

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-304

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

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1 Executive Summary

1.1 Recommendations

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation II (OCPB/DPE-II), the information contained in the NDA is acceptable, provided that a mutually satisfactory agreement can be reached between the Applicant and the Agency with respect to the language in the package insert (see section 3: Detailed Labeling Recommendations).

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of CPB Findings

Johnson & Johnson Pharmaceutical Research and Development, L.L.C. (J&JPRD), on behalf of Ortho-McNeil-Janssen-Pharmaceuticals, Inc. (OMJPI), submitted on 1/23/08, the New Drug Application 22-304, tapentadol hydrochloride Immediate Release Tablets for the relief of moderate to severe acute pain with 50-, 75- and 100-mg doses every 4 to 6 h as needed in all patients at least 18 years of age. Throughout the submission the following notations were also used for tapentadol HCl: CG5503 and R331333. It is noted that many of the studies were conducted by Grünenthal GmbH, Aachen Germany (GRT).

The NDA contained extensive Clinical Pharmacology and Biopharmaceutics program. There were 6 Phase 2 studies to gather preliminary efficacy and safety information. The phase 2

studies included 2 single- and/or multiple-dose, studies of acute pain following third molar extraction (KF5503/02 and KF5503/04), a single- and multiple-dose study in subjects with chronic non-malignant pain (KF5503/08), a single-dose study in subjects with acute pain following bunionectomy (KF5503/05), and 2 multiple-dose studies in subjects with acute pain following bunionectomy (KF5503/21 and KF5503/22). There were 2 pivotal Phase 3 studies in inpatient (KF5503/32; bunionectomy) and outpatient settings (KF5503/33; end-stage degenerative joint disease of the hip or knee) supporting the proposed indication. Both studies used fixed dose with flexible dosing regimen of Q4 to 6h. Additionally, there was 1 Phase 3 safety study to assess the safety of tapentadol dosed as flexible doses of 50 mg or 100 mg every 4 to 6 hours, as needed, over a 90-day period in subjects with low back pain or pain from osteoarthritis of the hip or knee. []

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Tapentadol is a centrally active antinociceptive drug for the relief of moderate to severe acute pain. Tapentadol is 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. Tapentadol is a pure enantiomer and has no clinically-relevant active metabolites. No enantiomeric interconversion has been observed. Tapentadol is the only active moiety and tapentadol was measured appropriately in serum and urine. Since the metabolites (inactive) are excreted in the urine, glucuronide metabolites were measured in hepatic and renal studies.

Tapentadol HCl is freely soluble in water, 0.1 N HCl and simulated intestinal fluid (34 and 35 g/100 mL, respectively). Its solubility decreases at higher pH. The hydrochloride salt was used []

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Phase 3 studies

In Study KF5503/32, a bunionectomy study, there was a trend of increasing efficacy (SPID48) with increasing tapentadol dose (50mg, 75mg, and 100 mg). In Study KF5503/33, an end-stage degenerative joint disease of the hip or knee study, it appears that there was no dose related increase in efficacy (SPID at Day 5) from 50mg to 75mg. Nevertheless, both tapentadol doses were found to be efficacious.

The observed treatment emergent adverse events (TEAEs) appear to be dose-related. Common adverse events appear to increase with increase in tapentadol doses.

Population Pharmacokinetics and exposure-response information

The overall information from the population PK model supported the pharmacokinetic findings from the Phase 1 and 2 studies. Additionally, the overall information obtained from the exposure-response model exercise also supported the findings from the Phase 3 studies. It is noted that each of the Phase 2/3 studies used in the modeling had a different study design and duration, inconsistent dosing regimens including flexible dosing schemes, inconsistent rules regarding the supplemental rescue usage, as well as different primary efficacy variables, and, these studies are not pooled and separate analysis was performed for each of the studies.

