicant for tables and clarifications; however no additional datasets were requested.

3.2 Compliance with Good Clinical Practices

The Division of Scientific Investigations (DSI) conducted routine inspections of 4 study sites involved in studies KF5503/32, KF5503/33, and KF5503/34. The study sites were selected based on the number of enrolled study subjects. DSI inspected the following investigators:

Table 2

Name of CI, IRB, or Sponsor site # and location	Protocol	Inspection Dates	Final Classification
Richard A. Pollak M.D. San Antonio, TX	KF5503/ 32	5/13-19/08	NAI
Ira J. Gottlieb, M.D. Pasadena, MD	KF5503/ 32	5/27-29/08	VAI
James P. Beretta, M.D. Birmingham, AL	KF5503/ 34	6/3-5/08	VAI
Marc Afilalo, M.D. Montreal, QC H3T1 E7 Canada	KF5503/ 33	7/14-17/08	NAI

Source: Evaluation of Clinical Inspections, DSI, September 10, 2008

According to the DSI review, the data from all inspected sites appear acceptable in support of the pending application.

All studies performed in support of this application included adequate informed consent. There were no protocol violations that affected the integrity or results of the studies. Dr. Jonathan Norton, (the statistical reviewer) assessed the impact of two irregularities discovered for Study KF5503/32 during the DSI inspection (failure to file documents associated with monitoring visits in a timely manner and failure to fully report all information relevant to safety and efficacy data in the clinical study report). These issues

were satisfactorily resolved by the Applicant as reported by DSI. Dr. Norton reanalyzed the primary endpoint omitting relevant subjects from the analysis, and the results were consistent with the results obtained when these subjects were included. See Dr. Norton's statistical review for details of this analysis.

Study KF5503/31, site 011006

The Applicant conducted an investigation of the clinical investigator site of Dr. Jonathan Hummel on 02-04 October 2007. The purpose of the investigation was to verify concerns regarding duplicate ECG tracing across multiple subjects. As a result of this investigation, potential non-compliance with the good clinical trial practices was identified.

Dr. Hummel's site conducted two phase 3 clinical trials, R331333-PAI-3001 (Total Hip Replacement Surgery Pain) and R331333-PAI-3004 (Safety), associated with the Acute Pain Indication

The results of the investigation were as follows:

The following Critical observations were noted:

ECG Tracings:

- Identical ECG tracings were transmitted to [redacted] for multiple subjects and visits.
- The ECG acquisition times were after 5:00 pm, when the study coordinator stated that no procedures were performed after this time.

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Lab Reports:

- There were at least two instances where the screening laboratory data (clinical chemistry, hematology, urinalysis) for two subjects were identical with each other.

The following Major observations were noted:

- The Pain Scales to be completed by the subjects only, were noted to have similar handwriting and marks from one subject to another.
- There was an inconsistency in source data regarding the screening ECG for subjects. For example:
 - The source notes stated that the ECG was unable to be acquired, which was entered into the Electronic Case Report Form (eCRF) as, "UNABLE TO OBTAIN". However, an ECG tracing from [redacted] clearly labeled for the subject and visit was available and this ECG tracing was duplicate of the qualifying visit ECG.

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Study KF5503/31 was ongoing at the time of the cutoff date of 3 October 2007 for the NDA submission, and because this study was not a pivotal study it was not included in the NDA. The safety data from this study was described in the 4-Month Safety Update, with the data from site 011006 described separately. The efficacy data from the study

KF5503/31 was not provided because the clinical study report was in progress when the 4-Month Safety Update was submitted. In the efficacy analysis of KF5503/31 that is part of the clinical study report, the ITT analysis set excluded the subjects from site 011006.

DSI was consulted on July 2, 2008, to perform a "for cause" inspection of Dr. Hummel, however since this study site is outside of the United States this inspection could not be carried out. The data obtained did not contribute to findings of efficacy for tapentadol IR, this investigator is not involved any other INDs.

3.3 Financial Disclosures

The Applicant adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. These arrangements do not raise questions about the integrity of the data.

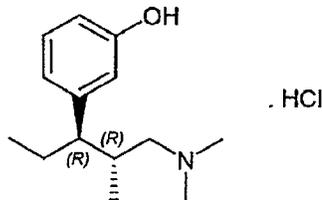
One clinical investigator, [REDACTED] JMD, a sub-investigator who participated in study KF5503/33 reported equity interest in the sponsor of the covered study: stock in excess of \$50,000. The study site enrolled and randomized [REDACTED] a total of 674 subjects. The Applicant stated that steps taken to minimize bias included the fact that the study was a double-blind, placebo-controlled trial consisting of multiple sites from which the data was pooled. This appears to be acceptable especially given the small proportion of patients enrolled by this investigator.

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4 SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

Tapentadol HCL tablets are immediate-release film-coated tablets. The chemical name is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The structural formula is:



The molecular weight of tapentadol HCl is 257.80, and the molecular formula is $C_{14}H_{23}NO \cdot HCl$. The n-octanol:water partition coefficient log P value is 2.87. The pKa values are 9.34 and 10.45. In addition to the active ingredient tapentadol HCl, tablets also contain the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, magnesium stearate, and Opadry® II, a proprietary film-coating mixture containing polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and aluminum lake coloring.

The CMC reviewer did not report any issues related to the approvability of tapentadol IR.

4.2 Clinical Microbiology (if applicable)

This product is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

In preclinical studies, tapentadol IR was found to be a potent μ -opioid receptor agonist and indirect noradrenergic reuptake inhibitor. Potent antinociceptive effects in animal models were demonstrated in animal models of acute, chronic, inflammatory, and neuropathic pain. No active metabolites were detected.

In toxicological studies with tapentadol, the most common systemic effects of tapentadol are related to the mu-opioid receptor pharmacodynamic properties of the compound. At high doses of tapentadol, transient, dose-dependent and predominantly CNS-related findings were observed, e.g. fearfulness, sedation or excited behavior, recumbency and hunched posture, impaired respiratory function, and rarely, convulsions. In addition, cardiovascular effects (including QT prolongation), respiratory depression, and dose dependent inhibition of GI motility were reported.

Genotoxic, reproductive toxicology, carcinogenicity, immunotoxicity, and Olney Lesion studies were negative.

No issues were reported related to the approvability of tapentadol IR, and no additional nonclinical studies were recommended by the Pharmacology/Toxicology reviewer, Dr. Kathleen Young. Please see her review for details.

4.4 Clinical Pharmacology

For a detailed review of the clinical pharmacology aspects of this application, please see Dr. David Lee's review.

4.4.1 Mechanism of Action

Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. Although its exact mechanism is unknown, analgesic efficacy is thought to be due to mu-opioid agonist activity and the inhibition of norepinephrine reuptake.

4.4.2 Pharmacodynamics

Tapentadol is 18-times less potent than morphine in binding to the human mu-opioid receptor and is 2-3 times less potent in producing analgesia in animal models, consistent with its dual mode of action. Unlike morphine, tapentadol has been shown to inhibit norepinephrine reuptake in the brains of rats resulting in increased norepinephrine concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid antagonists (e.g., naloxone), whereas the norepinephrine reuptake inhibition is sensitive to norepinephrine modulators. Tapentadol exerts its pharmacodynamic effects directly without a pharmacologically active metabolite.

In a thorough QT study, no significant effect of therapeutic and suprathreshold doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

4.4.3 Pharmacokinetics

Absorption

Tapentadol is rapidly and completely absorbed after oral administration. Mean absolute bioavailability after single-dose administration (fasting) is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing. The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

Dose-proportional increases in the C_{max} and AUC values of tapentadol have been observed over the oral therapeutic dose range.

A multiple (every 6 hour) dose study with doses ranging from 75 to 175 mg tapentadol showed a mean accumulation factor of 1.6 for the parent drug and 1.8 for the major metabolite tapentadol-O-glucuronide, which are primarily determined by the dosing interval and apparent half-life of tapentadol and its metabolite.

Food effect

The AUC and C_{max} increased by 25% and 16%, respectively, when tapentadol IR was administered after a high-fat, high-calorie breakfast. Tapentadol IR may be given with or without food.

Distribution

Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (V_z) for tapentadol is 540 +/- 98 L. The plasma protein binding is low and amounts to approximately 20%.

Metabolism and elimination

About 97% of the parent compound is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation. A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.

Special populations

Elderly

The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean Cmax observed in the elderly subject group compared to young adult subjects. No dose adjustment is recommended.

Renal impairment

AUC and Cmax of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

No dosage adjustment is proposed for patients with mild and moderate renal impairment, however tapentadol IR is not recommended for use in patients with severe renal impairment.

Hepatic Impairment

Administration of tapentadol IR resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for Cmax; and 1.2 and 1.4, respectively, for t1/2. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment, resulting in lower peak serum concentrations with no changes in exposure or renal elimination.

No dosage adjustment is recommended for patients with mild hepatic impairment. The recommendation for patients with moderate hepatic impairment is use with caution, and initial dosing of 50mg every 4 hours.

Drug-drug interactions were assessed and are discussed in Section 7.5.4.

5 SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Thirty-one clinical trials have been completed during the development of Tapentadol IR (20 Phase 1, and 11 Phase 2/3 double-blind studies). Two additional Phase 3 studies (KF5503/38 and KF5503/37) were ongoing at the time of the 4-month safety update. The following table describes the completed Phase 2 and 3 studies. A description of all Phase 1 studies is located in Section 9.4. Phase 1 studies were not reviewed individually.

b(4)

Table 3

GRT /J&JPRD Study No.	Brief Description of Study
Phase 2	
KF5503/02 0000\Mod5.3.5.1\KF550 3/02	Randomized, double-blind, placebo- and active-controlled (ibuprofen 400 mg and tramadol HCl 150 mg), parallel-group single-dose study of tapentadol HCl IR (43 mg, 64 mg, 86 mg, 129 mg, and 172 mg) conducted in subjects with moderate to severe postoperative pain (third molar) extraction.
KF5503/04 0000\Mod5.3.5.1\KF550 3/04	Randomized, double-blind, placebo- and active-controlled (ibuprofen 400 mg and morphine sulfate 60 mg), parallel-group single- and multiple-dose study of tapentadol IR (21 mg, 43 mg, 64 mg, 86 mg, and 172 mg) in subjects with moderate to severe postoperative dental pain. During the multiple-dose phase, subjects took study drug every 6 hours for 2 days.
KF5503/05 0000\Mod5.3.5.1\KF550 3/05	Randomized, double-blind, parallel-group, single-dose, dose-ranging, placebo- and active-controlled (morphine sulfate 60 mg and ibuprofen 400 mg) of tapentadol IR (21 mg, 43 mg, 64 mg, 86 mg, and 172 mg) conducted in subjects with moderate to severe pain following orthopedic surgery (bunionectomy).
KF5503/08 0000\Mod5.3.5.1\KF550 3/08	Randomized, double-blind, parallel-group, single- and multiple-dose study of tapentadol IR (21 mg and 43 mg) in subjects with moderate to severe chronic nonmalignant pain. During the multiple-dose phase, subjects took study drug every 6 hours for 5 days.
KF5503/21 0000\Mod5.3.5.1\KF550 3/21	Randomized, double-blind, parallel-group, placebo- and active-controlled (oxycodone HCl IR 10 mg), multiple-dose study of tapentadol IR (50 mg and 100 mg) conducted in subjects with moderate to severe acute pain following orthopedic surgery (bunionectomy). Subjects took study drug every 4 to 6 hours on Days 2 through 5 (up to 7 doses on Day 2; up to 6 doses on Days 3 and 4; and up to 1 dose on Day 5).
KF5503/22 R331333-PAI-2003 0000\Mod5.3.5.1\KF550 3/22	Randomized, double-blind, parallel-group, placebo- and active-controlled (oxycodone HCl IR 10 mg), multiple-dose study of tapentadol IR (50 mg and 100 mg) conducted in subjects with moderate to severe acute pain following orthopedic surgery (bunionectomy). Subjects took 3 doses every 4 hours over a 12-hour period of tapentadol IR (80-80-80 mg; 120-120-120 mg; 120-60-60 mg or 160-80-80 mg) or oxycodone IR (10-10-10 mg).
Phase 3	
KF5503/31 R331333-PAI-3001 ^{a,b}	A randomized, double-blind, placebo- and active-control (oxycodone HCl IR 10 mg) parallel-group study to evaluate the efficacy and safety of tapentadol IR (50 mg, 75 mg, or 100 mg) in subjects with acute pain following primary unilateral total hip replacement surgery from osteoarthritis of the knee using a fixed-dose treatment regimen (every 4-6 hours for 3 days) followed by a 9-day optional open-label extension to evaluate the safety of tapentadol IR (50 mg or 100 mg) using a fixed-dose treatment regimen.
KF5503/32 R331333-PAI-3003 0000\Mod5.3.5.1\KF550 3/32	Randomized, double-blind, placebo- and active-controlled parallel-group, multiple-dose study conducted in subjects with acute postoperative pain following bunionectomy. Subjects took tapentadol IR (50, 75, or 100 mg), oxycodone HCl IR (15 mg), or placebo with the first dose interval of 1 to 6 hours, then every 4 to 6 hours for 72 hours during the double-blind period. Subjects were offered an option to receive tapentadol IR (every 4 to 6 hours as needed for analgesia for up to 9 days) in an open-label extension phase.
KF5503/33 R331333-PAI-3002 0000\Mod5.3.5.1\KF550 3/33	Randomized, double-blind, placebo- and active-controlled parallel-group, multiple-dose study conducted in subjects with moderate to severe pain who were candidates for elective primary total or partial joint replacement of the hip or knee due to chronic osteoarthritis. Subjects took tapentadol IR (50 or 75 mg), oxycodone HCl IR 10 mg, or placebo with the first dose administered in the evening of Day 1, then every 4 to 6 hours relative to the previous dose during waking hours for up to 10 days. Subjects in the 75-mg tapentadol IR group took 50 mg on Day 1 and 75 mg on Days 2 to 10.

<u>Completed Studies (Continued)</u>	
Phase 3 Continued	
KF5503/34 R331333-PAI-3004 0000Mod5.3.5.1\KF5503/34	Randomized, double-blind, active-controlled, parallel-group, multiple-dose study conducted in subjects with chronic pain from low back pain or osteoarthritis of the hip or knee of at least three months duration. Subjects took tapentadol IR (50 or 100 mg) or oxycodone HCl IR (10 or 15 mg) every 4 to 6 hours as needed for up to 90 days.
KF5503/37 R331333-PAI-3017 ^a	A randomized, double-blind, placebo- and active-control (morphine sulfate IR 30 mg) parallel-group study to evaluate the efficacy and safety of tapentadol IR (75 mg) in subjects with acute pain following bunionectomy using a fixed-dose treatment regimen (first dose interval 1 to 6 hours, remaining intervals every 4 to 6 hours) for 3 days.

Source: ISS, p. 51

Phase 2 studies KF5503/21 and KF5503/22 provided data regarding doses and dosing intervals to be applied to the Phase 3 trials. Studies KF5503/32 and KF5503/33, the pivotal Phase 3 efficacy trials, were reviewed individually in Section 5.3 Discussion of Individual Studies.

5.2 Review Strategy

The Applicant identified two trials as contributing to evidence of efficacy (KF5503/32 and KF5503/33) in the management of acute moderate-to-severe pain. These studies were reviewed individually for study design and conduct, as well as assessment of the validity of the Applicant's efficacy conclusions. The reviews are located in Section 5.3.

The Applicant's efficacy conclusions were cross-checked by the statistical reviewer, Dr. Jonathan Norton, via analysis of primary data to reproduce the results.

Data from the pooled Phase 2/3 multiple-dose, double-blind safety analysis set were used to establish the safety of tapentadol IR, augmented by uncontrolled and single-dose studies. The data were reviewed to identify serious and common adverse effects of the drug in each treatment population, and in the total population. Additionally, all deaths were identified, and narratives/CRFs examined for evidence of causality.

5.3 Discussion of Individual Studies

Individual Study Reviews

Protocol R331333PAI3003 (J&JPRD); KF5503/32 (Grünenthal); Phase 3

Title: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Doses of CG5503 Immediate-Release Formulation in the Treatment of Acute Pain from Bunionectomy Followed by a Voluntary Open-Label Extension

Date issued: Original protocol issued May 1, 2006; Amendments submitted June 29, 2006 and July 14, 2006.

Objectives:

- **Primary:** to demonstrate the efficacy of three doses of CG5503 (50, 75, and 100mg) immediate-release (IR) versus placebo using the sum of pain intensity difference at 48 hours (SPID48) to measure analgesic effect and to assess the

safety and tolerability of repeated doses of CG5503 IR over the double-blind treatment period in subjects with acute pain following bunionectomy

- **Secondary:**
 - Comparison of the effect of CG5503 IR on the time to the first rescue pain medication during the double-blind treatment period
 - Evaluation of the effect of CG5503 IR versus placebo with the distribution of responder rates for each time point (at 12, 24, 48, and 72 hours)
 - Evaluation of the efficacy of CG5503 IR by examining the total effect on pain relief (PAR) and pain intensity (PI) over the 72-hour double-blind period
 - Evaluation of time from the initial dose to onset of perceptible pain relief and meaningful pain relief measured by a double stopwatch method
 - Assessment of Patient Global Impression of Change (PGIC) at the end of the double-blind treatment period
 - Evaluation of the adverse event rates for nausea and vomiting across treatment groups in the double-blind treatment period
 - Evaluation of pharmacokinetic (PK) parameters of CG5503 IR in this study population using the population PK approach
 - Evaluation of the safety for subjects participating in the open-label extension period
 - Exploration of the efficacy of oxycodone IR in comparison with CG5503 IR and placebo.

Study design: This study was to have been a randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter study with a voluntary open-label extension period to evaluate the efficacy and safety of the administration of multiple doses of CG5503 IR in men and women 18 to 80 years of age, inclusive, who are undergoing bunionectomy.

Study drug:

- CG5503 IR: 50, 75, and 100mg capsules during double-blind period, tablets during open-label period
- Oxycodone 15mg capsules
- Placebo capsules
- All will be identical during double-blind period

Study conduct:

- 1) Screening period (Days -28 to -2 up to the first surgical incision), during which subjects were to have been evaluated for study entry
- 2) Surgical period (Day -1) was to have started with the first surgical incision and continue until the end of the continuous popliteal sciatic block or systemic analgesia, which was to have terminated at approximately 3:00 a.m. on the morning after surgery.
- 3) Qualification period (Day 1) was to have occurred up to a maximum of 9 hours after termination of the continuous popliteal sciatic block or systemic analgesia (no earlier than

10 hours after the first surgical incision). Subjects were to have qualified for entry into the double-blind treatment period (random assignment) once their pain score was ≥ 4 on an 11-point numerical rating scale (NRS).

4) Double-blind treatment period was to have started on Day 1 immediately following random assignment of subjects to a treatment group. The inpatient double-blind treatment period was to have been 72 hours in duration and include a final end-of-double-blind evaluation for all subjects.

5) Voluntary 9-day open-label extension period: Consenting, medically stable subjects who completed the double-blind treatment period were to have been eligible to enter the nonrandomized 9-day open-label extension on an outpatient basis (beginning on Day 4 after the end-of-double-blind evaluation). A follow-up visit for safety assessments was to have occurred between Days 13 and 18 for all subjects who participated in the open-label extension period.

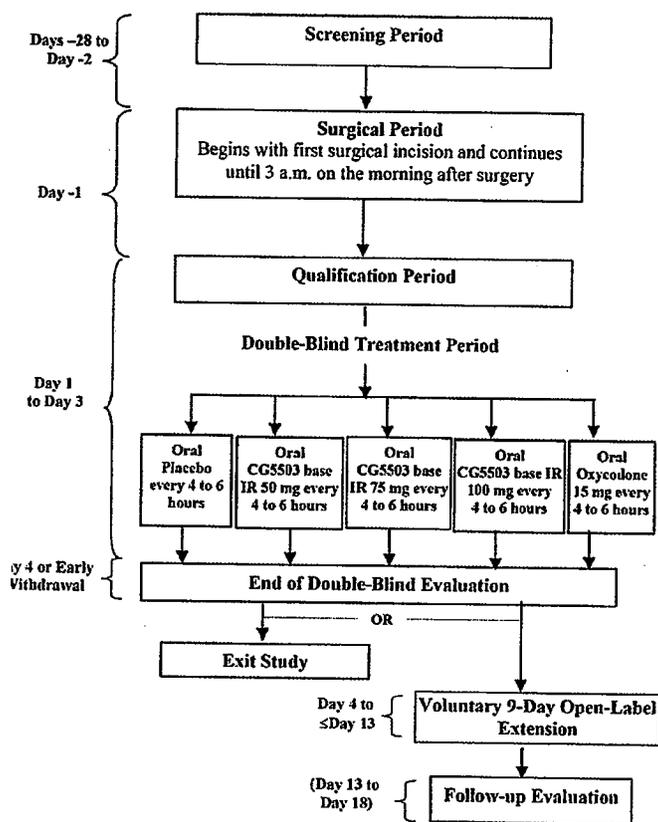
The study, including the screening and open-label extension, was to have been a maximum duration of 46 days.