Thorough QT study

No significant QT prolongation effect of tapentadol was detected. (Dr. Christine Garnett; Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, 7/1/08)

Inter- and intra-subject variability

For the C_{max} of tapentadol dose-normalized to 100 mg, the inter subject CV was estimated at 39% and the intra-subject CV was estimated at 20%. For the AUC of tapentadol dose-normalized to 100 mg, the inter-subject CV was estimated at 34%, whereas the intra-subject CV was estimated at around 13%.

Pediatric

Pediatric data has not been submitted seeking approval of pediatric indications at this stage. Instead, the package insert will state 'safety and effectiveness has not been established in pediatric patients less than 18 years of age'. The Applicant requested a 'staged' deferral of the requirement to conduct pain studies in the pediatric population. The Applicant proposed that trials be conducted in a step-wise manner to gather adequate pharmacokinetic, safety and efficacy information in the older children before exposing younger age groups. Adequacy of this plan is currently ongoing discussion in the review team.

Gender

Men and women showed that women in general had about 20% higher C_{max} and AUC values. After bodyweight correction in this pooled analysis (men had about 20% higher body weight), the mean oral clearance was very similar between men and women. No dose adjustment is recommended due to gender differences.

Race

No separate studies were conducted to evaluate the effects of race on the PK of tapentadol. However, comparison of PK data obtained in Japanese subjects in study R331333-PAI-1027 to historical data shows that PK is similar in Japanese subjects as compared to non-Japanese subjects. Additionally, the C_{max} and AUC values increased with an increase in tapentadol doses (10, 20, 40 mg) in Japanese subjects. No dose adjustment is recommended due to race differences.

Elderly

PK characteristics for tapentadol were similar in elderly (65 to 78 years of age) and healthy subjects, suggesting that age has no impact on the PK of tapentadol. No specific dose adjustment for elderly is needed; however, due to the fact that elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection.

Hepatic

The tapentadol C_{max} values increased 1.4- and 2.54-fold in subjects with mild or moderate hepatic impairment, respectively, versus subjects with normal hepatic function. The AUC of tapentadol was increased 1.7- and 4.2-fold in subjects with mild and moderate hepatic impairment, respectively, versus subjects with normal hepatic function. Severe impairment subjects were not tested. The terminal elimination half-life of tapentadol was increased 1.4-fold in subjects with moderate hepatic impairment, compared to healthy subjects. The mean CL/F of tapentadol decreased 3.6-fold (ratio of arithmetic means) in subjects with moderate hepatic impairment, compared to healthy subjects, but the amount excreted over 48 hours remained below 5% of the total dose.

The serum tapentadol-O-glucuronide AUC values were comparable for all subjects.

No dose adjustment is needed in mild impairment subjects. In moderate impairment, the tapentadol should be used with caution and should be initiated at 50 mg every 8 hours followed by either shortening or lengthening the dosing interval for further treatment. Tapentadol has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended.

Renal

Total exposure to tapentadol was not different between normal and subjects with renal impairment, indicating that a reduced renal functioning does not influence the single-dose PK of orally administered tapentadol.

Data for tapentadol-O-glucuronide demonstrate that C_{max} increased 1.2-, 1.3-, and 1.4-fold for mild, moderate, and severe renal impairment subjects, respectively, compared with healthy subjects. The AUC data showed a 1.5-, 2.5-, and 5.5-fold increase for mild, moderate, and severe renal impairment subjects, respectively, compared with healthy subjects. The mean terminal half-life of tapentadol-O-glucuronide increased 3.3-fold in subjects with severe renal impairment compared to subjects with normal renal function.

Because of the significant accumulation potential of tapentadol-O-glucuronide in severe renal impairment group, the Applicant proposed that tapentadol use is not recommended in this group. However, this metabolite is inactive and not recommending the use of tapentadol based on accumulation potential of an inactive metabolite is not justified. Therefore, it is recommended

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Drug-Drug interaction

Metoclopramide, omeprazole, naproxen, acetylsalicylic acid and acetaminophen did not affect tapentadol pharmacokinetics. However, the serum C_{max} and AUC levels of tapentadol were elevated in the presence of probenecid, approximately 30% and 57%, respectively, as compared with the control. The elimination half-life of tapentadol in the control was 4.1 hours and was 4.4 hours when tapentadol IR was co-administered with probenecid. The tapentadol-O-glucuronide C_{max} and AUC values were reduced in the presence of probenecid.

Metoclopramide - Tapentadol 80 mg was either administered alone or one hour after the 5th dose of metoclopramide (6 doses of 20 mg, Q6h). The C_{max} and AUCs were comparable between the two treatments for both tapentadol and tapentadol-O-glucuronide.

Omeprazole - Tapentadol IR (80 mg) was administered either alone or 2 hours after the last administration of omeprazole once daily for 4 days. Serum PK parameters of tapentadol and tapentadol-O-glucuronide were similar when tapentadol IR was administered either alone or with omeprazole.

Probenecid - Tapentadol IR (80 mg) was administered either alone or together with the third administration of probenecid 500 mg b.i.d. for 2 days. The serum C_{max} and AUC levels of tapentadol were elevated in the presence of probenecid, approximately 30% and 57%, respectively, as compared with the control. The tapentadol-O-glucuronide C_{max} and AUC values were reduced in the presence of probenecid.

Naproxen and acetylsalicylic acid (ASA) - Subjects received a single oral dose of tapentadol 80 mg alone or in combination with naproxen (together with the third dose of 500 mg b.i.d. for 2 days) and in combination with ASA (together with the second dose of 325 mg ASA once daily for 2 days). C_{max} and exposure of tapentadol was similar in all treatment groups, indicating that co-administration of either naproxen or ASA has no influence on the oral PK of tapentadol.

Acetaminophen - Subjects received a single oral dose of tapentadol IR 80 mg alone or in combination with acetaminophen (together with the fifth dose of 1000 mg acetaminophen Q6h for 2 days). Concentrations of tapentadol were similar after administration of tapentadol IR alone and after co-administration with acetaminophen.

Bioequivalence

80-mg  capsule formula and the 80-mg  film-coated tablet manufactured  were bioequivalent (Study PAI-1016).

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Absolute Bioavailability

The absolute oral bioavailability of tapentadol capsules (using 86 mg dose) was 32.0%.

Protein Binding

Tapentadol protein binding is approximately 20%, mainly to albumin, and protein binding is independent of drug and protein concentration.

Mass balance, Metabolism, Induction, and Inhibition Potential

More than 95% of the dose was excreted within 24 hours after intake and an average of 99.9% of the dose was recovered after approximately 5 days. Total urinary excretion amounted to 99% of the dose. Only a few percent (mean: 3%) was excreted as unchanged CG5503 base, 69% was

excreted as conjugates. Approx. 27% should be excreted as other metabolites. Fecal excretion amounted to approximately 1%, and excretion in CO₂ was negligible.

The main metabolic pathways for the elimination of tapentadol in all species are direct glucuronidation and sulphatation.

Tapentadol is not an inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in vitro.

Tapentadol is not an inducer of CYP1A2, CYP2C9 and CYP3A4 in vitro.

Single dose linearity

AUC or C_{max} values increased linearly with increase in doses from 50 - 150 mg.

Multiple dose linearity

Study HP5503/13 showed that, at 75, 100, 125, 150 and 175 mg, AUC or C_{max} values increased linearly with increases in doses.

Food effect

C_{max} and AUC increased by 16% and 25% with food, respectively. The t_{max} was prolonged by about 1.5 hours with a median t_{max} of 3.00 hours (range: 1.02-6.00 hours) in the fed state and 1.50 hours (range: 1.00-4.00 hours) in the fasted state. The Applicant discussed the food effect during the drug development program and, with Agency's concurrence; the Applicant did not restrict the use of tapentadol with respect to meal consumption.