Approximately 600 eligible subjects were to have been randomly assigned to 1 of 5 treatment groups in a 1:1:1:1:1 ratio. Treatments were 50, 75, or 100mg of CG5503 IR, 15mg oxycodone, or placebo. Subjects who required rescue medication other than the study drug were to have been withdrawn from the study.

The study flow chart is presented below:

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Figure 1



Source: CSR R331333-PAI-3003 (KF5503/32) p. 1367

Inclusion/Exclusion criteria

Inclusion criteria:

- Man or woman, between 18 and 80 years of age, inclusive
- Signed an informed consent
- In countries where pharmacogenomics testing is allowed, signed an informed consent for genetic testing, indicating whether they do or do not wish to participate in the genetic part of the study
- ASA status ≤ 3
- Scheduled to undergo primary unilateral first metatarsal bunionectomy
- Women must be postmenopausal, surgically sterile, or practicing or agree to practice an effective method of birth control or male partner sterilization
- Women of childbearing potential must have a negative serum β -human chorionic gonadotropin (β -hCG) pregnancy test at screening and a negative urine pregnancy test before surgery.
- Baseline pain intensity ≥ 4 on an 11-point (0 to 10) pain intensity NRS, rated within 30 minutes before randomization

- Qualifying baseline pain intensity measurements occur within 9 hours of termination of the continuous popliteal sciatic block or systemic analgesia, during the postoperative surgical period

Exclusion criteria:

- History of seizure disorder or epilepsy suggested by the presence of any of the following:
 - Mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year of screening
 - Severe traumatic brain injury, episode(s) of unconsciousness of more than 24 hours duration, or posttraumatic amnesia of more than 24 hours duration within 15 years of screening
- History of malignancy within the past 2 years before the start of the study, with the exception of basal cell carcinoma
- History of alcohol or drug abuse
- Evidence of active infections that may spread to other areas of the body (e.g., osteomyelitis, pyogenic infection of the hip, Hepatitis B or C, or other overt infections) or a history of human immunodeficiency virus (HIV) 1 or 2
- Clinical laboratory values reflecting moderate or severe renal insufficiency, or hepatic impairment based on alanine aminotransaminase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN)
- Clinical laboratory values outside acceptable limits for surgery in the opinion of the investigator
- Concomitant autoimmune inflammatory conditions
- Acute crystal-induced arthropathy within 6 months before screening
- A clinically significant disease that in the investigator's opinion may affect efficacy or safety assessments
- Currently treated with anticonvulsants, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), neuroleptics, or serotonin norepinephrine reuptake inhibitor (SNRI) (selective serotonin reuptake inhibitor (SSRI) treatments are allowed if taken for at least 30 days before the screening period of the study at an unchanged dose)
- Received an experimental drug or used an experimental medical device within 30 days before screening or have participated in a previous study of CG5503
- Contraindications to, or history of allergy or hypersensitivity to CG5503, oxycodone, hydromorphone, morphine, or fentanyl, or their excipients
- Systemic steroid therapy, excluding inhalers, within the 3 months before screening
- Undergoing concomitant surgical procedures in addition to primary bunionectomy
- Will need postoperative Intensive Care Unit care
- Women who plan to become pregnant during the study, or who are breast-feeding
- History of pending litigation due to chronic pain or disability

Procedures

Randomization and blinding: Eligible subjects were to have been randomly assigned to 1 of 5 treatment groups based on a computer-generated randomization scheme prepared by the Applicant before the study. The randomization was to have been balanced by using permuted blocks of treatments and stratified by study center.

Treatments

- Double-blind period
 - After random assignment, study drug (50-, 75-, or 100-mg CG5503 base IR, 15-mg oxycodone IR, or placebo) was to have been administered as a single oral dose once every 4 to 6 hours
 - The next dose may be given as soon as 4 hours after the previous dose but must be given by 6 hours after
 - The second dose on Day 1 may be given as early as 1 hour but no later than 6 hours after the first dose.
 - Study drug may be given up to a maximum of 7 times for Day 1 (due to an early second dose) and 6 times for Days 2 and 3.
 - All doses of study drug should be administered with approximately 120 mL of water with or without food. Study drug must be swallowed whole and not chewed, divided, dissolved, or crushed.
 - Subjects requesting additional analgesic medication beyond the study drug will be withdrawn from the study for lack of efficacy.

The table below shows the maximum allowable doses in 24 hours of each treatment.

Table 4

Treatment	Treatment Schedule* and Maximum Allowable Dose in 24 Hours				
	Placebo	CG5503 base IR 50 mg	CG5503 base IR 75 mg	CG5503 base IR 100 mg	Oxycodone IR 15 mg
Maximum dose (mg), Day 1	0	350	525	700	105
Maximum dose (mg), Days 2 and 3	0	300	450	600	90

Source: CSR R331333-PAI-3003 (KF5503/32) p. 1376

- Open-label treatment period
 - CG5503 IR was to have been provided as a 9-day supply
 - Single day's supply was to have contained six doses of CG5503 IR (each dose was to have been one to two tablets of 50 mg each)
 - Subjects were to have been instructed to take one or two tablets every 4-6 hours as needed for analgesia for up to nine days
 - Subjects were to have returned all unused study drug at the final follow-up visit.

Concomitant therapy

- Prohibited medications
 - Anticonvulsants, MAOIs, TCAs, neuroleptics, SNRI (SSRIs allowed if taken for at least 30 days prior to screening at stable dose)
 - Analgesics other than study drug including opioids, Tramadol, NSAIDs, ASA (except for cardiovascular prophylaxis)

- Sedatives used as minor tranquilizers may be used prn if approved
- Prescription analgesic medications were to have been prohibited in the open-label extension period.

Rescue medication

- Any patient requiring rescue medication during the double-blind period was to have been withdrawn from study due to lack of efficacy
- Pain assessments were to have been made prior to administration of rescue
- Medication for nausea and vomiting was to have been allowed during the double-blind period as follows:
 - Metoclopramide 5-10mg IV or IM prn
 - If not effective, second line antiemetic may be administered

Procedure schedule

The time and events schedule below summarizes the frequency and timing of the efficacy, safety, tolerability, PK and other measurements during the study.

Table 5

TIME AND EVENTS SCHEDULE

	Period: Study Day:	Screening -28 to -2	Surgical ^a -1	Qualification ^b 1	Double-Blind Treatment ^c 1 to 3	End of Double-Blind Evaluation or Early Withdrawal ^d 4	Voluntary 9-Day Open-Label Extension ^e 4 to <13	Follow-up Evaluation ^f 13 to 18
Screening/Administrative								
Informed consent (for double-blind and open-label extension)		X						
Pharmacogenomic, informed consent		X						
Inclusion/exclusion criteria		X		X				
Preoperative medical history		X						
Physical examination, including weight		X (+ height)				X		
Pregnancy test		X (serum)	X (urine) ^g					X (urine)
Urine drug test		X						
Randomization				X ^h				
Pharmacokinetic/Pharmacogenomics								
Pharmacokinetic sample collection					X ⁱ			
Pharmacogenomic sample					X (Day 1)			
Surgery and Pain Control								
Bunionectomy			X					
Begin/Terminate continuous popliteal sciatic block ^j			X					
Pain Intensity (11-point NRS)				X	X ^k	X		
Pain Relief (5-point NRS)					X ^k	X		
Administer study drug					X ^l		X	
Patient Global Impression of Change ^m						X		
Safety								
Clinical laboratory tests (includes serology at screening)		X		X		X		X
12-lead electrocardiogram		X		X		X		
Vital signs ⁿ		X	X	X	X ⁿ	X		X
Concomitant therapy		X	X	X	X	X	X	X
Adverse events		X	X	X	X	X ^o	X	X

Footnote for this table are found on the next page

Source: CSR R331333-PAI-3003 (KF5503/32) p. 1356

Procedure highlights

- Surgical period

- Defined as time that begins with first surgical incision for bunionectomy and continues to termination of continuous popliteal sciatic block or systemic analgesia
- Anesthesia used and duration of surgery was to have been recorded in CRF
- Post-operative analgesia was to have been provided using a continuous popliteal sciatic block up to approximately 3 a.m. on the morning after surgery
- Breakthrough postoperative pain during this period was to have been managed using acetaminophen, ketorolac, and/or hydrocodone/APAP
- Qualification period
 - After terminating the continuous popliteal sciatic block or systemic analgesia, and if not sleeping, subjects were to have been assessed regularly for an increase in pain intensity sufficient to qualify the subject for entry into the double-blind treatment period.
 - To qualify for entry into the double-blind treatment period, the following criteria were to have been met regarding the qualifying pain intensity:
 - Occur no earlier than 10 hours after first surgical incision.
 - Occur within 9 hours after termination of the continuous popliteal sciatic block or systemic analgesia
 - Rated as ≥ 4 on an 11-point NRS, recorded within 30 minutes before randomization.
 - Subjects who met the criteria above were to have been randomly assigned on a 1:1:1:1:1 basis to receive 1 of 5 study drugs during the double-blind treatment period. All baseline measures (e.g., clinical laboratories, ECG, and vital signs) were to have been completed before randomization during the qualification
- Double-blind treatment period
 - All subjects were to have been given study drug to which they were randomly assigned
 - If pain not adequately managed with first dose of study drug, second dose may be given as early as 1 hour after first dose, but no later than 6 hours.
 - All subsequent drug administration was to have been 4-6 hours from previous dose
- End of double-blind treatment period
 - At the end of 72 hours (on Day 4) or earlier, in the case of early withdrawal, all subjects were to have undergone an end-of-double-blind evaluation.
 - For subjects not participating in the open-label extension or withdrawing early, adverse events were to have been collected for 48 hours after the last administration of study drug.
- Open-label treatment period

- Subjects who completed double-blind period and deemed medically stable after final evaluation were to have been eligible to enroll in voluntary 9-day open-label period
- Participating subjects required to return for follow-up safety evaluation between days 13 and 18.
- Subjects were to have been contacted on Day 5 by telephone by study nurse and asked “how are you doing?”

Outcome measures

Efficacy

- Assessments were to have been made
 - At 12, 24, 48, and 72 hours from the first dose of study drug
 - For the first dose only, at -0.5, 1.0, 1.5, 2.0, and every 2 hours thereafter until the next dose
 - For doses after the first dose, predose and every 2 hours thereafter until the next dose
- Measurements (see Section 9.4 for scales)
 - Pain intensity (PI)-11 point NRS
 - Pain relief (PAR)-5 point NRS
 - Patient global impression of change (PGIC)-measured once at end of double-blind treatment period
 - Double-stopwatch method-first dose only
 - Time to perceptible pain relief
 - Time to meaningful pain relief

Safety

- Data collected according to Time and Events table above
- Adverse events until 48 hours after last dose
- Clinical laboratory tests (See Section 9.4 for laboratory panels)
 - Hematology panel, serum chemistry panel, urinalyses
- ECGs, vital signs, physical exam, serology, urine drug screens
- Pulse oximetry- immediately before the first dose, continuously for 6 hours after first dose, and at 12, 24, 48 and 72 hours following the first dose
- Pregnancy tests

Pharmacokinetics

- Four venous blood samples of 4 ml were to have been collected for determination of serum concentrations of CG5503 base and oxycodone:
- Samples were to have been collected on Day 1 at approximately 1 and 3 hours after first study drug administration, predose, and 2 hours post third study drug administration on Day 2

Pharmacogenomics

- On Day 1 or after, one blood sample of 10ml was to have been collected from subjects who gave informed consent for this aspect of the study
- Goal was to have been to determine whether genetic variables may affect PK, efficacy and safety of CG5503 IR.

Efficacy Endpoints

Primary endpoint

- SPID48 relative to the first dose of study drug
 - Pain intensity difference (PID) was to have been calculated at each assessment time point as follows:

$$\text{PID} = \text{Baseline PI} - \text{Current PI}$$

- SPID was to have been calculated using the following formula

$$\text{SPID} = \sum W_i * \text{PID}_i$$

where the sum includes all observations collected from baseline to 48 hours and W_i is the time elapsed from the previous observation (PID_{i-1}) to the current observation (PID_i).

Secondary endpoints

- Time from first dose to the first use of rescue medication. Subjects who complete/withdraw from the study without taking rescue medication will be censored at the time of completion or withdrawal
- Distribution of responder rates. Percent change from baseline in pain intensity at 48 hours will be calculated using an 11-point NRS. Subjects without a 48-hour pain value will be assigned the worst possible score. Responder rates for a given percent change value will be defined as the proportion of subjects above that threshold value. The distribution of responder rates at 48 hours, as defined above, will be determined for each treatment group. Similar calculations will be carried out for percent change from baseline in an 11-point NRS at 12, 24, and 72 hours.
- The SPID at 12, 24, and 72 hours relative to first dose
- The TOTPAR, and SPRID, at 12, 24, 48, and 72 hours relative to first dose
 - $\text{TOTPAR} = \text{total pain relief} = \sum W_i * \text{PAR}_i$
 - $\text{SPRID} = \text{sum of total pain relief and pain intensity difference} = \text{SPID} + \text{TOTPAR}$
- PGIC at the end of double-blind evaluation
- Time from the initial dose to onset of perceptible pain relief and meaningful pain relief, as measured by a double stopwatch method. Subjects without pain relief will be censored at 12 hours from the initial dose or at the time of early withdrawal, whichever occurs first.

Subject completion/withdrawal

- Double-blind treatment period: subject was to have been withdrawn due to
 - Lack of efficacy: defined as requiring rescue medication
 - Withdrawal of consent
 - Safety reasons according to investigator
 - Pregnancy
 - Lost to follow-up

- Open-label extension period: same as above except loss of efficacy

Statistical Methods

Sample size determination

- Based on effect size of 0.48 of 48 hour SPID relative to placebo noted in Phase 2 study KF5503/21
- The primary efficacy hypothesis for this study was to have been tested by comparing each of the three CG5503 IR dosage regimens with placebo with adjustment for multiple comparisons.
- Assuming the standard effect size of 0.48 discussed above, using the Bonferroni adjustment, it was estimated that approximately 120 subjects for each treatment group would provide 90% power to show that at least one CG5503 IR dosage group was statistically different from placebo at an overall alpha level of 0.05.
- Based upon this calculation, a total of 600 subjects were anticipated to be randomly assigned during the double-blind treatment period.

Subject information analyses

- Demographic and baseline characteristics as well as study withdrawal and reasons for study withdrawal were to have been summarized by treatment

Primary efficacy analyses

- Efficacy analysis was to have been based on the ITT population, that is all randomized subjects who took at least one dose of double-blind study medication and had baseline pain assessment
- SPID48 was to have been calculated as the weighted sum of the PIDs collected up to 48 hours
- Imputation methods for calculation of SPID48 were to have been:
 - LOCF for any subject withdrawn prematurely from double-blind period
 - BOCF for any subject without post-baseline pain values
 - Linear interpolation approach for intermittent missing PI scores
- SPID48 was to have been analyzed using an analysis of covariance (ANCOVA) model.
 - The model will include treatment and investigator as factors and baseline PI score as a covariate
 - Treatment effects will be estimated based on least-squares means of difference
 - P values that adjust for multiple comparisons using the Hochberg procedure will be presented for the SPID48 for each CG5503 IR dose regimen compared with placebo

Secondary efficacy analyses

- Details of all secondary analyses will not be provided here
- Time to first rescue will be estimated using Kaplan-Meier, and Hochberg analysis will be applied for multiple tests of significance.
- For the remaining secondary analyses, there will be no correction for multiplicity

- The distribution of responder rates at 48 hours will be determined for each treatment group and compared using the Cochran-Mantel-Haenszel test controlling for investigator center. Response rates for achieving 30% and 50% improvement in pain intensity will be assessed.
- Sensitivity of the primary efficacy analysis will be evaluated by analyzing the primary endpoint using different imputation rules

Protocol amendments

The original protocol was issued May 1, 2006. Two amendments were submitted to the Agency: June 29, 2006 and July 14, 2006. The trial commenced on August 2, 2006.

Amendment INT-1 (June 29, 2006)

- Dosage form of CG5503 IR during the open-label period was changed from capsules to tablets; text was changed throughout the protocol

Amendment INT-2 (July 14, 2006)

- Exclusion criteria was modified from an exclusion of persons experiencing severe traumatic brain injury, episodes of unconsciousness, or posttraumatic amnesia... to exclude those unconscious for more than 24 hours.
- The protocol was changed from specifying a stepwise approach in managing postoperative pain (i.e., with acetaminophen, ketorolac, and/or hydrocodone/acetaminophen combination in that order) to only listing the approved analgesics.
- The stopwatch measurements for assessing times to perceptible and meaningful pain relief were limited to 12 hours due to the limitations of

Reviewer's comment: The above protocol amendments would not be expected to have an important affect on the conduct of the study or the analyses related to efficacy of the study drug. Both protocol amendments were issued before the first subject was screened.

Results

The study was conducted from August 2, 2006-May 23, 2007 at five sites in the United States.

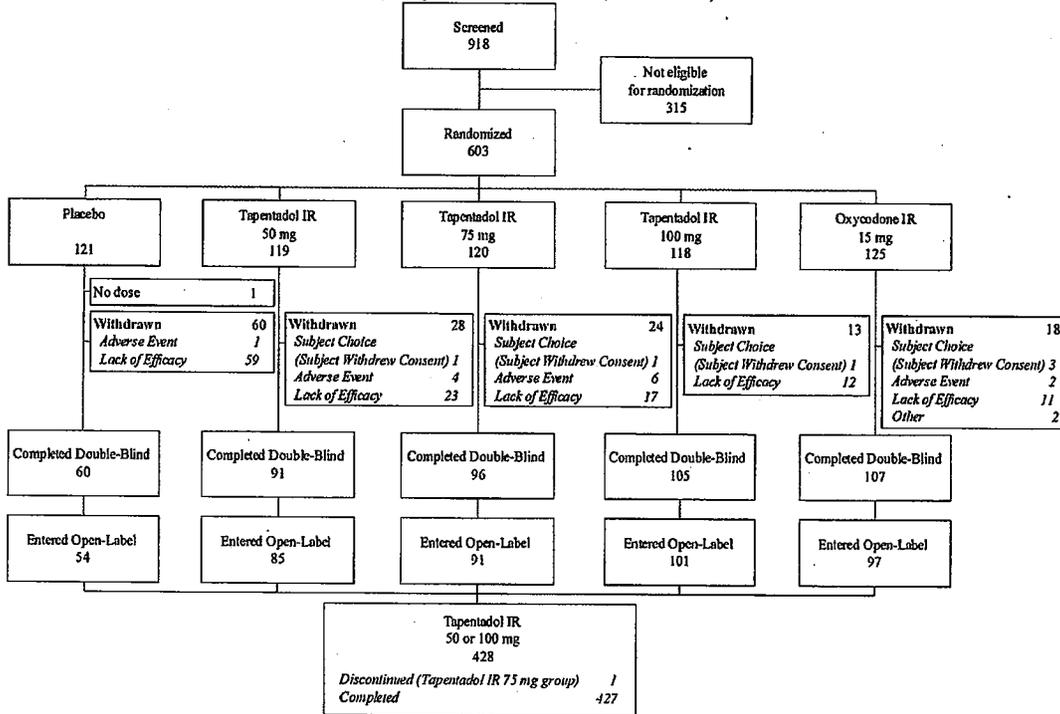
Subject Disposition

A total of 918 subjects were screened, and 603 were randomized. For the double-blind period, the 603 subjects were randomized to the 5 treatment groups in a 1:1:1:1:1 ratio (121 subjects in the placebo, 119 in the tapentadol IR 50 mg, 120 in the tapentadol IR 75 mg, 118 in the tapentadol IR 100 mg, and 125 in the oxycodone HCl IR 15 mg groups). Of the randomized subjects, 602 subjects received study drug. One subject (301006) was enrolled and randomized to the placebo group, but did not receive treatment because at entry the subject recorded a pain intensity of 2, whereas the inclusion requirement was ≥ 4 .