In Phase 3 studies, all doses of study treatment were administered with approximately 120 mL of water, with or without food. Study treatment was swallowed whole and not chewed, divided, dissolved, or crushed.

BCS class I assessment

The Applicant requested a biowaiver from conducting an in vivo bioequivalence study comparing the TBM 100 mg IR tapentadol tablet and the 100 mg IR capsule formulation used in Clinical development; the bioequivalence study between IR capsules and tablets was performed at the 80-mg dose strength. In support of the request, the Applicant presented the information regarding the physicochemical properties, the composition, formulation, and pharmacokinetic characteristics of the drug product, the dissolution test results, and the manufacturing method and scale. During the review, additional information regarding the stability of tapentadol in simulated gastric fluid (SGF), USP, and simulated intestinal fluid (SIF) was requested. Overall, adequate data showing that tapentadol is highly soluble, highly permeable, and that the tablet formulation is rapidly dissolving has been submitted. This information was forwarded to the BCS Committee and the BCS Committee concurred on the Class I designation for tapentadol.

Analytical Methodology

An LC-MS/MS method was used for the quantification of tapentadol and its O-glucuronide and the O-sulfate metabolites in plasma. The method had a validated range of 0.2 to 200 ng/mL, 5.00 to 400 ng/mL and 10.0 to 5,000 ng/mL for tapentadol, tapentadol-O-sulfate and tapentadol-O-glucuronide, respectively. Similarly an LC-MS/MS method was used for the quantification of tapentadol and its O-glucuronide in urine. The method had a validated range of 10 to 10,000 ng/mL and 500 to 100,000 ng/mL for tapentadol and tapentadol-O-glucuronide, respectively.

Population pharmacokinetic analysis

Six Phase 1 studies and six Phase 2/3 studies were used in the Nonlinear mixed effects modeling (NONMEM®). A two-compartment PK model with zero-order release followed by first-order absorption and first-order elimination described the individual tapentadol PK profiles. The CL/F and V2/F parameters were identified as parameters which may be affected by various covariates. As body weight increased, both CL/F and V2/F increased almost linearly. However, the body weight effect may not be clinically important due to minimal significance. The model predicted CL/F values for men were about 16% higher than that for women. Total bilirubin (TB) and total protein (TP) the majority of the subjects were healthy subjects, were identified as statistically significant covariates on CL/F. Overall, where applicable the findings from these analyses were in agreement with findings from standalone PK studies.

Renal impairment population PK analysis

The database for the population PK analysis of tapentadol and its metabolite tapentadol-o-glucuronide consisted of 40 subjects with varying degree of renal impairment from a single Phase 1 study. A three-compartment model with 1st order elimination best described the PK of tapentadol following oral administration. The most important covariate was CRCL on the clearance of the metabolite. Simulations indicate dosing to subjects with mild renal impairment, moderate or severe renal impairment resulted in up to 1.5, 2.5 and 8.7 fold higher exposure to tapentadol-O-glucuronide compared to subjects with normal renal function, while the exposures to tapentadol was not affected. However, it should be noted that tapentadol-o-glucuronide is an inactive metabolite and its accumulation in renal impairment subjects is not expected to be a significant safety issue.

Exposure-response analysis

Data from two Phase 3 studies (PAI-3002/KF5503/33 and PAI-3003/KF5503/32) and 2 Phase 2B studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22) were used. Each of these studies had a different study design and duration, inconsistent dosing regimens including flexible dosing schemes, inconsistent rules regarding the supplemental rescue usage, as well as different primary efficacy variables. The models built were either linear models ($Y_i = \beta_0 + \beta_1 \cdot Dose_i + \beta_2 \cdot Bpain_i + \epsilon_i$) or simple E_{max} models:

$$Y_i = E_0 + \frac{E_{max} \cdot Exposure_i}{EC50 + Exposure_i} + \epsilon_i$$

Clear exposure-efficacy response relationships were observed for all efficacy variables (e.g. SPID 5D for PAI-3002/KF5503/33). Among the selected demographic variables examined (age, body weight, baseline pain, sex, and race), only baseline pain intensity significantly affected the analgesic response profile of tapentadol IR. Subjects with higher baseline pain intensity had higher pain reductions.

Exposure-adverse event analysis

There are 6 main adverse events (nausea, vomiting, constipation, dizziness, somnolence, and pruritus) that can occur from taking opioids. These AEs have also been observed in the Phase 2 and 3 studies for tapentadol IR. The objectives of this analysis were (1) to assess the potential relationships between the occurrence of selected adverse events after oral administration of tapentadol IR and the extent of drug exposure, and (2) to identify potential risk factors that influence the occurrence of AEs following tapentadol IR administration. Nausea, vomiting, constipation, dizziness, somnolence, and pruritus were selected for analysis. Constipation and pruritus appeared to be associated with average exposure measures (average concentration, average daily dose, and average daily AUC). Dizziness and somnolence tended to be associated with peak exposure (C_{max}). Onset of somnolence was reported to be rapid, and after 10h very few subjects reported new occurrences. The occurrence of the first incidences of nausea and vomiting was associated with exposure (randomized dose or AUC_{ss} calculated from randomized dose) following the first dose of tapentadol IR.

Overall, adequate data characterizing the Clinical Pharmacology and Biopharmaceutics aspects of tapentadol IR tablets was provided.

2 QBR

2.1 General Attributes of the Drug and Drug Product

2.1.1 What are the highlights of the chemistry and physical-chemical properties of tapentadol?

Tapentadol HCl is freely soluble in water, 0.1 N HCl and simulated intestinal fluid (34 g/100 mL and 35 g/100 mL, respectively). Its solubility decreases at higher pH. The hydrochloride salt was used.

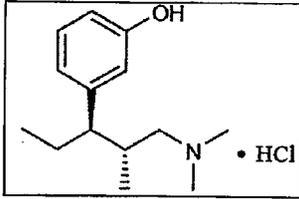
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Tapentadol HCl is 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. Its molecular formula is $C_{14}H_{23}NO \cdot HCl$ and it has a molecular weight of 257.80 g/mol for the hydrochloride salt and 221.34 g/mol for the free base. Tapentadol hydrochloride has 2 chiral centers leading to 4 possible stereoisomers. However, the proposed product is a pure stereoisomer with the absolute configuration (1R, 2R). The pK_{a1} and pK_{a2} are 9.34 (phenolic OH) and 10.45 ($HN(CH_3)_2^+$), respectively. The n-octanol/water partition coefficient (logP) is 2.87. Tapentadol HCl is freely soluble in water, 0.1 N HCl and simulated intestinal fluid (34 and 35 g/100 mL, respectively). Its solubility decreases at higher pH (to 5.8 g/100 mL at $pH=7.63$ and 3.4 g/100 mL at $pH=12.48$), which is likely due to the conversion from HCl salt to free base form. This decrease in pH dependent solubility does not affect its

overall high solubility at the highest proposed strength of 100 mg tablet. The hydrochloride salt was used

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Chemical Structure of tapentadol HCl



2.1.2 What are the highlights of the pharmaceutical development of tapentadol tablet formulation?

2.1.2.1 What is tapentadol to-be-marketed formulation?

Film coated immediate release Tablets (50-, 75-, and 100-mg) are proposed for marketing.

The Target Formulation Composition for Tapentadol Tablets (50-, 75- and 100-mg) is shown below;

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The three strengths are _____

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2.1.2.2 How was the tapentadol IR Formulation developed?

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Intravenous Formulations

Tapentadol hydrochloride was formulated either as a 1% (w/v) solution for injection (10 mg/mL) or as a solution for infusion (10-80 mg per 50 mL).