Four-hundred twenty-eight subjects entered the open-label period, and 405 received study drug.

Figure 2 below illustrates the subject disposition.

Figure 2: Subject Disposition Study KF5503/32



Source: CSR R331333-PAI-3003 (KF5503/32), p. 67

The percentage of subjects who completed the double-blind period was lowest in the placebo group (50%) and higher in the active-treatment groups (76% to 89%) with the percentage increasing with increasing tapentadol IR dose, as shown in Table 6 below.

Table 6: Completion and Discontinuation Information for Double-Blind Period

	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone IR 15 mg (N=125)	Total (N=602)
Completion Status						
Reason for Withdrawal/termination	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	60 (50)	91 (76)	96 (80)	105 (89)	107 (86)	459 (76)
Withdrawn/Discontinued	60 (50)	28 (24)	24 (20)	13 (11)	18 (14)	143 (24)
Subject Choice ^a	0	1 (1)	1 (1)	1 (1)	3 (2)	6 (1)
Adverse Event	1 (1)	4 (3)	6 (5)	0	2 (2)	13 (2)
Lack of Efficacy	59 (49)	23 (19)	17 (14)	12 (10)	11 (9)	122 (20)
Other	0	0	0	0	2 (2)	2 (<1)

^a Subject withdrew consent

Source: CSR R331333-PAI-3003 (KF5503/32), p. 68

The majority of subjects who discontinued treatment during the double-blind period reported lack of efficacy as the reason (i.e., required rescue medication), with the highest percentage in the placebo group (49%). In the oxycodone HCl IR 15 mg group, 9% of subjects discontinued due to lack of efficacy. In the tapentadol IR groups, the percentage of discontinuations due to lack of efficacy was higher with lower doses (19% in the 50 mg, 14% in the 75 mg, and 10% in the 100 mg groups). The remaining subjects discontinued for reasons of adverse event, subject choice (withdrawal of consent), or other (principal investigator discretion).

Few subjects discontinued due to adverse events, and showed no pattern across the treatment groups. Details regarding discontinuations due to adverse events are discussed in Section 7.

Of the 459 subjects who completed the double-blind period, 428 (93%) entered the open-label period. Of those who entered, one subject discontinued during the open-label period after five days; the reason for discontinuation was categorized as "other" and further described as "subject stopped taking open-label medication and started taking Lortab 5/500mg prn". Study drug was provided for all subjects, however only 405 took study drug during the open label period.

Demographic and Baseline Characteristics

Demographic and baseline characteristics were balanced across the treatment groups. Most subjects were White (55%), Hispanic (22%), or Black (20%). A majority of subjects across the treatment groups were women (87%) and <65 years of age (94%). This is to be expected since bunions are more prevalent in females than males (estimates up to 10 times). In total, 75% of subjects were categorized as having severe baseline pain intensity (NRS pain intensity =6); the overall mean score was 7.0.

Time from anesthesia stop to first dose of study drug was similar for all treatments except the group receiving oxycodone. The time from anesthesia stop to first dose was a mean of 1.93 hours in this group, compared to 2.91 hours in the placebo group. The reason for this is not clear, since the baseline pain intensity scores for all of the treatment groups were comparable.

Table 7 below illustrates the demographic and baseline characteristics of the ITT population.

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Table 7: Demographic and Baseline Characteristics

(Study R331333-PAI-3003; KF5503/32: Intent-to-Treat Analysis Set)						
	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone IR 15 mg (N=125)	Total (N=602)
Sex, n (%)						
N	120	119	120	118	125	602
Male	12 (10)	18 (15)	13 (11)	19 (16)	15 (12)	77 (13)
Female	108 (90)	101 (85)	107 (89)	99 (84)	110 (88)	525 (87)
Racial/ethnic Group, n (%)						
N	120	119	120	118	125	602
White	68 (57)	56 (47)	71 (59)	62 (53)	76 (61)	333 (55)
Black	23 (19)	27 (23)	19 (16)	24 (20)	25 (20)	118 (20)
Hispanic	26 (22)	32 (27)	24 (20)	30 (25)	23 (18)	135 (22)
Other	3 (3)	4 (3)	6 (5)	2 (2)	1 (1)	16 (3)
Age (Years)						
N	120	119	120	118	125	602
Category, n (%)						
<65	111 (93)	113 (95)	114 (95)	111 (94)	119 (95)	568 (94)
≥65	9 (8)	6 (5)	6 (5)	7 (6)	6 (5)	34 (6)
Mean (SD)	44.3 (14.45)	41.5 (13.27)	44.8 (13.61)	44.4 (13.68)	46.4 (13.02)	44.3 (13.66)
Median	45.0	42.0	47.5	46.5	49.0	46.0
Range	(18;77)	(18;75)	(19;72)	(18;74)	(18;73)	(18;77)
Weight (kg)						
N	120	119	120	118	125	602
Mean (SD)	75.6 (17.28)	76.4 (19.00)	74.3 (16.96)	78.2 (18.92)	77.9 (17.14)	76.5 (17.87)
Median	69.5	71.8	71.4	74.6	74.5	72.0
Range	(46;129)	(49;148)	(47;135)	(48;127)	(48;150)	(46;150)
Baseline Body Mass Index (kg/m²)						
N	120	119	120	118	125	602
Mean (SD)	27.8 (6.00)	28.1 (5.77)	27.6 (6.17)	28.5 (5.85)	28.9 (6.03)	28.2 (5.96)
Median	26.6	27.7	26.8	28.0	27.6	27.4
Range	(16;46)	(19;48)	(16;53)	(19;44)	(19;35)	(16;55)
Baseline Pain Intensity Score						
N	120	119	120	118	125	602
Category, n (%)						
Moderate	31 (26)	25 (21)	32 (27)	33 (28)	27 (22)	148 (25)
Severe	89 (74)	94 (79)	88 (73)	85 (72)	98 (78)	454 (75)
Time from Anesthesia Stop to First Dose (hrs)^a						
N	120	119	120	118	125	602
Mean (SD)	2.91 (3.174)	2.41 (2.751)	2.50 (2.664)	2.72 (3.548)	1.93 (1.293)	2.49 (2.792)
Median	1.59	1.43	1.60	1.51	1.40	1.53
Range	(0.4;23.8)	(0.3;24.9)	(0.4;24.0)	(0.4;22.9)	(0.4;6.5)	(0.3;24.9)

^a For this study, anesthesia was defined as the popliteal block and does not include systemic analgesia used subsequent to the popliteal block.

Source: CSR R331333-PAI-3003 (KF5503/32), p. 71

In the open-label period, most subjects were women (87%) compared to men (13%). A majority of subjects were White (55%) and also included Black (19%), Hispanic (24%), and Other (2%) subjects. Most subjects were <65 years of age (84%) with a mean (standard deviation [SD]) value of 45.7 (13.4), and median (range) value of 48.0 (18-74). The predominance of women is consistent with the incidence of bunions in the population.

Medical history and physical exam findings were similar across all treatment groups for both the double-blind and open-label periods of the study, and did not represent any significant findings.

Prior and Concomitant Therapies

Medications taken prior to randomization

Prior medications for all treatment groups included opioid and non-opioid analgesics including ketorolac, antibiotics, cardiovascular medications, hormones, vitamins and nutritional supplements, and others. There did not appear to be notable differences among the treatment groups.

Post-surgical analgesics following bunionectomy were taken by approximately 60% of subjects, in a similar percentage across the treatment groups. Most subjects received ketorolac or hydrocodone/APAP. The reader is reminded that breakthrough postoperative pain during the surgical period (e.g., during the time the post-operative analgesia was to have been provided using a continuous popliteal sciatic block) was to have been managed using acetaminophen, ketorolac, and/or hydrocodone/APAP.

Concomitant Therapies during the Double-Blind Period (excluding analgesics and rescue)

The percentage of subjects taking concomitant medications during the double-blind period, excluding analgesics and rescue medications, was similar across all treatment groups (73% with placebo, 78% with tapentadol IR 50 mg, 77% with tapentadol IR 75 mg, 84% with tapentadol IR 100 mg, and 86% with oxycodone HCl IR 15 mg). The most commonly used concomitant medications (>10% in any active-treatment group) were metoclopramide hydrochloride, cephalexin, and multivitamins. Concomitant medications used by $\geq 5\%$ of subjects in any group are provided in Table X in Appendix X. Except for the following medications, there were no patterns for these concomitant medications among the treatment groups. Medications that were used in a higher percentage of subjects in the active-treatment groups compared to placebo included metoclopramide hydrochloride, ondansetron hydrochloride, and bisacodyl. The administration of these concomitant medications may have reflected treatment for the adverse events of nausea, vomiting, and constipation. Anti-emetic use was lower for all tapentadol treated groups than for the oxycodone HCl IR 15 mg group.

Rescue Medication during Double-Blind Period

According to the protocol, any subject requiring rescue medication during the double-blind period was to have been withdrawn from the study due to lack of efficacy. During the double-blind treatment period, a higher percentage of subjects in the placebo group (49%) took rescue medication compared with the active-treatment groups (Table X below). In the tapentadol IR groups, the percentage of subjects who took rescue medication was higher with lower doses (19% in the 50 mg group, 15% for the 75 mg group, and 10% for the 100 mg group). In the oxycodone HCl IR 15 mg group, 9% of subjects took rescue medication. The rescue medications that most subjects received were one or more of the following: ketorolac tromethamine, Vicodin (hydrocodone/acetaminophen), and morphine.

Following a retrospective review by the Applicant, three subjects were identified who took prior or concomitant medications during the double-blind period that were considered to be analgesics and were not immediately discontinued. All were recorded as

protocol deviations (Protocol Deviations below). Of these three subjects, one subject (304068 in the tapentadol IR 50 mg group) who took pethidine hydrochloride was identified during the double-blind period and resulted in study discontinuation for lack of efficacy. The remaining two subjects (one each in the tapentadol 50mg and 75 mg groups) completed the study before the protocol deviations were identified. Of those two subjects, one who took paracetamol during the double-blind period was included in the analysis for subjects who took rescue analgesic; one subject who took Alka-Seltzer at screening and continued taking it during the double-blind period was not included in the analysis for subjects who took rescue analgesic because the use of the analgesic began prior to the start of the study and was therefore considered prior therapy.

Table 8: First Rescue Analgesic for Subjects Who Discontinued Due to Lack of Efficacy
Double-Blind Period (Intent-to-Treat Analysis Set)

	Placebo (N=120) n (%)	Tapentadol IR 50 mg (N=119) n (%)	Tapentadol IR 75 mg (N=120) n (%)	Tapentadol IR 100 mg (N=118) n (%)	Oxycodone HCl IR 15 mg (N=125) n (%)
Total no. subjects with Rescue Analgesic	59 (49)	23 (19)	18 (15)	12 (10)	11 (9)
Ketorolac Tromethamine	33 (28)	13 (11)	9 (8)	6 (5)	5 (4)
Vicodin ^a	6 (5)	3 (3)	4 (3)	4 (3)	2 (2)
Morphine	7 (6)	4 (3)	1 (1)	2 (2)	3 (2)
Morphine Sulfate	2 (2)	0	0	0	0
Oxycocet	3 (3)	1 (1)	2 (2)	0	0
Paracetamol	0	0	1 (1)	0	0
Pethidine Hydrochloride	7 (6)	2 (2)	1 (1)	0	1 (1)
Procet ^b	1 (1)	0	0	0	0

^a Vicodin: hydrocodone/acetaminophen

^b Procet: hydrocodone/acetaminophen

Percentage is based on the number of subjects in each treatment group.

Includes Subject 305117 from the tapentadol IR 75 mg group who completed the double-blind period before the protocol deviation of taking concomitant rescue medication was identified.

Subjects who completed and started analgesic during the double-blind period are included.

The generic classifications are based on the World Health Organization dictionary, occasionally resulting in similar names for the same active component.

Source: CSR R331333-PAI-3003 (KF5503/32), p. 74

Concomitant Therapies during Open-Label Period

The percentage of subjects taking concomitant medications during the open-label period was 81%. Of these subjects, 27% took non-opioid analgesics and 7% took opioid analgesics. Non-analgesics were taken by 73% of the study population.

Protocol Deviations

Protocol deviations that were considered to be major were defined in the Statistical Analysis Plan and are listed below. A subject can be counted in more than 1 deviation category.

For double-blind treatment period:

- Used disallowed concomitant therapy during the double-blind treatment period;
- Second dose taken < 0.5 hour or > 7 hours;
- Any (3rd and beyond) dosing intervals that did not occur between 3 to 7 hours (exclusive) relative to the previous dose;

- Missed pain assessment at Hour 12, 24, 48 or 72 (If subject is still in the double-blind treatment period);
- Subject not discontinued from the study as per protocol;
- Took incorrect treatment other than randomized;
- Qualifying pain intensity measurement not within 9 hours after block discontinuation;
- Did not meet important inclusion/exclusion, which might impact the efficacy assessment

For open-label treatment period:

- Used disallowed concomitant therapy during the open-label treatment period.

The percentage of subjects with protocol deviations as specified in the SAP was 3% for the placebo group, 6%, 1%, and 2% for the tapentadol IR 50 mg, 75 mg, and 100 mg groups respectively, and 2% in the oxycodone HCl IR 15 mg group.

The table below illustrates the protocol deviations that occurred during the double-blind Period.

Table 9: Protocol Deviations Double-Blind Period; Safety Analysis Population

Protocol Deviation	Placebo (N=120) n(%)	Tapentadol IR mg			Oxycodone	Total (N=602) n(%)
		50 (N=119) n(%)	75 (N=120) n(%)	100 (N=118) n(%)	15 (N=125) n(%)	
Total # sub w/ deviations	3 (3)	7(6)	1(1)	2(2)	3(2)	16(3)
Regulatory requirement	2(2)	2(2)	0	0	1(1)	5(1)
Selection criteria not met	0	1(1)	0	0	0	1(<1)
Subject not d/c'ed as per protocol	0	1(1)	0	0	0	1(<1)
Took incorrect treatment	0	1(1)	0	2(2)	2(2)	5(1)
Used disallowed concomitant med	1(1)	2(2)	1(1)	0	0	4(1)

Source: Applicant Table 12, CSR R331333-PAI-3003 (KF5503/32), p. 76

The four protocol deviations related to regulatory requirements consisted of subjects signing incorrect versions of the informed consent form; however none of these affected the conduct of the study and the integrity of the subjects' data.

The one subject who was not discontinued according to protocol took another dose of study drug after rescue medication was administered.

The four subjects who used disallowed medication took "medication from wrong kit." Each subject took 1 incorrect tablet during the course of the study. Subjects were included in the analyses of their respective randomization groups.

During the open-label treatment, 6% of the subjects (24) had protocol deviations. All but one used concomitant therapy that was not allowed.

Exposure/Time to Second Dose

In terms of doses per day, the largest differences between the active- treatment and placebo groups were observed on Day 1. On Day 1, the majority of subjects in active-treatment groups took either five or six doses, but 40% of subjects in the placebo group took three or fewer doses. A large number of subjects in the placebo group discontinued during Day 1. On both Day 2 and Day 3, the majority of subjects in all groups took four doses corresponding to dosing every six hours. Details regarding exposure will be discussed in Section 7.

The protocol allowed each subject to take a second dose on Day 1 as soon as one hour after the first dose. More subjects (62%) in the placebo group required the second dose on Day 1 within three hours compared to all active-treatment groups (47% to 50% for tapentadol IR groups, 43% in the oxycodone HCl IR 15 mg group), as illustrated in the following table.

Table 10: Proportion of Subjects Taking Second Dose within 3 Hours of First Dose (Day1) during Double-Blind Treatment

Treatment Group	Placebo	Tapentadol IR			Oxycodone IR 15mg
		50mg	75mg	100mg	
N	120	119	120	118	125
Yes n (%)	74(62)	60(50)	56(47)	55(47)	54(43)
No n (%)	46(38)	59(50)	64(53)	63(53)	71(57)

Source: : Applicant Table 14, CSR R331333-PAI-3003 (KF5503/32), p. 79

The Applicant's table below shows the time to second dose for each treatment group. As would be expected, the placebo group had the shortest median time to second dose. Oxycodone had the longest time.

Table 11: Time to Second Dose

	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone HCl IR 15 mg (N=125)
Events (%)	118 (98.3)	117 (98.3)	117 (97.5)	117 (99.2)	122 (97.6)
Median	1.6	3.0	3.2	3.2	3.6
(95% CI) ^a	(1.5; 2.0)	(2.0; 3.4)	(2.2; 3.5)	(2.1; 4.3)	(2.3; 4.1)
Nominal p-value vs. placebo ^b		0.002	0.005	<0.001	<0.001

CSR R331333-PAI-3003 (KF5503/32), p.

During the open-label period, the average number of days that subjects took study drug was 6.9 days.

Pharmacokinetic analyses

Details regarding the PK analyses are included in the Biopharmaceutics Review.

Efficacy Results

Data Sets Analyzed

- The efficacy analysis was performed with the ITT analysis set that included all subjects who were randomized, received at least 1 dose of study drug, and had a non-missing baseline pain intensity score.
- One subject (301006) was excluded from the ITT analysis set. This subject in placebo group was not dosed and should not have been randomized because the baseline pain intensity was only two, whereas a score of ≥ 4 was required
- There were a total of nine subjects excluded from the ITT population for the Per Protocol population, five who took treatment other than that randomized, and four who used disallowed concomitant medication during the double-blind treatment period.

Primary Efficacy Analysis

The primary endpoint was the sum of pain intensity difference at 48 hours (SPID48). All tapentadol IR treatment groups showed a statistically significant (all p-values < 0.001 adjusted for multiple comparisons using the Hochberg procedure) improvement in pain on the primary efficacy variable compared with placebo with the LOCF imputation. There was a numerical trend of increasing efficacy with increasing tapentadol IR dose (mean SPID48: 119.1, 139.1, and 167.2 in the tapentadol IR 50 mg, 75 mg, 100 mg groups, respectively). Oxycodone HCl IR 15 mg (mean SPID48: 172.3) also showed a statistically significant (nominal p-value < 0.001) difference from placebo (mean SPID48: 172.3), validating the study assay sensitivity.

Table 12 summarizes the Applicant's analysis of the primary efficacy endpoint.

Table 12: Descriptive Statistics and Pairwise Comparison of SPID48 Using Hochberg Procedure-Primary Analysis, LOCF

	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone HCl IR 15 mg (N=125)
0-48 Hours					
Mean (SD)	24.5 (120.93)	119.1 (125.86)	139.1 (118.93)	167.2 (98.99)	172.3 (110.86)
Median (Range)	43.4 (-278;274)	127.6 (-185;402)	131.3 (-199;462)	158.5 (-94;408)	170.6 (-190;431)
LS Means (diff from placebo)	--	88.2	113.5	141.4	142.4
95% CI	--	60.71 to 115.59	86.12 to 140.81	113.98 to 168.90	115.28 to 169.47
Adjusted p-value vs. placebo ^a	--	< 0.001	< 0.001	< 0.001	

^a Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate. Adjusted p-values using Hochberg procedure. Oxycodone group is not included.
CSR R331333-PAI-3003 (KF5503/32), p. 86

For tapentadol IR, comparing subjects who took a second dose less than 3 hours after the initial dose (early second dose) with those who waited more than 3 hours to take the second dose, the mean SPID48 showed similar magnitudes and trends. The largest difference between subjects who took an early second dose was in the placebo group, where subjects taking an early second dose had a mean SPID48 of -2.0 compared to 67.2 for those who did not take an early second dose.

No notable differences were identified among subgroups based on racial groups (White, Black, Hispanic, and Other). The mean SPID48 values were higher for subjects with severe baseline pain intensity compared with those who had moderate baseline pain intensity. Because of imbalance in the numbers of subjects (subjects were predominantly female and <65 years of age), no conclusions could be drawn for age category (<65 and ≥65 years) or sex.

The Applicant was told by the Division (Type C meeting, December 2005, Pre-NDA meeting June 2007) that the imputation of missing data using LOCF for the primary analysis was not acceptable. The Applicant carried out sensitivity analyses of mean SPID48 based on the BOCF and WOCF imputations that showed similar results to those for the LOCF imputation. There were statistically significant differences for all active-treatment groups compared to placebo (see Table 13a).