Quantitative Composition of Tapentadol Hydrochloride Solution for Injection

Dosage Strength (tapentadol hydrochloride)	10 mg/1 mL	100 mg/10 mL
Formulation ^a	2439E	6082SF
Ingredient	Quantity	

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Quantitative Composition of Tapentadol Hydrochloride Solution for Infusion

Dosage Strength (tapentadol hydrochloride)	10 mg/50 mL	20 mg/50 mL	40 mg/50 mL	80 mg/50 mL
Formulation ^a	6037SF	6038SF	6039SF	6040SF
Ingredient	Quantity (mg)			

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Capsule Formulations

The Phase 1 and 2 clinical trial capsule batches were manufactured in doses ranging from 25 to 200 mg. The Phase 1 and 2 clinical trial capsule batches were manufactured in doses ranging from 25 to 200 mg by both Grünenthal GmbH and J&JPRD.

Quantitative Compositions of Grünenthal GmbH Capsule Batches Employed in Phase 1 and 2 Clinical Studies — 25- to 75-mg (Tapentadol Hydrochloride) per Capsule^a

Formulation ^b	6112SF	2476E	6071SF	6071SF/1	6072SF
Dosage Strength (tapentadol hydrochloride)	25	25	50	58	75
Ingredient	Function		Quantity Per Dosage Unit (mg)		

b(4)

Quantitative Compositions of Grünenthal GmbH Capsule Batches Employed in Phase 1 and 2 Clinical Studies (I — 100- to 200-mg (Tapentadol Hydrochloride) per Capsule^a

Formulation ^b	6073SF	6073SF/1	6074SF	6075SF
Dosage Strength (tapentadol hydrochloride)	100	116	150	200
Ingredient	Function		Quantity Per Dosage Unit (mg)	

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Quantitative Compositions of Tapentadol Capsule Batches Employed in Phase 1 and 2 Clinical Studies : 25- to 100-mg (free base equivalent) per Capsule

Formulation Number	007	002	003	009
Dosage Strength (mg free base equivalent)	25	50	80	100
Ingredient	Function	Quantity Per Dosage Unit (mg)		

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Film-Coated Tablets

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Batch Formula for Tapentadol Tablets from Formulation DOE

Ingredient	Function	Quantity ^a (% w/w)
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Bioequivalence of Film-Coated Tablet to Capsule Formulation

It is noted that a bioequivalence study () demonstrated equivalence between the 80-mg capsule formulation () and the 80-mg processed film-coated tablet () manufactured using the (above table).

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Over-Encapsulated Film-Coated Tablets for Phase 3 studies

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Quantitative Compositions of Tapentadol Over-Encapsulated Film-Coated Tablet Batches Used in Phase 3 Clinical Studies ()

Dosage Strength (mg as the free base equivalent)		50 mg	75 mg	100 mg
Formulation		001*	014	015
Ingredient	Function	Quantity	Quantity Per Dosage Unit (mg)	

[Redacted content]

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In order to link this over-encapsulated film-coated tablet with the to-be-marketed film-coated tablets, acceptable comparative dissolution data was provided.

Registration Stability

The tapentadol tablets (50-, 75- and 100-mg) registration stability batches were manufactured at a scale using the . The registration stability batches are identical to the proposed commercial tapentadol tablets except for a slight variation in the debossing code applied. The quantitative composition and formulation numbers of the registration stability batches are presented in the table below:

Quantitative Compositions of Registration Stability Batches (Proposed Commercial Formulation) of Tapentadol Tablets (50-, 75-, and 100-mg) ()

Dosage Strength (mg as the free base equivalent)		50 mg	75 mg	100 mg
Formulation		CA-018	CA-021	CA-023
Ingredient	Function	Quantity (% w/w)	Quantity Per Dosage Unit (mg)	

[Redacted content]

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NA = Not applicable

Thus the following tables show the formulations used in Phase 1, Phase 2 and Phase 3 studies:

Capsule formulations used in Biopharmaceutics studies

The following table shows the P1 and P2 capsule formulation used in biopharmaceutics studies. The dose filled amount range from mg. The weight conversion factor of tapentadol hydrochloride to the free-base equivalent is

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Composition of Tapentadol IR Capsules Used in Biopharmaceutics Studies

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Composition of tapentadol IR tablets

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2.1.3 What is the proposed mechanism of action?