Analysis of mean SPID48 based on the per protocol population showed similar results to those for the ITT population. There were statistically significant differences for all active-treatment groups compared with placebo (all nominal p-values <0.001).

The Applicant's table below illustrates the analyses for the primary endpoint utilizing LOCF, BOCF, and WOCF imputation methods, and secondary endpoint analyses.

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Table 13a: Summary of Efficacy Results: Comparison with Placebo: Bunionectomy
ITT Analysis Set

	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone HCl IR 15 mg (N=125)
SPID at Hour 48 (LOCF)				
LS Means diff. from placebo (95% CI)	88.2 (60.71, 115.59)	113.5 (86.12, 140.81)	141.4 (113.98, 168.90)	142.4 (115.28, 169.47)
Adjusted p-value vs. placebo ^{a,b}	<0.001	<0.001	<0.001	—
Unadjusted p-value vs. placebo ^a	—	—	—	<0.001
SPID at Hour 48 (BOCF) ^{a,c}	<0.001	<0.001	<0.001	<0.001
SPID at Hour 48 (WOCF) ^a	<0.001	<0.001	<0.001	<0.001
Two-part model on % change NRS and drop-out ^d	<0.001	<0.001	<0.001	<0.001
Pain assessment $\geq 30\%$ improved at Hour 48 ^e	<0.001	<0.001	<0.001	<0.001
Pain assessment $\geq 50\%$ improved at Hour 48 ^e	<0.001	<0.001	<0.001	<0.001
Distribution of Responders at Hour 48, Gehan test	<0.001	<0.001	<0.001	<0.001
Distribution of Responders at Hour 48, log-rank test	<0.001	<0.001	<0.001	<0.001
Distribution of Responders at Hour 48, Van Der Waerden test	<0.001	<0.001	<0.001	<0.001
Time to first rescue medication ^{c,f}	<0.001	<0.001	<0.001	<0.001
SPID at Hour 12 (LOCF) ^a	<0.001	<0.001	<0.001	<0.001
SPID at Hour 24 (LOCF) ^a	<0.001	<0.001	<0.001	<0.001
SPID at Hour 72 (LOCF) ^a	<0.001	<0.001	<0.001	<0.001
TOTPAR at Hour 48 (LOCF) ^a	<0.001	<0.001	<0.001	<0.001
SPRID at Hour 48 (LOCF) ^a	<0.001	<0.001	<0.001	<0.001
Time to confirmed perceptible pain relief ^f	0.005	<0.001	<0.001	<0.001
Patient Global Impression of Change ^g	<0.001	<0.001	<0.001	<0.001

^a Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate.

^b P-values adjusted for multiplicity using Hochberg procedure.

^c P-values for tapentadol groups are adjusted for multiplicity using Hochberg procedure. P-value for oxycodone group is not adjusted for multiplicity. ANCOVA model includes all treatment groups.

^d For percent change NRS at Hour 48 (observed case): ANCOVA model includes treatment as factors and baseline pain score as a covariate. For discontinuation: Logistic regression model includes treatment as factor and baseline pain score as a covariate.

^e P-value based on Generalized Cochran-Mantel-Haenszel test for general association controlling for center.

^f Log rank test stratified with center.

^g P-value based on Generalized Cochran-Mantel-Haenszel test for row mean scores differ controlling for center.

Source: MODULE 2.7 Clinical Summary; 2.7.3 Clinical Efficacy p. 35

The Applicant's analysis of the primary efficacy endpoint, using LOCF, BOCF, and WOCF imputations, was confirmed by the Agency's statistical reviewer, Jonathan Norton, PhD.

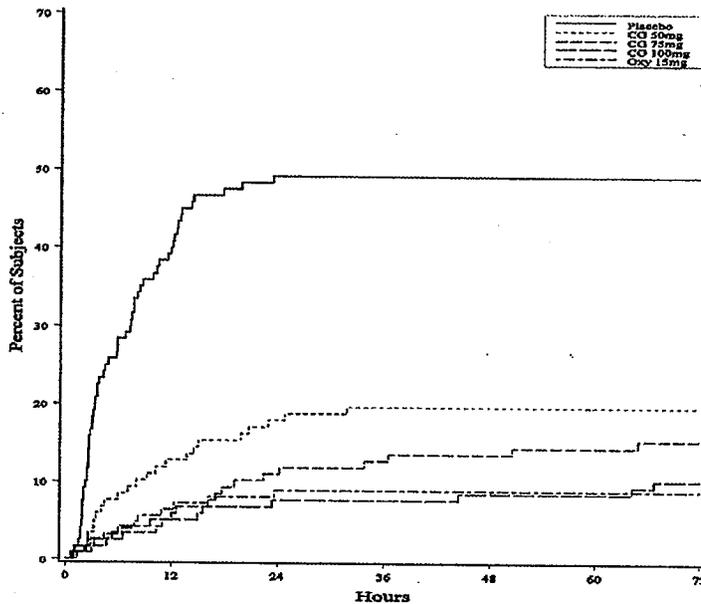
Secondary Efficacy Analyses

Time to Rescue Medication Use

The times to rescue medication use were longer with tapentadol IR versus placebo for all doses, and generally, longer times were found with higher tapentadol doses. In addition, the oxycodone HCl IR 15 mg group was also different from placebo.

The Applicant's figure below illustrates the time to rescue medication for all treatment groups.

Figure 3: Time to Rescue Medication



Source: CSR R331333-PAI-3003 (KF5503/32), p. 88

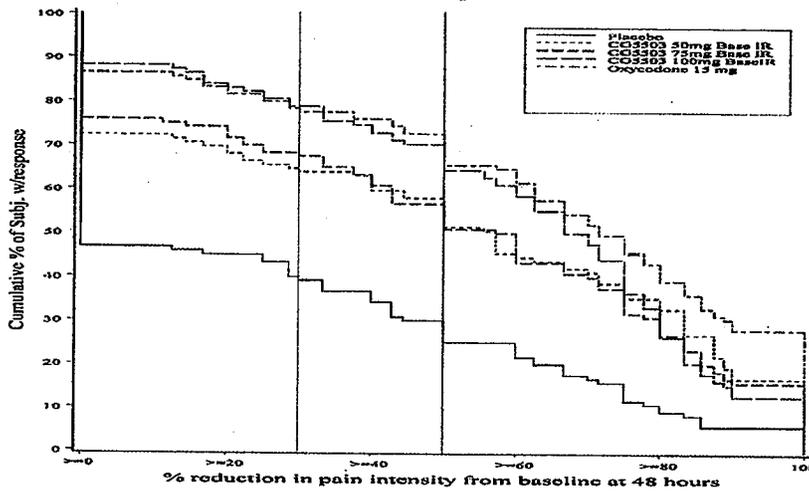
Cumulative Responder Analysis

The cumulative distribution of responders at 48 hours was analyzed, and all active-treatment groups were significantly different from placebo. The distribution is presented in Figure X.

The proportions of subjects who showed at least a 30% improvement in pain intensity at 48 hours was higher in the active-treatment groups compared with placebo: 40.0% in the placebo group, 64.7%, 68.3% and 78.8% of subjects in the tapentadol IR 50 mg, 75 mg and 100 mg groups, respectively, and 78.4% in the oxycodone HCl IR 15 mg group. The proportions of subjects who showed a 50% improvement in pain intensity at 48 hours were also higher in the active-treatment groups compared with placebo: 30.0% in the placebo group, 58.0%, 56.7%, and 70.3% of subjects in the tapentadol IR 50 mg, 75 mg, and 100 mg groups, respectively, and 72.8% in the oxycodone group.

Similar patterns were observed in the results at 12 and 24 hours. At 72 hours the oxycodone HCl IR 15 mg group demonstrated a slight numerical advantage over the tapentadol IR 100 mg group at 30% (84% and 80.5%, respectively) and 50% (77.6% and 72.9%, respectively) improvement in pain intensity

Figure 4: Cumulative Distribution of Responders at 48 Hours



Source: CSR R331333-PAI-3003 (KF5503/32), p. 90

Onset of Pain Relief

The two-stopwatch method was used to record when subjects experienced perceptible pain relief and meaningful pain relief. The Applicant's Table 13b below illustrates the onset of pain relief.

For perceptible pain relief, 80.0% to 97.5% of subjects reported perceptible pain relief in all treatment groups including placebo. The median time to perceptible pain relief was not different in terms of minutes between all treatment groups including placebo, ranging from 30 to 46 minutes.

For time to meaningful pain relief, all active-treatment groups showed a statistically significant shorter time compared with placebo (nominal p-value = 0.008 for tapentadol IR 50 mg; nominal p-values <0.001 for other active-treatment groups). Median time to meaningful pain relief ranged from 123.0 minutes to 94.0 minutes for the tapentadol IR treatment groups, 77.0 minutes for the oxycodone HCl IR 15 mg group, and 240.0 minutes for the placebo group. A numerical trend for tapentadol dose-response was observed for the median times to onset and percentage of subjects reporting meaningful pain relief.

For onset of confirmed perceptible pain relief (derived from perceptible and meaningful pain relief to evaluate the onset of analgesic effect) all active-treatment groups showed statistically significant shorter times to confirmed perceptible pain relief compared with placebo. The median times to confirmed perceptible pain relief did not exhibit dose-dependent behavior and were 46.0, 32.0, 37.0, and 31.0 minutes for tapentadol IR 50 mg, 75 mg, 100 mg and oxycodone HCl IR 15 mg, respectively. The median time was 100.0 minutes for placebo-treated subjects. These results indicated earlier times to onset of analgesic effect following active treatment.

Table 13b: Onset of Pain Relief

	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone HCl IR 15 mg (N=125)
Perceptible Relief					
Events (%)	96 (80.0)	105 (88.2)	116 (96.7)	115 (97.5)	121 (96.8)
Median	34.0	46.0	31.0	35.5	30.0
(95% CI) ^a	(27.0; 59.0)	(37.0; 58.0)	(28.0; 44.0)	(31.0; 42.0)	(28.0; 34.0)
Nominal p-value vs. placebo ^b		0.935	0.029	0.045	<0.001
Meaningful Relief					
Events (%)	65 (54.2)	94 (79.0)	101 (84.2)	103 (87.3)	107 (85.6)
Median	240.0	123.0	104.0	94.0	77.0
(95% CI) ^a	(155.0; 468.0)	(93.0; 164.0)	(71.0; 128.0)	(84.0; 118.0)	(60.0; 92.0)
Nominal p-value vs. placebo ^b		0.008	<0.001	<0.001	<0.001
Confirmed Perceptible Relief					
Events (%)	65 (54.2)	93 (78.2)	100 (83.3)	103 (87.3)	106 (84.8)
Median	100.0	46.0	32.0	37.0	31.0
(95% CI) ^a	(39.0;)	(37.0; 59.0)	(29.0; 46.0)	(32.0; 44.0)	(28.0; 36.0)
Nominal p-value vs. placebo ^b		0.005	<0.001	<0.001	<0.001

^a In minutes; based on Kaplan–Meier product limit estimates.

^b Pairwise comparison: Log rank test stratified with center.

Source: CSR KF5503/32, p. 97

Additional Secondary Endpoints

Table 13a illustrates the additional secondary endpoint analyses. All endpoints appear to support the findings of efficacy of all tested doses of Tapentadol IR in this study.

Non-Inferiority Comparison of Tapentadol IR 75mg and 100mg versus Oxycodone HCL IR 15 mg

The Applicant performed a non-inferiority comparison of Tapentadol IR 75mg versus oxycodone IR 15mg, and a similar post-hoc comparison of tapentadol IR 100mg versus oxycodone IR 15mg. The analyses factored in specific adverse event rates (nausea and vomiting). A non-inferiority margin of -48 (10% of the entire possible range of scores of 480) was prespecified in the statistical analysis plan. The Applicant's analysis established that tapentadol IR 100mg was non-inferior to oxycodone IR 15mg, but tapentadol 75mg was not, according to the criteria established by the Applicant.

b(4)

Applicant's Efficacy Conclusions

1. The efficacy of tapentadol IR in the treatment of acute pain during a 72-hour period following bunionectomy was robust.
2. All tapentadol IR treatment groups showed statistically significant improvement of pain in comparison with the placebo group for the primary efficacy variable, SPID48 with LOCF imputation for subjects who discontinued.
3. There was a numerical trend of increasing efficacy with increasing tapentadol IR dose.

4. Sensitivity analyses results using BOCF and WOCF imputations also showed statistically significant improvement for all active-treatment groups versus placebo.
5. Secondary efficacy analyses were as follows:
 - a. Time to first rescue was longer for all active-treatment groups versus placebo, and showed increasing times with increasing tapentadol dose.
 - b. The distribution of responder rates based on PI at 48 hours showed differences between each active-treatment group versus placebo.
 - i. Percentage of subjects who showed at least a 30% or 50% improvement in PI at 48 hours was higher in tapentadol IR and oxycodone groups than in placebo group.
 - c. A large percentage of subjects reported perceptible pain relief (using the two-stopwatch method) in all treatment groups including placebo (80% to 97.5%).
 - d. For time to meaningful pain relief, all active-treatment groups showed a significantly shorter time compared with placebo. Median time to meaningful pain relief ranged from 123 minutes to 94 minutes for the tapentadol IR treatment groups, 77 minutes for the oxycodone IR 15mg group, and 240 minutes for the placebo group.
 - e. The remaining secondary analyses supported the efficacy of tapentadol IR in the treatment of acute pain.
 - f. Tapentadol IR 100mg was non-inferior to oxycodone HCL IR 15mg.

Reviewer's Efficacy Conclusions

This reviewer is in agreement with the Applicant's findings of efficacy. Although the primary analysis was performed utilizing the LOCF method for the imputation of missing data, contrary to the Division's advice on numerous occasions, the Applicant did carry out sensitivity analyses using the BOCF and WOCF imputation methods. The sensitivity analyses supported the efficacy of tapentadol in the acute setting. In addition, analysis of the secondary endpoints showed results in favor of tapentadol.

There was a numerical separation of all doses of tapentadol IR as shown by the trend of increasing efficacy with increasing tapentadol IR dose based on the primary endpoint.

The oxycodone IR 15mg treatment group was included to provide assay sensitivity for the study. [

b(4)

b(4)

Protocol R331333PAI3002 (J&JPRD); KF5503/33 (Grünenthal); Phase 3

Title: A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Doses of CG5503 Immediate-Release Formulation in Subjects Awaiting Primary Joint Replacement Surgery for End-Stage Joint Disease

Date issued: Original protocol issued May 24, 2006, First version used in clinical study issued September 18, 2006

Objectives:

- **Primary:** to determine the efficacy of CG5503 immediate-release (IR) using the sum of pain intensity difference (SPID) over 5 days compared with placebo, and to assess the safety and tolerability of multiple doses of CG5503 IR in subjects who are eligible for elective primary total or partial joint replacement of the hip or knee due to chronic osteoarthritis

- **Secondary**
 - Compare the effect of CG5503 IR with placebo in time to the first rescue pain medication during the double-blind treatment period

 - Evaluate the effect of CG5503 IR with the distribution of responder rates based on percent change from baseline in pain intensity (PI) for each of the time point (Day 2, 5, and 10)

 - Demonstrate the efficacy of CG5503 IR using total pain relief (TOTPAR) and sum of total pain relief and sum of pain intensity difference (SPRID) over 2, 5, and 10 days; and SPID over 2 and 10 days

 - Evaluate patient global impression of change (PGIC) of study treatment at the end of the double-blind treatment period

 - Evaluate the adverse event rates across treatment groups (especially nausea and vomiting)

 - Explore sleep quality and bowel movement using questionnaires

- Explore the efficacy of oxycodone IR in comparison with CG5503 IR and placebo

Study design:

This study was to have been a randomized, double-blind, active- and placebo-controlled, parallel-group, multicenter, outpatient study to evaluate the efficacy and safety of multiple oral doses of CG5503 IR in treating chronic pain in subjects who are candidates for primary total or partial joint replacement surgery for end-stage degenerative joint disease of the hip or knee based on clinical and radiographic criteria defined by standard accepted guidelines appropriate in each country.

Study drug:

- CG5503 50mg and 75mg
- Oxycodone IR 10 mg
- Placebo

Study conduct:

Summary

A total of 624 subjects (156 per treatment group) were to have been assigned to one of the following groups:

- Placebo
- 50 mg CG5503 base IR
- 75 mg CG5503 base IR (includes a titration step of 50mg for Day 1, and 75mg for Days 2 to 10)
- 10mg oxycodone IR

Each subject was to have taken assigned treatment every 4 to 6 hours during waking hours throughout the double-blind outpatient treatment period. The study was to have been a maximum of 43 days in length.

All controlled-release opioid analgesics were to have prohibited within 28 days before screening and throughout the study. Products containing IR opioid analgesics were to have been allowed before screening if taken intermittently up to 4 days each week for the previous 28 days before screening. The IR opioid analgesic was to have been discontinued prior to the run-in period. The non-opioid component of combination products could be continued during the study. Non-opioid analgesics were to have been allowed throughout the study if taken on a stable regimen for at least 28 days before screening. Subjects were to have been asked to stop any ancillary physiotherapy (e.g., hot/cold pack, magnets), massage therapy, physical therapy, or acupuncture at screening.

All subjects were to have been asked to keep a diary. The diary was to have included a bowel movement questionnaire and a vomiting questionnaire, as well as entries for pain assessments.

Study Periods

The study was to have consisted of the following periods:

1. **Screening period (Days -28 through -8):** One clinic visit was to have been required within 21 days before run-in period to evaluate subjects for enrollment. At this visit, subjects were to have been instructed when to start the 7-day run-in period and when to start the diary.
2. **Run-in period (Days -7 through -1):** Subjects were to have had a minimum of 3 days of pain assessments during this period. During this period subjects' PI levels were to have been recorded in the diary twice daily for study qualification. A daily bowel movement questionnaire was to have been completed. Qualification for randomization was to have been based on the last 3 days of pain assessments during this period.
3. **Double-blind, outpatient treatment period (Days 1 through 10):** This period was to have required two clinic visits – one visit for randomization and one visit for mid-study evaluation.

Day 1: Visit for randomization (second clinic visit)

Qualification for randomization was to have been based on the following values from the last 3 days of pain assessments in the run-in period:

- mean PI score ≥ 5 (after rounding 4.5 and above to an integer) on an 11-point numerical rating scale (NRS), where the minimum single assessment score is =3

All subjects were to have started their first dose after they arrive home on Day 1. Subjects were to have been instructed to begin double-blind diary entries on the evening of Day 1 and continue pain-assessment entries approximately every 12 hours thereafter.

Day 6: Visit for the mid-study evaluation. (Third clinic visit)

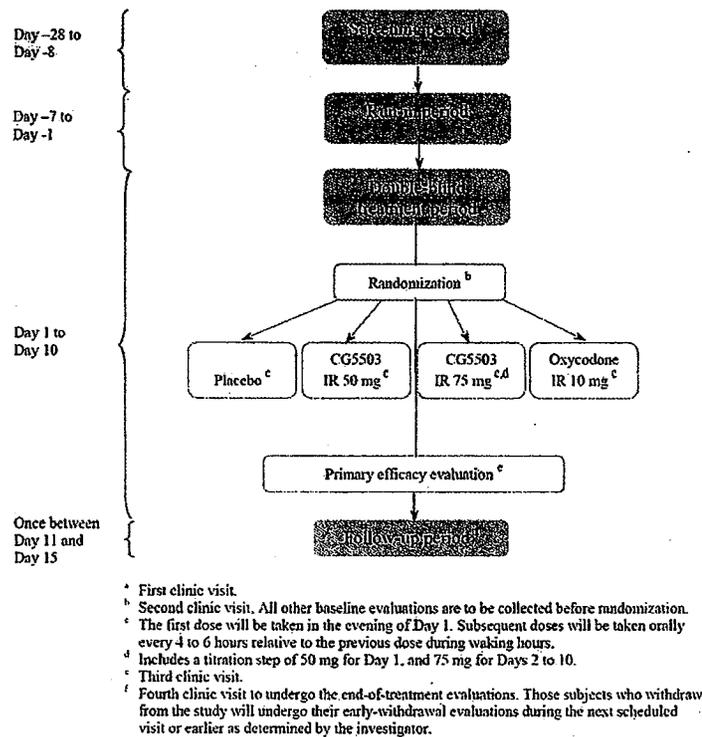
4. **Post-treatment period (Days 11 through 15):** End of treatment evaluation (fourth clinic visit)
5. **Follow-up 48 hours after last dose:** Telephone report of adverse events

Study completion

A subject was to have been considered to have completed the study only if the subject had finished the 10-day double-blind treatment and undergone the end-of-treatment evaluation during the post-treatment period. Subjects who withdrew after randomization were not to have been replaced.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 5: Study schematic



Source: Tapentadol: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 23

Study population:

Men and women between the ages of 18 and 80 years, inclusive, who have experienced chronic pain from non-inflammatory, end-stage degenerative joint disease of the hip or knee and are candidates for primary total or partial joint replacement

Inclusion/Exclusion criteria:

Inclusion criteria

1. Man or woman ages 18-80 inclusive
2. Signed consent
3. Clinical diagnosis OA of the hip or knee based on clinical and radiographic criteria by standard accepted guidelines; radiographic evidence of OA of the target joint must be recorded within previous 12 months.
4. Need primary unilateral total or partial joint replacement surgery
5. Require daily doses of analgesic medication for chronic pain consistent with Step 2 or higher of WHO Pain relief ladder including those that cannot tolerate daily non-opioid analgesics
6. Subjects should be dissatisfied with current analgesic regimen
7. Before randomization on Day 1, pain is not adequately controlled with the current stable analgesic regimen based on the following criteria:

- a. Mean PI is equal or greater than 5 (after rounding 4.5 and above to an integer) on an 11-point (0 to 10) NRS during the last 3 days of pain assessments during the run-in period
- b. Minimum single assessment PI score is equal or greater than 3 during the last 3 days of pain assessments during the run-in period
8. Women must be post-menopausal, surgically sterile, or practicing an effective means of birth control if they are sexually active before entry and throughout the study.
9. Negative serum pregnancy test

Exclusion criteria:

1. History of seizure, epilepsy suggested by the following:
 - a. Mild or moderate traumatic brain injury, stroke, TIA, brain neoplasm within one year of screening, or
 - b. Severe traumatic brain injury, episode(s) of unconsciousness of more than 24 hours duration or posttraumatic amnesia of more than 24 hours duration within 15 years of screening.
2. Received experimental drug or device within 28 days prior to study
3. Participated in 3 or more clinical trials of analgesics prior to this study
4. History of alcohol or drug abuse
5. Pending litigation due to history of chronic pain or disability
6. History of chronic hep B or C, or HIV, or presence of active hep B or C within three months before screening
7. Treated with anticonvulsants, MAOIs, tricyclic antidepressant, neuroleptics, or serotonin norepinephrine reuptake inhibitors within two weeks prior to screening (selective serotonin reuptake inhibitors treatments are allowed if taken for at least 28 days before screening at an unchanged dose)
8. Received IR opioid analgesic taken five days or more each week during the previous 28 days before screening. Products containing IR opioid analgesics taken four days or less each week are allowed
9. IR opioid analgesics must be discontinued prior to run-in period
10. History of malignancy within past six months, except basal cell carcinoma
11. Concomitant autoimmune inflammatory conditions involving target joint
12. Acute crystal-induced arthropathy within past six months
13. Steroid therapy within four weeks
14. Presence of any of the following
 - a. Major trauma to target joint within six months prior
 - b. Apparent avascular necrosis in target joint within six months prior
 - c. Intra-articular injections of steroids or hyaluronan in target joint within 3 months prior
15. Pregnancy or breastfeeding
16. Moderate or severe renal insufficiency
17. ALT or AST greater than three times upper limit of normal
18. Allergy or contraindication to CG5503 or oxycodone
19. Plan to undergo surgery during course of study
20. Clinically significant disease that could affect safety or efficacy assessments

Prohibitions and restrictions:

- No ingestion of alcohol or CNS depressants during study
- No operation of machinery or driving

Prohibited medications and therapies

- Controlled-release opioids
- Products containing IR opioids taken intermittently (up to 4 days each week before screening) were to have been discontinued prior to the run-in period, and resumed on Day 11
- Non-opioid analgesics, unless subject has been taking them on stable regimen for at least 28 days prior to screening
- Anticonvulsants, MAOIs, TCAs, neuroleptics, SNRIs (SSRIs allowed if taken for at least 28 days prior to screening at unchanged dose), systemic steroids, injectable hyaluronic acid
- Physiotherapy, massage therapy, physical therapy, acupuncture

Treatments:

- Double-blind treatment period: each subject was to have received one of the following treatments:
 - CG5503 base IR 50mg
 - CG5503 base IR 75mg
 - Oxycodone IR 10mg
 - Placebo
- Doses were to have been taken orally every four to six hours during waking hours
- All treatments were to have been provided as capsules of identical shape, color, and size
- A total of 60 doses were to have been provided to each study subject (up to 6 doses/day)

The table below shows the maximum amount of medication allowed for each 24 hour period.

Table 14

Maximum Amounts of Medication (Taken Every 4 to 6 hours) Received by a Subject During Each 24-hour Period				
Treatment	CG5503 base IR 50 mg	CG5503 base IR 75 mg*	Oxy-IR 10 mg	Placebo
Maximum dose (6 doses)	300 mg	450 mg	60 mg	N/A

* Includes a titration step of 50 mg for Day 1, and 75 mg for Days 2 to 10

Source: Tapentadol: Clinical Study Report R331333-PA1-3002 (KF5503/33), p. 45

Rescue medication: any subject requiring rescue medication was to have been withdrawn from the study due to lack of efficacy

Procedures:

Study procedures are summarized in the following table:

Table 15
TIME AND EVENTS SCHEDULE

Assessments/Procedures	Screening Period Study Day ^d -28 to -8	Run-in Period -7 to -1	Randomization	Double-Blind Treatment Period										Posttreatment Period End-of-Treatment/Early-Withdrawal Evaluation ^e 11 to 15			
				1	2	3	4	5	6 ^c	7	8	9	10				
Clinic visits	X		X							X							X
Informed consent	X																
Genetic informed consent	X																
Inclusion/exclusion criteria	X		X														
Physical examination, including weight and height ^d	X																X
Medical history	X																
Vital signs ^e	X		X							X							X
12-lead electrocardiogram	X		X							X							X
Clinical laboratory testing	X		X														X
Urine drug screen	X																X
Pregnancy test	X ^f		X ^g														X ^h
Serology for hepatitis B and C	X																X ⁱ
Dispense or collect diary	X		X														X
DNA sample collection if applicable			X														X
Randomization			X														
Study treatment dispensed or collected			X							X							X
Study treatment taken by subjects			X ^b		X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events ^j	X		X		X					X							X
Prior and concomitant therapy ^k	X		X		X					X							X
Bowel movement questionnaire ^l		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep evaluation questionnaire	X		X		X					X							
Vomiting questionnaire ^m			X		X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Evaluations																	
Pain intensity assessment (11-point numerical rating scale [NRS]) ⁿ		X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pain relief assessment (5-point NRS) ^o			X		X	X	X	X	X	X	X	X	X	X	X	X	
Patient global impression of change																	X

^a Those subjects who withdrew from the study will undergo their early-withdrawal evaluations during the next scheduled visit or earlier as determined by the investigator
^b Each study day will last from midnight (00:01) to midnight (24:00)
^c Mid-study evaluation. The visit may occur during Days 6 to 8
^d Height will be measured at screening only
^e After resting for 5 minutes
^f Serum test
^g Urine test
^h The first dose will be taken after arriving at home on Day 1
ⁱ Collected during clinic visits and includes the period since the previous clinic visit
^j Recorded each evening
^k Recorded at Day 1 clinic visit and each evening
^l Recorded each evening and morning

Source: Tapentadol: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 23 S

- Blood samples: The amount per subject was to have been 10ml for genotyping, ~37.5ml for hematology and chemistry, and 4ml for serology
- Screening period (Day -28 through Day -8):
 - Informed consent, meet I/E criteria
 - Subjects given 1-week home diary and instructed on completion of PI scale and bowel movement questionnaire
 - History, physical, vital signs, labs
- Run-in period (Day -7 through Day -1)
 - Discontinue intermittent IR opioids
 - Record PI over previous 12 hours using 11-point NRS at 12-hour intervals
 - Have minimum of three days of pain assessments

- Complete bowel movement questionnaire each PM
- Double-blind period (Day 1 through Day 10)
 - Day 1 clinic visit
 - Confirm I/E criteria, completion of at least 3 days of pain assessments during run-in
 - Mean PI (avg of 3 days) ≥ 5 (rounding 4.5 and above to 5) on 11-point NRS, and minimum single assessment at least 3.
 - Baseline measures recorded (VS, ECG, labs)
 - Vomiting and sleep evaluation questionnaires completed
 - Subjects provided with 60 doses of study treatment, and instructed to take first dose at home; subsequent doses to be taken every 4-6 hours during waking hours.
 - Instructed to begin diary entries starting on evening of Day 1 and continue every 12 hours until end of Day 10.
 - Day 6-8 mid study evaluations
 - Return unused study drug
 - Evaluations as per time and events schedule
- Post-treatment period (Day 11 -15)
 - PE, VS, ECG, labs
 - PGIC

Outcome measures:

- Pain intensity (PI): 11-point NRS
- Pain relief (PR): 5-point NRS
- Patient global impression of change (PGIC)

Efficacy endpoints:

- Primary endpoint: 5-day SPID
 - Pain intensity difference (PID) will be calculated as $PID = \text{Baseline PI} - \text{current PI}$, where baseline PI is the mean PI collected during the last three days of pain assessments during the run-in period
 - Sum of pain intensity difference (SPID) is a time weighted calculation over 5 days using the following formula: $SPID = \sum W_i * PID_i$; where the sum includes all observations collected from baseline to the end of Day 5 and W_i is the time elapsed from the previous observation (PID_{i-1}) to the current observation (PID_i)
- Secondary endpoints:
 - Time to first rescue from the first dose of study treatment
 - Distribution of responder rates Day 5
 - Percent change from baseline in PI at Day 5 will be calculated using 11-point NRS. Subjects without a Day 5 value will be assigned the worst possible score. Response rate for a given percent change value will be defined as the proportion of subjects

above that threshold value. The distribution of response rate at Day 5, as defined above, will be determined for each treatment group. Similar calculation will be carried for percent change from baseline in 11-point NRS at Day 2 and Day 10.

- SPID over 2 and 10 days
- TOTPAR (Total Pain Relief) and SPRID (Summed Total Pain Relief and Pain Intensity Difference) over 2, 5, and 10 days
- PGIC of study treatment on the end-of-treatment evaluation

Total Pain Relief

TOTPAR will be calculated over 2, 5, and 10 days using the following formula:
 $TOTPAR = \sum W_i * PARI_i$

Where the sum includes all observations collected from the evening of Day 1 to that particular time point (Day 2, 5 and 10 days) and W_i is the time elapsed from the previous observation ($PARI_{i-1}$) to the current observation ($PARI_i$).

Sum of Total Pain Relief and Sum of Pain Intensity Difference

SPRID will be calculated over 2, 5, and 10 days using the following formula:
 $SPRID = SPID + TOTPAR$.

Pharmacogenomics:

In countries where PG testing is allowed, a single 10ml blood sample will be collected for PG analysis.

Safety evaluations:

- Adverse events
- Clinical lab tests
- ECGs
- VS, PE

Other evaluations:

- Serum and urine pregnancy tests
- Urine drug screen, serology
- Bowel movement questionnaire (Section 9.4)
- Sleep evaluation (Section 9.4)
- Record of vomiting experience
- Joint radiograph if needed to determine eligibility

Subject completion/withdrawal

- A subject will be considered to have completed the study if he or she completes the 10-day double-blind treatment period and the end-of-treatment evaluation performed during the post-treatment period.
- A subject will be withdrawn from the study for any of the following reasons:

- Lack of efficacy (defined as requiring rescue medication during the double-blind period)
- The investigator believes that for safety reasons it is in the best interest of the subject to stop treatment
- Withdrawal of consent
- Pregnancy
- Lost to follow-up

Statistical methods:

Sample size

The Applicant based the sample size calculation on the completed Phase 2b multi-dose four week study of CG5503 prolonged release formulation on subjects with osteoarthritis (KF5503/19). The effect size of VAS on day 8 relative to placebo was 0.37. A study with Ultracet showed a standard effect size of 0.45. The Applicant determined that an effect size of 0.4 would be considered clinically and statistically significant in pain relief compared with placebo for the CG5503 base IR 50mg dose in subjects waiting for primary total or partial joint replacement surgery.

Assuming the above effect size, it was determined that approximately 156 subjects for each treatment group will provide 90% power to show that at least one CG5503 IR dose group is statistically different from placebo at an overall alpha level of 0.05. Based upon this calculation, a total of 624 subjects would need to be randomized.

Demographics and baseline characteristics

Demographic and baseline characteristics as well as study discontinuation and reason(s) for discontinuation will be summarized by treatment.

Efficacy analyses

1. Primary efficacy analysis
 - a. Efficacy is based on all randomized subjects who take at least one dose of study treatment and have a baseline pain assessment
 - b. Primary endpoint is 5-day SPID (calculation described above)
 - c. Imputation methods
 - i. Pain intensity values will be imputed using LOCF (last observation carried forward) for time points after the subjects prematurely discontinue from the double-blind treatment.
 - ii. BOCF (baseline observation carried forward) will be applied for all subjects who do not have post-baseline pain values
 - iii. Intermittent missing PI scores will be imputed using a linear interpolation approach.
 - d. Descriptive statistics will be presented for the SPID at all analysis time points
 - e. SPID will be analyzed using an analysis of covariance (ANCOVA) model
 - i. Treatment and investigator will be included as factors
 - ii. Baseline PI score will be covariate

- iii. Treatment effect will be estimated based on least-squares means of the difference
 - iv. P-values that adjust for multiple comparisons using the Hochberg procedure will be presented for the SPID over 5 days for each CG5503 IR dose regimen versus placebo
2. Secondary efficacy analysis
 - a. Time to first rescue medicine: estimated by Kaplan-Meier estimate
 - b. Remaining analyses will be two-sided at 0.05 alpha levels.
 - c. No multiple comparison adjustments will be made

Safety analyses

1. Based on all randomized subjects who took at least one dose of study treatment
2. Adverse events
 - a. MedDRA coding
 - b. Treatment emergent AEs will be summarized for double-blind period for each treatment group by body system, preferred term, intensity, and relationship to study treatment
 - c. AEs of special interest (nausea, vomiting, constipation) will be summarized and compared among treatment groups
3. Clinical labs, ECGs will be summarized by treatment groups

Protocol amendments *

*Only amendments considered significant are listed.

Amendment INT-1 (September 18, 2006)

1. The activities associated with the mid-study visit are safety related, rather than efficacy. The efficacy scores will be captured in the diary.
2. Codeine or Tramadol are allowed during screening if taken less than 4 days each week, but must be discontinued prior to run-in. This will allow greater subject participation.
3. Subjects must have a minimum of 3 days of pain assessments during the run-in period.

Since this amendment was submitted prior to initiation of enrollment, these changes do not affect the study analysis.

Amendment INT-2 (November 21, 2006)

There were no important changes made to the protocol with this amendment.

Amendment INT-3 (March 22, 2007)

1. Intermittent IR opioids are allowed before screening intermittently, and must be discontinued during run-in period.
2. Subjects who were offered joint surgery but declined are allowed in study.
3. Subjects with joint radiographs beyond the previous 12 months will require verification to determine subject eligibility

This amendment would not appear to affect the study analysis.

Amendment INT-4 (August 29, 2007)

There were no important changes made to the protocol with this amendment.

Results:

Subject disposition

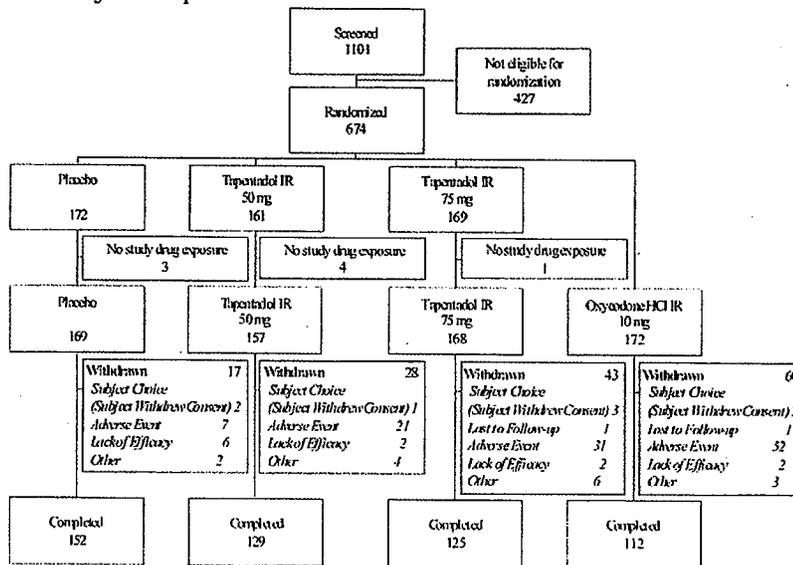
The study was conducted from 24 October 2006 to 22 August 2007 in the United States (48 sites), Canada (20 sites), the United Kingdom (5 sites), Australia (3 sites), and New Zealand (5 sites). A total of 1101 subjects were screened, and 674 subjects were randomized: 172 subjects to placebo, 161 subjects to tapentadol IR 50 mg, 169 subjects to tapentadol IR 75 mg, and 172 subjects to oxycodone HCl IR group.

Of the 674 randomized subjects, eight did not take study medication (three in the placebo group [two subjects for “other” reasons, described below, and one subject withdrew consent], four in the tapentadol IR 50 mg group [three subjects lost to follow-up, one subject withdrew consent], and one in the tapentadol IR 75 mg group [subject withdrew consent]). These subjects were excluded from all safety and efficacy analyses.

There were two subjects in the placebo group who discontinued due to “other” reasons. For one of these subjects (203937), a non-treatment-emergent adverse event (atrial fibrillation) was noted (this subject is not included in any of the displays or listing of adverse events). The second subject who discontinued due to “other” reason (203153) met an exclusion criterion (SSRI regimen not stable for 28 days prior to screening) (this subject was not included in any of the displays or listing of protocol deviations).

The figure below illustrates the disposition of study subjects.

Figure 6: Subject Disposition



Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 69

The percentage of subjects who completed the double-blind treatment period was highest in the placebo group (90%) and lower in the active-treatment groups (65% to 82%) with the lowest percentage in the oxycodone IR group, as shown in the table below.

Table 16: Completion/Discontinuation Information: Double-Blind Period

Completion Status Reason for Withdrawal	Placebo	Tapentadol IR 50 mg	Tapentadol IR 75 mg	Oxycodone HCl IR 10 mg	Total
	(N=169) n (%)	(N=157) n (%)	(N=168) n (%)	(N=172) n (%)	(N=666) n (%)
Completed ^a	152(90)	129(82)	125(74)	112(65)	518(78)
Withdrawn ^a	17(10)	28(18)	43(26)	60(35)	148(22)
Subject Choice (subject withdrew consent)	2(1)	1(1)	3(2)	2(1)	8(1)
Lost to Follow-up	0	0	1(1)	1(1)	2(<1)
Adverse Event	7(4)	21(13)	31(18)	52(30)	111(17)
Lack of Efficacy ^b	6(4)	2(1)	2(1)	2(1)	12(2)
Other	2(1)	4(3)	6(4)	3(2)	15(2)

Note: Percentages calculated with the number of subjects in each group as denominator.

^b Lack of efficacy defined as use of rescue medication during db period

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 70

The 15 subjects who withdrew for “other” reasons were reviewed. Lack of efficacy or no pain relief was noted in the CRFs for seven patients, two in the placebo group, one in the tapentadol IR 50mg group, two in the tapentadol 75mg group, and two in the oxycodone group. These were not included in the lack of efficacy category above because these patients did not request rescue medication.

When all discontinuations due to lack of efficacy are combined, the results for each treatment group are as follows:

Table 17: Discontinuations due to Lack of Efficacy

Treatment	Number Discontinued due to Lack of Efficacy	Percent of Treatment Group
Placebo	8	4.7
Tapentadol IR 50 mg	3	2
Tapentadol IR 75mg	4	2.4
Oxycodone IR 10mg	4	2.3
Total	19	2.9

One subject in the tapentadol IR 75mg group was not able to tolerate the drug due to the AEs of nausea, diarrhea, fever, and headache. This increased the percentage of subjects in that group withdrawing from 18 to 19%.

Three subjects had issues with drug compliance (one in the tapentadol IR 50mg group and two in the tapentadol IR 75mg group), and four subjects discontinued due to miscellaneous reasons.

Demographic and Baseline Characteristics

The Applicant's table below illustrates the demographic and baseline characteristics of the study population. Most subjects were white (91%). Fifty-one percent of subjects across all treatment groups were male, and 61% were less than 65 years of age. The majority of subjects were enrolled in the United States or Canada (53% and 34% respectively). A total of 69% of the subjects were categorized as having severe baseline pain intensity (NRS pain intensity ≥ 6).

Table 18: Demographic and Baseline Characteristics (ITT analysis set)

	Placebo (N=169)	Tapentadol IR 50 mg (N=153)	Tapentadol IR 75 mg (N=166)	Oxycodone HCl IR 10 mg (N=171)	Total (N=659)
Sex, n (%)					
N	169	153	166	171	659
Male	80 (47)	79 (52)	88 (53)	88 (51)	335 (51)
Female	89 (53)	74 (48)	78 (47)	83 (49)	324 (49)
Racial/ethnic Group, n (%)					
N	169	153	166	171	659
White	158 (93)	138 (90)	148 (89)	156 (91)	600 (91)
Black	9 (5)	5 (3)	6 (4)	10 (6)	30 (5)
Hispanic	0	5 (3)	7 (4)	3 (2)	15 (2)
Other	2 (1)	5 (3)	5 (3)	2 (1)	14 (2)
Age (Years)					
N	169	153	166	171	659
Category, n (%)					
<65	104 (62)	91 (59)	103 (62)	101 (59)	399 (61)
≥ 65	65 (38)	62 (41)	63 (38)	70 (41)	260 (39)
Mean (SD)	61.3 (10.08)	60.6 (10.16)	60.8 (10.04)	62.1 (9.05)	61.2 (9.83)
Median	62.0	60.0	61.5	62.0	62.0
Range	(20;79)	(31;79)	(34;78)	(41;79)	(20;79)
Weight (kg)					
N	169	153	166	171	659
Mean (SD)	98.4 (24.96)	96.4 (25.02)	97.2 (22.03)	96.1 (22.95)	97.0 (23.71)
Median	93.8	92.5	95.1	93.0	93.4
Range	(48;175)	(54;200)	(54;181)	(54;181)	(48;200)
Body Mass Index (kg/m²)					
N	168	151	166	171	656
Mean (SD)	33.8 (7.71)	33.0 (8.02)	33.6 (7.79)	33.2 (6.86)	33.4 (7.58)
Median	32.1	31.2	32.8	32.2	32.0
Range	(19;60)	(21;76)	(21;64)	(20;52)	(19;76)
Pain Intensity Score					
N	169	153	166	171	659
Category, n (%)					
Moderate	48 (28)	43 (28)	52 (31)	60 (35)	203 (31)
Severe	121 (72)	110 (72)	114 (69)	111 (65)	456 (69)
Country, n (%)					
N	169	153	166	171	659
Australia	6 (4)	4 (3)	4 (2)	5 (3)	19 (3)
Canada	55 (33)	55 (36)	57 (34)	57 (33)	224 (34)
New Zealand	10 (6)	10 (7)	11 (7)	11 (6)	42 (6)
United Kingdom	6 (4)	6 (4)	6 (4)	6 (4)	24 (4)
United States	92 (54)	78 (51)	88 (53)	92 (54)	350 (53)

Note: Percentages calculated with the number of subjects in each group as denominator.
Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 72

The subjects' medical histories and abnormal physical examination findings at screening were balanced across the treatment groups.

Prior and Concomitant Therapies

Medications used by more than 10% of subjects in all treatment groups included paracetamol, ibuprofen, atorvastatin calcium, and acetylsalicylic acid. Seventeen percent of subjects had used opioids, 18% in the placebo group, 15% in the tapentadol IR 50mg group, 17% in the tapentadol IR 75mg group, and 16% in the oxycodone group.

The overall percentage of subjects taking concomitant medications during the double-blind treatment period, excluding analgesics, was similar across treatment groups (84% in placebo, 83% in tapentadol IR 50mg, 86% in tapentadol IR 75mg, and 90% in oxycodone IR groups). The most commonly used concomitant medications (10%) in the placebo group were multivitamins and atorvastatin calcium. The most commonly used concomitant medications ($\geq 10\%$) in any treatment group were multivitamins, atorvastatin calcium, and levothyroxine sodium.

The percentage of subjects taking non-opioid-analgesic concomitant medications during the double-blind period was similar across treatment groups (83% in the placebo, 83% in the tapentadol IR 50 mg, 83% in the tapentadol IR 75 mg, and 80% in the oxycodone HCl IR groups). The most commonly used non-opioid analgesics ($>10\%$) in any treatment group were ibuprofen, paracetamol, acetylsalicylic acid, and celecoxib. The Applicant's table below shows the non-opioid analgesics used by at least 5% of subjects in any treatment group. The percentage use for each drug across treatment groups is similar.

Table 19: Non-Opioid Analgesics Used in at Least 5% of Subjects in any Treatment Group: Double-Blind Treatment Period

Derived Generic Term	Placebo	Tapentadol IR 50 mg	Tapentadol IR 75 mg	Oxycodone HCl IR 10 mg	Total
	(N=169) n (%)	(N=157) n (%)	(N=168) n (%)	(N=172) n (%)	(N=666) n (%)
Total no. subjects	140 (83)	130 (83)	140 (83)	137 (80)	547 (82)
Paracetamol	48 (28)	45 (29)	43 (26)	48 (28)	184 (28)
Acetylsalicylic Acid	36 (21)	36 (23)	42 (25)	33 (19)	147 (22)
Ibuprofen	38 (22)	33 (21)	40 (24)	24 (14)	135 (20)
Naproxen Sodium	14 (8)	11 (7)	17 (10)	13 (8)	55 (8)
Celecoxib	13 (8)	15 (10)	14 (8)	28 (16)	70 (11)
Naproxen	11 (7)	9 (6)	12 (7)	6 (3)	38 (6)
Meloxicam	9 (5)	10 (6)	8 (5)	6 (3)	33 (5)
Diclofenac	10 (6)	10 (6)	3 (2)	12 (7)	35 (5)

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 75

The percentage of subjects taking opioid analgesic concomitant medication was also similar in all treatment groups (3% in the placebo, 1% in the tapentadol IR 50 mg, 2% in the tapentadol IR 75 mg, and 2% in the oxycodone IR 10 mg groups). These percentages reflect subjects whose opioid use was a protocol deviation (13 subjects) and subjects who took opioid medication following their last dose of study drug (2 subjects). Less than 5% of the subjects used opioid analgesics concomitant medication in any treatment group as illustrated in the table below.

Table 20: Opioid Analgesics used During Double-Blind Treatment Period

Derived Generic Term	Placebo	Tapentadol IR 50 mg	Tapentadol IR 75 mg	Oxycodone HCl IR 10 mg	Total
	(N=169) n (%)	(N=157) n (%)	(N=168) n (%)	(N=172) n (%)	(N=666) n (%)
Total no. subjects With Concomitant Medication	5 (3)	2 (1)	4 (2)	4 (2)	15 (2)
Tramadol	0	1 (1)	2 (1)	1 (1)	4 (1)
Panadeine Co	4 (2)	0	1 (1)	2 (1)	7 (1)
Ultracet	0	0	1 (1)	0	1 (<1)
Paracetamol W/tramadol	0	1 (1)	0	0	1 (<1)
Paramol-118	0	0	0	1 (1)	1 (<1)
Propacet	1 (1)	0	0	0	1 (<1)

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 76

The percentage of subjects who took rescue medication (who discontinued due to lack of efficacy) was similar across treatment groups (4% in the placebo, 3% in the tapentadol IR 50 mg, 3% in the tapentadol IR 75 mg, and 1% in the oxycodone HCl IR groups), although the highest percentage was in the placebo group.

Protocol Deviations

Protocol deviations that were considered to be major are defined below. A subject could be counted in more than 1 deviation category.

- Used disallowed concomitant treatment
- Took <3 doses of study drug per day in Day 2 to Day 5 of the double-blind treatment period
- Took <3 doses of study drug per day in 2 or more days during Day 6 through Day 10 of the double-blind treatment period (i.e., subjects were allowed 1 day during Days 6 through Day 10 in which they could take <3 doses)
- Subject not discontinued from the study as per protocol;
- Took incorrect treatment other than randomized
- Had his/her first exposure to study drug more than 1 day after the day in which the subject was randomized
- Did not meet important inclusion/exclusion criteria which might impact the efficacy assessment

The percentage of subjects in the safety analysis set with protocol deviations as specified in the SAP was 18% in the placebo, 23% in the tapentadol IR 50 mg, 23% in the tapentadol IR 75 mg, and 26% in the oxycodone HCl IR groups.

There was no pattern in reasons for protocol deviations across treatment groups. The most common among these ($\geq 5\%$) were the following: use of forbidden medication, taking less than 3 doses of study drug per day between Days 2 and 5, and taking less than 3 doses of study drug per day on more than 1 day between Days 6 and 10.

The proportion of “forbidden medication” was similar across all treatment groups (between 4% and 5%). Those medications were commonly analgesics, including duloxetine, diclofenac, acetaminophen, tramadol and ibuprofen.

There were a total of 133 (20%) subjects excluded from the per protocol (PP) analysis set. The proportions from each treatment group were as follows: placebo-17%, tapentadol 50mg-19%, tapentadol 75mg-20%, and oxycodone-25%.

Extent of exposure

Mean total daily doses for Day 2 through Day 5 and for Day 2 through Day 10 of treatment period are presented in Table X and Table X, respectively. Day 1 is not included in these summaries, because subjects in the tapentadol IR 75 mg group received a titrating dose of 50 mg on Day 1 and because the dosing was more variable for all groups on Day 1, as the treatment was not initiated until the subjects returned home from their randomization visit. The dosing and exposure were different for the subjects in the tapentadol IR 50 mg and tapentadol IR 75 mg groups. The mean total daily dose for Day 2 through Day 5 of treatment was 186 mg in the tapentadol IR 50 mg group and 274 mg in the tapentadol IR 75 mg group. The mean total daily dose for Day 2 through Day 10 of treatment period was 189 mg in the tapentadol IR 50 mg group and 272 mg in the tapentadol IR 75 mg group.

Table 21: Extent of Exposure (mg)-Day 2-5 of Double-Blind Treatment Period

Derived Generic Term	Placebo (N=169) n (%)	Tapentadol IR 50 mg (N=157) n (%)	Tapentadol IR 75 mg (N=168) n (%)	Oxycodone HCl IR 10 mg (N=172) n (%)
Mean Total Daily Dose (mg) per Subject				
<u>Day 2-5 Summary</u>				
N	166	156	168	159
Mean (SD)	0.00 (0.000)	186.38 (51.095)	274.29 (89.976)	32.83 (11.122)
Median	0.00	187.50	281.25	32.50
Range ^a	(0.0:0.0)	(50.0:300.0)	(37.5:450.0)	(10.0:60.0)

^a Range of daily means

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 80

Table 22: Extent of Exposure (mg)-Day 2-10 of Double-Blind Treatment Period

Derived Generic Term	Placebo (N=169) n (%)	Tapentadol IR 50 mg (N=157) n (%)	Tapentadol IR 75 mg (N=168) n (%)	Oxycodone HCl IR 10 mg (N=172) n (%)
Mean Total Daily Dose (mg) per Subject				
<u>Day 2-10 Summary</u>				
N	166	156	168	159
Mean (SD)	0.00 (0.000)	189.05 (52.195)	272.42 (89.295)	33.24 (10.971)
Median	0.00	194.44	275.00	33.33
Range ^a	(0.0:0.0)	(50.0:300.0)	(50.0:450.0)	(10.0:60.0)

^a Range of daily means

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 81

The median total number of doses taken during the first 5 days of treatment was similar in both tapentadol IR groups (18 tablets in the tapentadol IR 50 mg group and 17 tablets in the tapentadol IR 75 mg group). The median total number of doses taken during the 10-day treatment period was also similar in both tapentadol IR groups (36 tablets in the tapentadol IR 50 mg group and 33 tablets in the tapentadol IR 75 mg group). For both of

these time periods, subjects in the placebo group took the most tablets (medians were 19.0 for Days 1 to 5 and 38.0 for Days 1 to 10), subjects in the oxycodone HCl IR group took the fewest (medians were 15.0 for Days 1 to 5 and 29.0 for Days 1 to 10).

The total number of doses taken on each day during the first 5 days of treatment is as follows. On Days 2 through 5, the median number of doses taken was 4 in all treatment groups, except for the oxycodone HCl IR group on Day 2 (3 tablets).

Efficacy Results

All efficacy analyses were performed with the ITT analysis set, which included all randomized subjects who received at least 1 dose of study drug and had a non-missing baseline pain assessment.

Some efficacy analyses were also performed with the PP analysis set, which was a subset of the ITT analysis set and included subjects who were not excluded from the ITT analysis due to protocol deviations.

Primary Efficacy Analysis

The primary efficacy endpoint was the sum of pain intensity difference (SPID) for Day 5. Both tapentadol IR treatment groups showed a significant (all p-values <0.001 adjusted for multiple comparisons using the Hochberg procedure) improvement in pain for the primary efficacy variable of 5-day SPID compared with placebo using LOCF (last observation carried forward) imputation. There was no separation of the two tapentadol IR doses, as shown by no numerical trend of increasing efficacy was observed with increasing tapentadol IR dose (mean 5-day SPID: 229.2 and 223.8 in the tapentadol IR 50 mg and tapentadol IR 75 mg groups, respectively). Oxycodone HCl IR 10 mg (mean 5-day SPID: 236.5) also showed a significant (nominal p-value <0.001) difference from placebo (mean 5-day SPID: 130.6), validating the study assay sensitivity.

The actual treatment effect size of the tapentadol treatment groups was not large. When the mean SPIDs of tapentadol IR 50mg 100mg are compared to placebo, the treatment effect sizes are 99 and 93, respectively, out of a total possible score of 1200, which translates into less than one point on the 11 point VAS scale.

The Applicant's analysis is shown in Table 23 below:

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Table 23: Descriptive Statistics and Pairwise Comparison of SPID at Day 5 (LOCF)

	Placebo (N=169) n (%)	Tapentadol IR 50 mg (N=153) n (%)	Tapentadol IR 75 mg (N=166) n (%)	Oxycodone HCl IR 10 mg (N=171) n (%)
Day 1-5				
N	169	153	166	171
Mean (SD)	130.6 (182.77)	229.2 (228.92)	223.8 (217.76)	236.5 (222.82)
Median	86.6	164.1	210.2	206.7
(Range)	(-358;695)	(-480;881)	(-308;823)	(-268;884)
LS Means (diff from placebo)	--	101.2	97.5	111.9
95% CI	--	54.58 to 147.89	51.81 to 143.26	66.49 to 157.38
Raw p-value	--	<0.001	<0.001	<0.001
Adjusted p-value using Hochberg	--	<0.001	<0.001	--

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 85

The Applicant's analysis of mean 5-day SPID results based on BOCF (baseline observation carried forward) imputation showed similar results to those observed using the LOCF imputation. Significant improvement in pain of both tapentadol IR treatment groups in comparison with the placebo group was observed (nominal p-values <0.001). As a post-hoc analysis, p-values were adjusted for multiple comparisons using the Hochberg procedure. Results were similar to those observed using the LOCF imputation (adjusted p-values <0.001).

Table 24: Descriptive Statistics and Pairwise Comparison of SPID at Day 5 (BOCF)

Treatment Group	Placebo	Tapentadol 50mg	Tapentadol 75mg	Oxycodone 10mg
N	169	153	166	171
Mean (SD)	131.1(180)	219.5 (221)	207.2 (206)	202.3 (204)
LS Means	-	217.7	205.7	204.5
95% CI	-	48.18-136.09	37.02-123.18	36.08-121.71
Raw P-value	-	<0.001	<0.001	<0.001
Hochberg correction	-	<0.001	<0.001	-

The Applicant's analysis of mean 5-day SPID results based on WOCF (worst observation carried forward), and modified LOCF imputations showed similar results to those observed using the LOCF imputation. A significant difference was observed for all active treatment groups compared with placebo (all nominal p-values <0.001).

Modified LOCF was defined as follows: For subjects who experienced a clinically meaningful benefit as defined by end of treatment PGIC scores of 'much improved' or 'very much improved', SPID was calculated using LOCF imputation. For subjects with any other PGIC scores at the end of the double-blind treatment period, pain measurements after discontinuation were imputed according to the BOCF principle.

No notable differences in 5-day SPID were identified within subgroups based on age (<65 and ≥65 years old). Because of the imbalance in the number of subjects in the racial groups (91% white), no conclusions could be drawn. For the tapentadol IR groups and the

placebo group, notably higher 5-day SPID values were observed for women compared to men. For the oxycodone HCL IR group, the 5-day SPID values were lower for women compared to men. Subjects with severe baseline pain intensity had higher 5-day SPID values than those with moderate pain intensity for all treatment groups.

Analysis of mean 5-day SPID based on the PP analysis set showed similar results to those for the ITT analysis set. There were significant differences for all active treatment groups compared with placebo (all nominal p-values <0.001).

There was no effect of study center on the results.

The primary efficacy analysis, using LOCF, BOCF and WOCF imputations, was reproduced by Dr Norton.

Secondary Efficacy Analysis

The following table illustrates the analyses of the secondary efficacy variables.

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Table 25: Summary of Efficacy Results (ITT population)

	Tapentadol IR 50mg (N=153)	Tapentadol IR 75mg (N=166)	Oxycodone HCl IR 10mg (N=171)
5-day SPID (LOCF)			
LS Means diff. from placebo (95% CI)	101.2 (54.58, 147.89)	97.5 (51.81, 143.26)	111.9 (66.49, 157.38)
Adjusted p-value vs. placebo ^{a, b}	<0.001	<0.001	–
Unadjusted p-value vs. placebo ^a	–	–	<0.001
5-day SPID (BOCF) ^{a, c}	<0.001	<0.001	–
5-day SPID (WOCF) ^a	<0.001	<0.001	<0.001
Two-part model on % change NRS and drop-out ^d	0.003	<0.001	<0.001
Pain assessment ≥30% improved at Day 5 ^e	0.028	0.033	0.091
Pain assessment ≥50% improved at Day 5 ^e	0.003	0.002	0.007
Distribution of responders at Day 5, Gehan test	0.011	0.107	0.626
Distribution of responders at Day 5, Log-rank test	<0.001	0.003	0.016
Distribution of responders at Day 5, Van Der Waerden test	0.005	0.070	0.503
Time to first rescue medication ^{c, f}	0.626	0.626	0.142
2-day SPID (LOCF) ^a	<0.001	<0.001	<0.001
10-day SPID (LOCF) ^a	<0.001	<0.001	<0.001
5-day TOTPAR (LOCF) ^a	<0.001	<0.001	<0.001
5-day SPRID (LOCF) ^a	<0.001	<0.001	<0.001
Patient Global Impression of Change ^g	<0.001	<0.001	0.005

^a Based on analysis of covariance model with factors of treatment, pooled center, and baseline pain intensity as a covariate.

^b P-values adjusted for multiplicity using Hochberg procedure.

^c P-values for tapentadol groups are adjusted for multiplicity using Hochberg procedure. P-value for oxycodone group is not adjusted for multiplicity. ANCOVA model includes all treatment groups.

^d For percent change NRS on Day 5 (observed case): ANCOVA model includes treatment, pooled center as factors and baseline pain score as a covariate. For discontinuation: Logistic regression model includes treatment as a factor and baseline pain score as a covariate.

^e P-value based on Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled center.

^f Log rank test stratified with pooled center.

^g P-value based on Generalized Cochran-Mantel-Haenszel test for row mean scores differ controlling for pooled center.

Higher value in SPID indicates greater pain relief.

Higher value in TOTPAR, SPRID indicates greater pain relief.

1. Time to Rescue Medication use

- a. Four percent of subjects in the placebo group, 3% of subjects in each of the tapentadol IR groups, and 1% of subjects in the oxycodone IR 10 mg group used rescue medication.
- b. The median time to first rescue medication could not be calculated for any active treatment group because less than 50% of subjects took rescue medication during the double-blind treatment period.
- c. There were no significant differences in the distribution of time to first rescue medication use between the tapentadol IR groups and placebo (log-

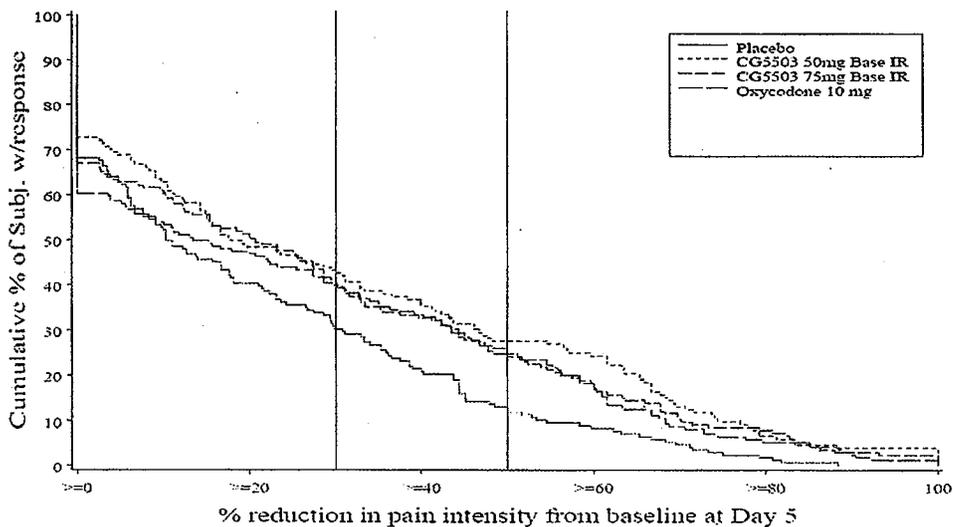
rank p-values=0.626; Hochberg procedure for tapentadol IR 50 mg and tapentadol IR 75 mg). The oxycodone HCl IR 10 mg group also did not show a significant difference from placebo with nominal p-value=0.142.

2. Distribution of Responder Rates

- a. The proportion of subjects who showed at least 30% improvement in pain intensity at Day 5 was 30% in the placebo group, 43% and 41% in the tapentadol IR 50 mg and 75 mg groups, respectively, and 40% in the oxycodone IR 10 mg group (active group p-values versus placebo: 0.028, 0.033, and 0.091, respectively).
- b. The proportion of subjects who showed 50% improvement in pain intensity at Day 5 was 13% in the placebo group, 28% and 26% in the tapentadol IR 50 mg and 75 mg groups, respectively, and 25% in the oxycodone IR 10 mg group (active group p-values versus placebo: 0.003, 0.002, and 0.007, respectively).

The cumulative distribution of responders at Day 5 is presented in the Applicant's Figure 7 below:

Figure 7: Cumulative Distribution of Responder rates Based on Percent Change from Baseline in Pain Intensity at Day 5



Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 89

The Applicant's table below illustrates the comparison of the distribution of responder rates using pain intensity at day 5 in the ITT population.

Table 26: Comparison of the Distribution of Responder Rates Using Pain Intensity at Day 5 in the ITT Population.

	Placebo (N=169) n (%)	Tapentadol IR 50 mg (N=153) n (%)	Tapentadol IR 75 mg (N=166) n (%)	Oxycodone HCl IR 10 mg (N=171) n (%)
Day 5				
≥30% improved, n (%)	51 (30.2)	66 (43.1)	68 (41.0)	68 (39.8)
p-value versus placebo ^a		0.028	0.033	0.091
≥50% improved, n (%)	22 (13.0)	42 (27.5)	43 (25.9)	42 (24.6)
p-value versus placebo ^a	--	0.003	0.002	0.007
Comparisons of distribution of responders				
Gehan p-value (vs. placebo)	--	0.011	0.107	0.626
Logrank p-value (vs. placebo)	--	<0.001	0.003	0.016

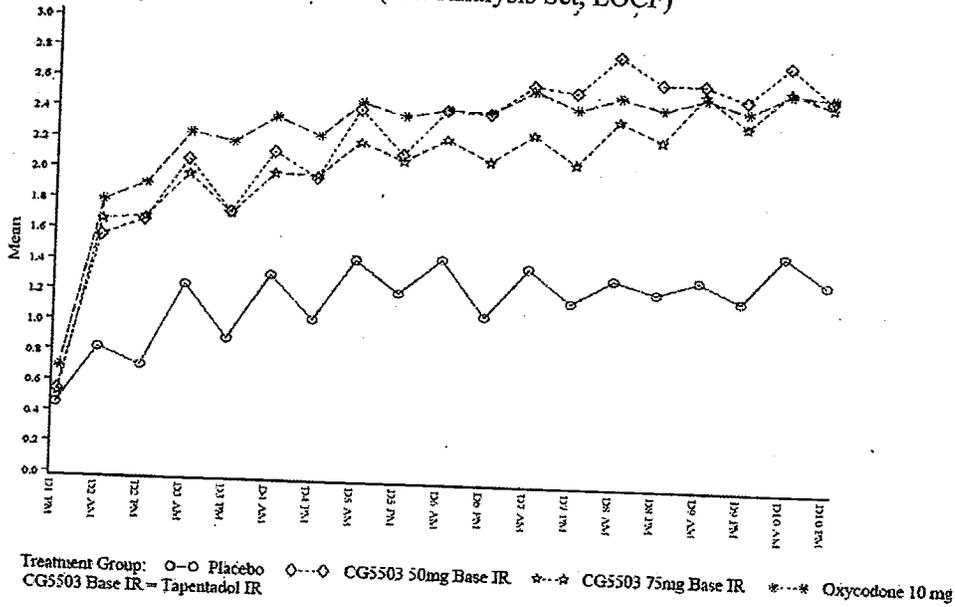
^a Pairwise comparison: Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled center

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 90

3. The following are the results of the analyses of the remainder of the secondary efficacy variables. These analyses were not corrected for multiplicity.
 - a. There were significant differences from placebo for the 2-day and 10-day SPIDs for both tapentadol treatment groups.
 1. Oxycodone also showed a significant difference from placebo.
 - b. Pain intensity difference over time: overall, subjects experienced greater improvement in pain intensity with all active treatment groups compared with placebo starting on the first day of treatment. Figure 8 shows the mean pain intensity difference over time for all treatment groups.

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Figure 8: Mean PID Over Time (ITT Analysis Set, LOCF)



Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 93

- c. Pain relief over time (PAR) showed higher values in all active treatment groups compared with placebo.
- d. Total pain relief and pain intensity over time (PRID) showed higher values in all active treatment groups compared with placebo.
- e. Total pain relief (TOTPAR) at Day 5 showed significant improvement in pain in all active treatment groups compared with placebo. Mean values for TOTPAR were similar in the tapentadol 75mg and oxycodone 10mg groups.
- f. Sum of total pain relief and sum of pain intensity difference (SPRID) at 5 days showed differences in all tapentadol IR treatment groups compared with placebo. A numerical trend of dose response was not observed. The mean 5-day SPRID value was higher for subjects in the tapentadol IR 50mg group than in the 75mg group. The descriptive statistics in shown in the table below:

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Despite the fact that on multiple occasions the Applicant was told that the LOCF imputation was not appropriate for analysis of the primary efficacy variable, the Applicant chose to use LOCF as the primary imputation method for missing pain scores. The Applicant did however carry out sensitivity analyses of the primary efficacy variables for both studies using more conservative imputation methods to account for missing pain score data. These methods included BOCF and WOCF. For both the ITT population and PP population, analyses using these methods of imputation resulted in statistically significant efficacy findings. The statistical analyses for the two efficacy studies using LOCF and BOCF imputations are shown below.

Study KF5503/32: Bunionectomy

Table 29: Descriptive Statistics and Pairwise Comparison of SPID48 Using Hochberg Procedure-Primary Analysis, LOCF ; KF5503/32 Bunionectomy

	Placebo (N=120)	Tapentadol IR 50 mg (N=119)	Tapentadol IR 75 mg (N=120)	Tapentadol IR 100 mg (N=118)	Oxycodone HCl IR 15 mg (N=125)
0-48 Hours					
Mean (SD)	24.5 (120.93)	119.1 (125.86)	139.1 (118.93)	167.2 (98.99)	172.3 (110.86)
Median (Range)	43.4 (-278;274)	127.6 (-185;402)	131.3 (-199;462)	158.5 (-94;408)	170.6 (-190;431)
LS Means (diff from placebo)	--	88.2	113.5	141.4	142.4
95% CI	--	60.71 to 115.59	86.12 to 140.81	113.98 to 168.90	115.28 to 169.47
Adjusted p-value vs. placebo ^a	--	<0.001	<0.001	<0.001	

^a Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate. Adjusted p-values using Hochberg procedure. Oxycodone group is not included.
CSR R331333-PAI-3003 (KF5503/32), p. 86

Table 30: Pairwise Comparison of SPID 48: BOCF Imputation
KF5503/32 Bunionectomy

Treatment Group	Placebo	Tapentadol 50mg	Tapentadol 75mg	Tapentadol 100mg	Oxycodone 15mg
N	120	119	120	118	125
Mean	60.1	125.5	142.3	166.6	169.5
LS Mean	-	65.4	82.2	106.5	109.4
95% CI	-	41.4-89.4	58.24-106.11	82.5-130.56	85.6-133.08
Raw P-value	-	<0.001	<0.001	<0.001	<0.001

Study KF5503/33: End-stage joint disease

**Table 31: Descriptive Statistics and Pairwise Comparison of SPID at Day 5 (LOCF)
Study KF5503/33: Degenerative Joint Disease**

	Placebo (N=169) n (%)	Tapentadol IR 50 mg (N=153) n (%)	Tapentadol IR 75 mg (N=166) n (%)	Oxycodone HCl IR 10 mg (N=171) n (%)
Day 1-5				
N	169	153	166	171
Mean (SD)	130.6 (182.77)	229.2 (228.92)	223.8 (217.76)	236.5 (222.82)
Median (Range)	86.6 (-358;695)	164.1 (-480;881)	210.2 (-308;823)	206.7 (-268;884)
LS Means (diff from placebo)	--	101.2	97.5	111.9
95% CI	--	54.58 to 147.89	51.81 to 143.26	66.49 to 157.38
Raw p-value	--	<0.001	<0.001	<0.001
Adjusted p-value using Hochberg	--	<0.001	<0.001	--

Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 85

**Table 32: Descriptive Statistics and Pairwise Comparison of SPID at Day 5 (BOCF)
Study KF5503/33: Degenerative Joint Disease**

Treatment Group	Placebo	Tapentadol 50mg	Tapentadol 75mg	Oxycodone 10mg
N	169	153	166	171
Mean (SD)	131.1(180)	219.5 (221)	207.2 (206)	202.3 (204)
LS Mean	-	217.7	205.7	204.5
95% CI	-	48.18-136.09	37.02-123.18	36.08-121.71
Raw P-value	-	<0.001	<0.001	<0.001
Hochberg correction	-	<0.001	<0.001	-

The primary efficacy analysis was confirmed by the statistical reviewer, Dr. Jonathan Norton.

All tested doses were effective in study KF5503/32, with a clear dose response. However, in study KF5503/33, although there was efficacy for each dose, there was no dose response. Additionally, the overall treatment effect in KF5503/33 for both doses although statistically significant, was not large (less than one point on the VAS 11-point scale). This finding may relate to the differences between the study populations in that the subjects in KF5503/33 were allowed to maintain a stable background non-opioid analgesic regimen. It is also possible that because the subjects in KF5503/33 had long-standing pain their response to treatment may have been different than post-operative subjects suffering acute pain.

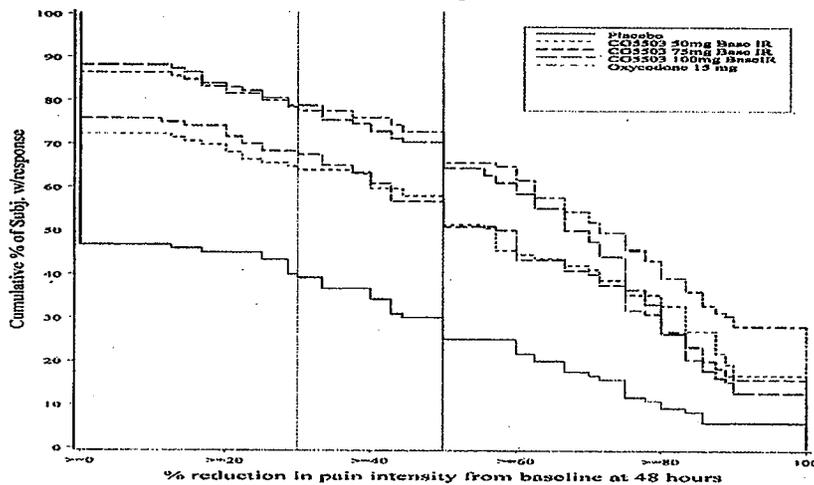
As stated below in Sections 6.1.2 through and including 6.1.5, the study designs, doses and dosing intervals, and the endpoints selected for primary analyses, are appropriate for the proposed indication. The selection of a chronic pain population in Study KF5503/33 allowed for the assessment of efficacy for a longer period of time than in the typical acute pain setting, such as the bunionectomy patients in study KF5503/32. As is often the case

in acute pain models, the degree of pain wanes fairly quickly in the days following the surgery/injury. By studying the drug in a chronic pain population the efficacy over a longer period of time, five days in this case, could be measured.

A number of secondary endpoints were evaluated in order to further characterize the efficacy of tapentadol IR. Responder analyses were carried out for both Phase 3 studies. The proportion of subjects who showed a $\geq 30\%$ and $\geq 50\%$ improvement in pain intensity from baseline at 48 hours (KF5503/32) and at 5 days (KF5503/33) was significantly higher in the tapentadol IR treatment groups compared with placebo.

The cumulative distribution of responders at 48 hours (KF5503/32) was significantly different from placebo for 50mg, 75mg and 100mg. For KF5503/33, a statistically significant difference was observed between the tapentadol IR 50 mg group and placebo. The proportion of subjects who showed 50% improvement in pain intensity at Day 5 was 13% in the placebo group, 28% and 26% in the tapentadol IR 50 mg and 75 mg groups, respectively, and 25% in the oxycodone IR 10 mg group. See Figures 9 and 10 below.

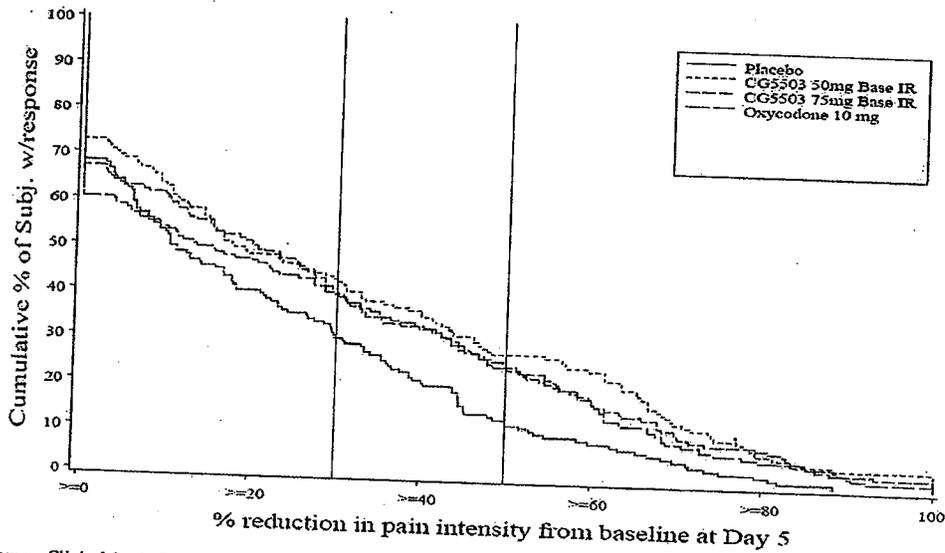
Figure 9: Cumulative Distribution of Responders at 48 Hours



Source: CSR R331333-PAI-3003 (KF5503/32), p. 90

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Figure 10: Cumulative Distribution of Responder rates Based on Percent Change from Baseline in Pain Intensity at Day 5



Source: Clinical Study Report R331333-PAI-3002 (KF5503/33), p. 89

The remainder of the secondary endpoint analyses (time to first rescue, SPID at other time points, onset of analgesic effect, total pain relief, and patient global impression of change) support findings of efficacy for tapentadol IR. See Section 6.6 for details.

In both Phase 3 studies, the Applicant included an active comparator (oxycodone) in order to demonstrate assay sensitivity. Additionally, the Applicant carried out non-inferiority analyses between the tapentadol treatment groups and the oxycodone treatment groups. The Division determined that

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6.1 Proposed Indication

The proposed indication is the relief of moderate-to-severe acute pain.

6.2 Methods/Study Design

The Sponsor has conducted two Phase 3 efficacy studies (KF5503/32 Bunionectomy and KF5503/33 Degenerative Joint Disease) to assess the efficacy and safety of tapentadol IR in the relief of moderate to severe pain. Both studies used a fixed dose with a flexible administration regimen of every 4 to 6 hours. The study designs and results for both studies are described in detail in Section 5.3.

KF5503/32 was a multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled, inpatient study that examined the efficacy, safety, and pharmacokinetics of multiple doses of 50 mg, 75 mg, and 100 mg of tapentadol IR for the

relief of moderate to severe postoperative pain following a bunionectomy. The active comparator was oxycodone HCl IR 15 mg. Subjects took study drug every 4 to 6 hours for 3 days (with the option of taking the second dose as early as 1 hour but no later than 6 hours after the first study drug administration [i.e., "early second dose"]). For inclusion, a baseline pain intensity of ≥ 4 on the 11-point (0 to 10) pain intensity numeric rating scale (NRS) rated within 30 minutes before randomization was required.

KF5503/33 was a multicenter, randomized, double-blind, parallel-group, active- and placebo-controlled, outpatient study to evaluate the efficacy and safety of multiple doses of 50-mg or 75-mg (with a titration step of 50-mg of tapentadol IR on Day 1) of tapentadol IR for the relief of moderate to severe pain in subjects with end-stage degenerative joint disease of the hip or knee. The active comparator was oxycodone HCl IR 10 mg. Subjects took study drug every 4 to 6 hours during waking hours for 10 days. For inclusion, subjects were required to have the following during the last 3 days of pain assessments during the run-in period: (1) a mean pain intensity score ≥ 5 (after rounding 4.5 and above to an integer) and (2) a minimum single pain intensity assessment score of ≥ 3 .

The use of rescue analgesic medication was not allowed during the double-blind periods of the KF5503/32 and KF5503/33 studies; however, for subjects in KF5503/33, the use of prior stable non-opioid analgesic regimens was permitted during the study.

A third Phase 3 study to examine the safety of tapentadol IR over a 90-day period also had a secondary objective of examining efficacy over this period of time at 50 or 100 mg every 4 to 6 hrs and is a supportive study for efficacy.

6.3 Demographics

Demographics for studies KF5503/32 and KF5503/33 are described in detail in Section 5.3.

6.4 Patient Disposition

Patient disposition for studies KF5503/32 and KF5503/33 are described in detail in Section 5.3.

6.5 Analysis of the Primary Endpoint(s)

The primary efficacy endpoints selected for the two pivotal studies were SPID48 (sum of pain intensity difference at 48 hours) in study KF5503/32 (bunionectomy), and 5-day SPID in study KF5503/33 (degenerative joint disease), are acceptable. These were agreed upon with the Applicant at a Type C meeting held on December 16, 2005 and the pre-NDA meeting held on June 5, 2007.

The endpoints incorporate the measurement of pain intensity, which is a fundamental measure that defines the efficacy of an analgesic, and is supported by Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) Recommendations for Core Outcome Measures in Chronic Pain Trials.

SPIDs are weighted calculations over a defined time period, where PID (pain intensity difference) is calculated as the baseline pain intensity minus the current pain intensity. The formula used to calculate SPID is $SPID = \sum W_i * PID_i$; where the sum includes all observations collected from baseline to the end of Day 5 and W_i is the time elapsed from the previous observation (PID_{i-1}) to the current observation (PID_i). They are often used in the analysis of analgesic efficacy for acute pain indications.

Imputation methods

During a Type C meeting (December 16, 2005) and the pre-NDA meeting (June 5, 2007) held between the Division and the Applicant, the Applicant was told that utilizing last observation carried forward (LOCF) to impute missing data for the primary efficacy analysis would not be acceptable because this method could assign a good score to patients who dropped out of the study early due to adverse events and/or inability to tolerate the study drug. The Applicant stated that they intended to retain the analysis using LOCF, however sensitivity analyses would be carried out using more conservative imputation strategies including baseline observation carried forward (BOCF) and worst observation carried forward (WOCF). The Applicant completed the analysis of the primary efficacy endpoint using all three imputation methods. The Applicant's approach is acceptable and allows for adequate interpretation of the efficacy analysis.

Study Design

The designs of the two adequate and well-controlled Phase 3 trials meet the regulatory requirements for AWC trials, and are appropriate to assess the efficacy of tapentadol IR for the treatment of acute pain. In terms of pain models, two patient populations were assessed, one of which was a typical, acute post-operative population (bunionectomy patients) in KF5503/32. The population studied in KF5503/33 was unusual for a trial conducted to establish efficacy in the management of acute pain, in that it was a chronic pain population (end-stage degenerative joint disease). Pain of the hip or knee from end-stage degenerative joint disease was deemed appropriate for study in this setting for the following reasons:

1. Pain experienced by this population is often moderate or severe, and is therefore appropriate to evaluate the analgesic effect of repeated doses of study treatment.
2. A relatively constant level of pain requiring continuous analgesia is maintained, as compared with post op pain that typically decreases within days of surgery.
3. More information regarding the sustained efficacy of tapentadol IR can be obtained.

Because of the varied populations studied, the efficacy findings are appropriate for generalization to a broader population.

Dose Selection

The Applicant presented the following rationale for dose selection for the Phase 3 studies.

The tapentadol IR doses (50, 75, and 100 mg) used in the pivotal Phase 3 studies were selected based on the results from several Phase 2 studies. Tapentadol IR 50 mg was selected as the lower limit of the dose range for KF5503/32 and KF5503/33 based on the following results:

- In a single-dose bunionectomy study KF5503/05, tapentadol IR doses of 43 mg, 64 mg, 86 mg, and 172 mg produced statistically significant pain relief compared with placebo and showed a dose-response relationship.
- In Phase 2b multiple-dose bunionectomy studies (KF5503/21 and KF5503/22), tapentadol IR doses between 50 mg and 120 mg demonstrated statistically superior efficacy versus placebo. In KF5503/21, tapentadol IR 50 mg given every 4 to 6 hours over 3 days produced similar efficacy results with oxycodone HCl IR 10 mg, the active control.
- Single-dose Phase 2 studies (KF5503/04 and KF5503/05) did not show statistically significant results with 21-mg tapentadol IR compared with placebo, suggesting that this dose was unlikely to demonstrate clinically relevant pain relief.

Tapentadol IR 100 mg was chosen as the highest dose to be tested, as it provided numerically greater efficacy than oxycodone HCl IR 10 mg while maintaining an acceptable tolerability profile based on the following data:

- In KF5503/21, tapentadol IR 100 mg showed a statistically significant improvement in pain compared with placebo for the primary efficacy variable (SPI₂₄ [verbal rating scale, VRS]) on Study Day 3 (p-value <0.001) with an acceptable tolerability profile.
- In KF5503/22, tapentadol IR 80 mg and 120 mg given every 4 hours over a 12 hour period showed a numerical increase in the primary efficacy variable (SPRID₁₂) compared with oxycodone HCl IR 10 mg, but the typical dose-related increase in opioid-related adverse events observed between 80-mg and 120-mg tapentadol IR were accompanied by only a modest increase in efficacy in this clinical setting.
- In study KF5503/22, doses as high as 186mg of tapentadol were administered. Doses above 93 mg showed a higher incidence of treatment emergent common adverse events (>5%) than in subjects receiving 10mg oxycodone IR. Specifically, nausea, vomiting, and dizziness occurred in greater than 50% of the subjects receiving 140mg to 186mg of tapentadol IR. Additionally, there were no SAES at doses less than 140mg.

For KF5503/32, an intermediate dose of tapentadol IR 75 mg was included to evaluate the efficacy and tolerability profile of a dose between the chosen highest and lowest dose. For KF5503/33, the maximum dose tested was 75 mg because the risks of a fixed dose regimen of 100 mg had not been well characterized in the elderly outpatient population of subjects participating in the study, particularly since there was minimal clinical experience with tapentadol IR in this pain model (end-stage degenerative joint disease). Accordingly, the maximum dose tested was chosen to be 75 mg with a titration step of 50-mg tapentadol IR on Study Day 1, reflecting standard clinical practice of upward titration from a lower dose of analgesics with central nervous system activity.

The rationale for dose selection as presented by the Applicant is acceptable.

Dosing interval

The Applicant presented the following rationale for the selection of the dosing intervals in the Phase 3 studies.

The single- and multiple-dose efficacy of tapentadol IR has been well characterized in 3 Phase 2 studies (KF5503/02, KF5503/04, and KF5503/05) conducted in the postoperative dental surgery and bunionectomy pain models. In these studies, the time to first use of rescue medication after the start of tapentadol IR treatment ranged from approximately 3 to 8 hours following dental surgery (KF5503/02 and KF5503/04) and 2 to 3 hours immediately following bunionectomy (KF5503/05). A previous multiple-dose Phase 2 study (KF5503/21) incorporated a flexible dosing schedule of 4 to 6 hours for 3 days. In this study, the pain immediately following surgery was controlled by a popliteal block. Administration of the first dose of study drug occurred in the morning following the day of surgery after termination of the popliteal block. Subjects could take the second dose of study drug as early as 1 hour after the first dose. The median time between the intake of the first and second dose of tapentadol IR ranged from approximately 3 hours to 4 hours. Based on the data above, a flexible dosing schedule of 4 to 6 hours was expected to provide a sufficient level and duration of pain relief to subjects until the administration of a subsequent dose and this dosing schedule was also consistent with the pharmacokinetic characteristics of tapentadol IR.

The rationale for the dosing interval as presented by the Applicant is acceptable.

Minimization of bias

Minimization of bias in both pivotal studies was accomplished by blinding, randomization, and a prespecified statistical analytic plan.

6.6 Secondary endpoint(s)

Secondary endpoints that were evaluated in the two Phase 3 efficacy studies include the following:

- Distribution of responder rates using pain intensity
- Rescue medication usage
- Additional pain intensity and pain relief variables: PAR, PIR, PRID, TOTPAR, SPID, and SPRID (Defined in Section 5.4)
- Time to perceptible, meaningful and confirmed perceptible pain relief (study KF5503/32 only)
- Patient Global Impression of Change (PGIC)
- Active comparator versus placebo for assay sensitivity

These endpoints were evaluated without multiplicity correction; however they do provide useful information in support of the efficacy findings.

The Applicant also carried out a non-inferiority analysis for tapentadol IR doses of 75mg and 100mg for KF5503/32 and at doses of 50mg and 75mg for KF5503/33, comparing oxycodone IR 15mg and 10 mg respectively. The non-inferiority margin for these analyses was set at 10% of the entire possible range of the primary endpoint. Details of

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these analyses are described in the individual study reviews in Section 5.3. Although the Applicant's result showed that tapentadol 50mg and 100mg were non-inferior to oxycodone 10mg and 15mg respectively, the Division determined that _____ for the following reasons:

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6.7 Subpopulations

KF5503/32 Bunionectomy

For the primary efficacy variable (SPID38), no notable differences were identified among subgroups based on racial groups (White, Black, Hispanic, and other). The mean SPID48 values were higher for subjects with severe baseline pain intensity, defined as pain intensity of six or greater (144.8 for tapentadol IR 50 mg, 162.6 for tapentadol IR 75 mg, and 188.5 for tapentadol IR 100 mg) compared with those who had moderate baseline pain intensity, defined as pain intensity of four and a half to six (22.3 for tapentadol IR 50 mg, 74.5 for tapentadol IR 75 mg, and 112.6 for tapentadol IR 100 mg). Because the majority of subjects were female (87%) and <65 years of age (94%), no conclusions could be drawn by age category (<65 and ≥65 years) or sex.

Subgroup analysis was carried out by the Applicant for subjects who received an early second dose of tapentadol IR. In this study, the second dose could be given as early as one hour after the first dose. An early second dose was defined for the analysis as a dose given within 3 hours of the first dose.

The mean baseline pain intensity score was higher for subjects who took an early second dose (7.5) compared with those who did not (6.6). Consistent with this observation is that a higher percentage of placebo-treated subjects who did not take an early second dose completed the double-blind period compared with subjects who did (70% and 38%, respectively). In contrast, 70% to 87% of tapentadol-IR treated subjects who took an early second dose completed the double-blind period. These results support the efficacy of tapentadol IR and the utility of flexible dosing during the start of treatment to address initial pain intensity.

The mean SPID48 values were similar for tapentadol IR-treated subjects who took a second dose less than 3 hours after the initial dose (early second dose; reload) and with those subjects who waited more than 3 hours to take the second dose within each treatment group. The largest difference in mean SPID48 between subjects who took an

early second dose compared to those subjects who did not was in the placebo group with a mean SPID48 of -2.0 (i.e., no improvement in pain intensity) compared to 67.2 for those who did not take an early second dose.

The cumulative distribution of responder rates was calculated for subjects who took an early second dose and for subjects who did not take an early second dose. The overall patterns and trends for the cumulative distribution of responders for all tapentadol IR treatment groups compared with placebo were similar regardless of whether subjects took an early second dose or did not.

KF5503/33 Degenerative Joint Disease

No notable differences were identified within subgroups based on age (<65 and ≥65 years). Because the majority of subjects were white (91%), no conclusions could be drawn for racial groups (White, Black, Hispanic, and Other). A notably higher 5-day SPID value for the tapentadol IR 50 mg group was observed in women (265.3) compared with men (195.3) and for subjects in both tapentadol IR groups with severe baseline pain intensity (265.2 for tapentadol IR 50 mg and 236.3 for tapentadol IR 75 mg) compared to subjects with moderate baseline pain intensity (137.1 for tapentadol IR 50 mg and 196.2 for tapentadol IR 75 mg).

6.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose and dosing interval selection for the Phase 3 studies are described above in Section 6.8.

The dosing recommendation proposed for tapentadol IR is 50 mg, 75 mg, or 100 mg every 4 to 6 hours as needed. This dosing recommendation is based on the efficacy shown in the 2 pivotal Phase 3 studies in two pain models that included men and women with a median age of 46 years (range from 18 to 77 years) for the bunionectomy study and 62 years (range from 20 to 79 years) for the end-stage degenerative joint disease study. Both inpatient (following a bunionectomy) and outpatient (end-stage degenerative joint disease) subjects had decreased pain intensity over a time period of 3 to 10 days, respectively.

In the post-operative pain model (KF5503/32 Bunionectomy), a dose relationship was present for efficacy across the tapentadol IR doses of 50 mg to 100 mg with all doses significantly different from placebo on the primary efficacy variable, SPID48. In addition, there was a dose relationship between serum levels of tapentadol and the primary efficacy variable for doses of 50 mg, 75 mg, and 100 mg. Upon dose normalization to 75 mg, an approximate dose proportional increase was observed in serum concentration of tapentadol. The interested reader is referred to the Biopharmaceutics review for details related to the pharmacokinetics of tapentadol.

In the second pain model (KF5503/33 Degenerative Joint Disease), the efficacy of tapentadol IR 50 mg and tapentadol IR 75 mg was similar although a dose-response relationship was observed in the incidence of adverse events and the mean total daily dose was different for the subjects in the tapentadol IR 50 mg and tapentadol IR 75 mg

groups. The mean total daily dose for Day 2 through Day 5 of treatment was 186 mg in the tapentadol IR 50 mg group and 274 mg in the tapentadol IR 75 mg group. The lack of a dose-response for efficacy between the dose groups might have been attributed to the study design in which subjects were permitted to maintain a stable non-opioid analgesic therapy during the study (a total of 82% of subjects maintained their non-opioid analgesic regimen) and may have varied their dose. There is not enough information to make a definitive conclusion regarding the lack of dose response in this trial.

6.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

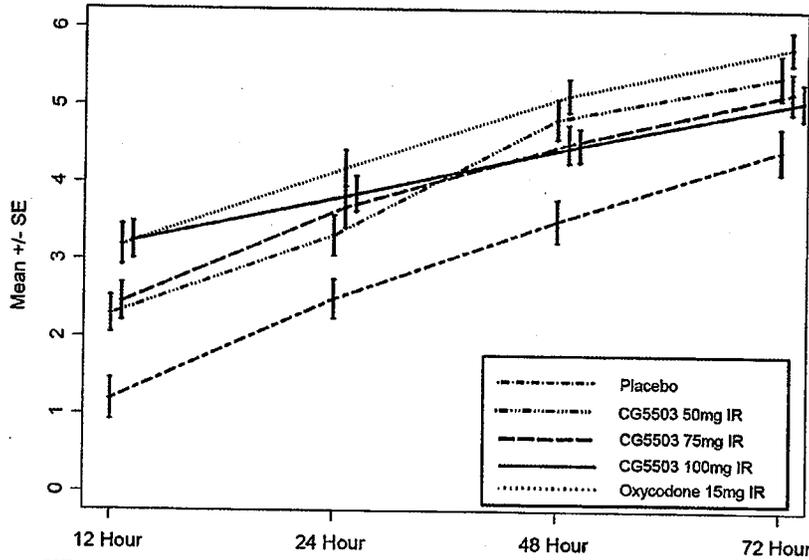
Onset of analgesia was evaluated in study KF5503/32 (bunionectomy). For time to meaningful pain relief, all active-treatment groups showed a significantly shorter time compared with placebo. Median time to meaningful pain relief ranged from 123 minutes (50mg tapentadol) to 94 minutes (100mg tapentadol) for the tapentadol IR treatment groups, 77 minutes for the oxycodone IR 15mg group, and 240 minutes for the placebo group.

The persistence of efficacy with tapentadol IR treatment can be inferred from the increase in pain intensity difference over time, especially in outpatient pain models when pain levels are stable. The persistence of efficacy is described below for the inpatient, post-operative study, KF5503/32, for and for periods of 10 days (KF5503/33) and 90 days (KF5503/34) in an outpatient setting.

Pain intensity difference over the 72-hour double-blind treatment period in study KF5503/32 (bunionectomy) is shown in the Applicant's figure below. Overall, subjects experienced a trend of greater improvement in pain in the tapentadol IR treatment groups compared with placebo based on the mean 11-point NRS PID score across the time points of 12, 24, 48, and 72 hours.

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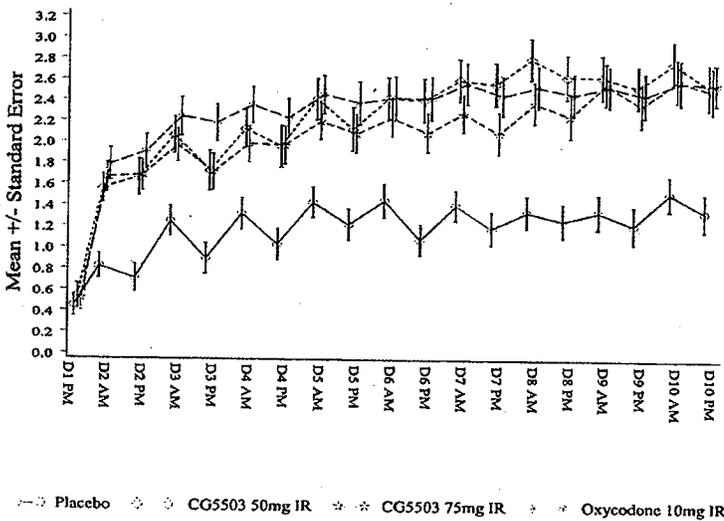
Figure 11: Pain over Time (PID): Study KF5503/32 ITT Analysis Set



Source: ISE, P. 64

In study KF5503/33 (degenerative joint disease), subjects experienced greater improvement in pain intensity in both tapentadol IR treatment groups (50 and 75mg) compared with placebo starting on the first day of treatment. PID values for the tapentadol IR groups from the morning of Day 2 to the evening of Day 10 indicated greater improvement in pain intensity compared with placebo. Similar responses based on PID values were observed for both tapentadol IR treatment groups. Figure X below illustrates this finding.

Figure 12: Mean Pain Intensity Difference over Time: KF5503/33 ITT Analysis



Source: ISE, p. 65

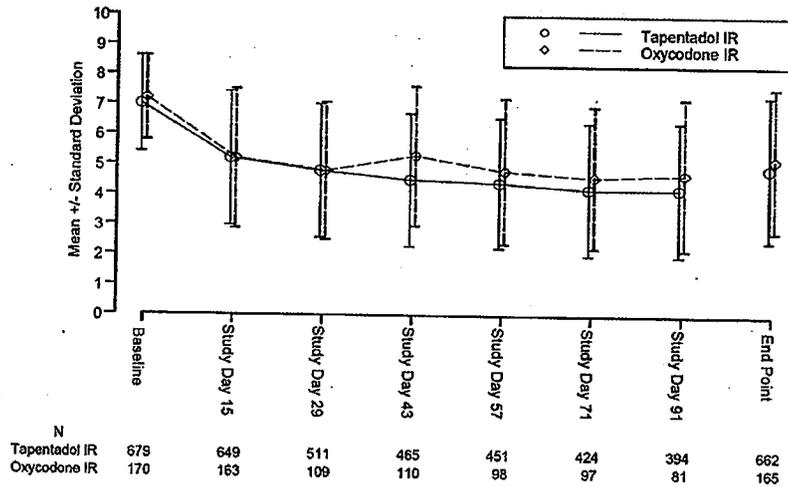
Subjects in this study experienced moderate to severe pain due to end-stage degenerative joint disease. Pain levels in this study model (assuming a stable non-opioid regimen) were likely to be stable due to the nature of the pain. During the 10-day exposure, the mean daily dose in the 2 tapentadol IR groups (50 mg and 75 mg) rose slightly from Day 2 to Day 10: 187.5 mg to 205.8 mg and 274.1 mg to 295.7 mg, respectively. In the oxycodone HCl IR 10 mg group the mean daily dose rose from 32.8 mg to 37.9 mg. The cumulative percentage of subjects with $\geq 50\%$ improvement in pain intensity from baseline increased from the analysis on Day 2 to Day 5, and to Day 10 in both tapentadol IR treatment groups.

Study KF5503/34 was a randomized, double-blind, active-control, parallel-group, multicenter, safety study of tapentadol IR in subjects with a clinical diagnosis (present for at least 3 months) of lower back pain or pain from osteoarthritis of the knee or hip. The primary objective of this study was to evaluate the safety profile of tapentadol IR with flexible doses of either 50 mg or 100 mg taken every 4 to 6 hours (600 mg maximum total daily dose), as needed, over an exposure of 90 days in comparison to oxycodone HCl IR with flexible doses of either 10 mg or 15 mg. Although this was a safety study, pain intensity was assessed at each visit (Study Days 1, 15, 29, 43, 57, 71, and 91) over the 90-day double-blind treatment period and provided an assessment for the maintenance of effect over this extended period of time.

The mean pain intensity using an 11-point NRS was 7.0 at baseline and decreased (i.e., showed improvement in pain) to a mean score of 4.9 at endpoint (i.e., the last non-missing observation assessed during the double-blind treatment period) with tapentadol IR as shown in Figure X below. This level of improvement was maintained from Day 29 with tapentadol IR. A comparable improvement was observed with oxycodone HCl IR (mean change in pain intensity from baseline to endpoint: -2.2 for tapentadol IR group and -1.9 for the oxycodone IR group).

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Figure 13: Pain Intensity Score over Time: 90-Day Safety Study KF5503/34



This study showed a decrease in pain intensity over the period of the study with tapentadol IR, while the mean total daily dose increased on average by approximately 10% from Day 15 to Day 71, that is from 285 mg, the average of mean total daily dose over the treatment period up to Day 15, to 312 mg, the average of mean total daily dose over the treatment period between Day 57 to Day 71. Also, the mean daily dose over time for subjects who completed the study in the tapentadol IR group appeared to be relatively stable after Day 15 overall.

In summary, the maintenance of pain relief in study KF5503/34 was shown by the stable reduced mean pain intensity accompanied by a mild increase in mean daily dose of tapentadol IR.

The tolerance of analgesic effect with opioids develops over time. A mild tolerance developing over a 90-day period of treatment in outpatient subjects (KF5503/34) was suggested by a 10% increase in mean daily dose at the end of that period while efficacy remained stable with tapentadol IR. However, because the data were limited in scope, no definitive conclusions can be made.

6.10 Additional Efficacy Issues/Analyses

Refer to [Section 3](#) for issues related to study conduct, good clinical practices and submission integrity. There were no issues identified that effect the analysis of efficacy in this submission.