Tapentadol is both a μ -opioid receptor (MOR) agonist and an inhibitor of norepinephrine (NE) re-uptake.

Tapentadol is a centrally active antinociceptive drug developed for the relief of moderate to severe acute pain. The proposed mechanism of action for tapentadol is that it is 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. Tapentadol is a pure enantiomer and has no clinically-relevant active metabolites. No enantiomeric inter-conversion has been observed.

It is noted that tapentadol has a similar mechanism of action to that of tramadol. Tramadol is indicated for the management of moderate to severe pain. Tramadol also has a dual mechanism of pain relief: binding of tramadol and M1 metabolite to μ -opioid receptors (low affinity binding of tramadol and higher affinity binding of the O-demethylated metabolite M1) and weak inhibition of reuptake of norepinephrine and serotonin, which inhibits pain transmission in the spinal cord.

The apparent difference between tapentadol and tramadol is that tramadol inhibits reuptake of serotonin as well.

2.1.4 What are the proposed dosage and route of administration?

Tapentadol HCl tablet is taken orally. The proposed tapentadol dosage and administration is as follows:

DOSAGE AND ADMINISTRATION



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2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials?

Two pivotal Phase 3 efficacy studies (KF5503/32 Bunionectomy and KF5503/33 Degenerative Joint Disease) were conducted 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 dosing regimen of every 4 to 6 hours. The use of rescue analgesic medication was not allowed during the double-blind periods of the KF5503/32 and KF5503/33 studies; however, for KF5503/33, the use of prior stable non-opioid analgesic regimens was permitted during the study. A third Phase 3 study, KF5503/33, examined the safety as a primary objective of tapentadol IR over a 90-day period. It also had a secondary objective of examining efficacy over this period of time at 50 or 100 mg Q4H to Q6H and is a supportive study for efficacy. The primary efficacy variables were the sum of pain intensity difference (SPID) over 48 hours and over the first 5 days of treatment for KF5503/32 and KF5503/33, respectively. The secondary variables include Distribution of responder rates using pain intensity, Rescue medication usage, Additional pain intensity and pain relief variables, Time to perceptible, meaningful, and confirmed perceptible pain relief, and Patient global impression of change.

Study 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 Q4H to Q6H for 3 days (with the option of taking the second dose as early as 1 h, but no later than 6 h after the first study drug administration). 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.

Study 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 Q4H to Q6H 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 .

Study KF5503/34 was a multicenter, randomized, double-blind, parallel-group, active-controlled, outpatient study to evaluate the safety of multiple flexible doses of 50-mg or 100-mg of tapentadol IR taken Q4H to Q6H for 90 days in the relief of moderate to severe pain in subjects with a clinical diagnosis (present for at least 3 months) of low back pain or pain from osteoarthritis of the knee or hip. The active comparator was oxycodone HCl IR 10 or 15 mg. Prior stable non-opioid analgesics use was allowed during the study. For inclusion, subjects were required to have a baseline pain intensity (post-washout) score ≥ 4 on an 11-point numerical rating scale.

Primary efficacy variables

The primary efficacy variables were the sum of pain intensity difference (SPID) over 48 hours and over the first 5 days of treatment for KF5503/32 and KF5503/33, respectively. An analysis of covariance (ANCOVA) was used to assess the primary efficacy variables (SPID48 for KF5503/32 and 5-day SPID for KF5503/33 with LOCF) with the factors of treatment, center (pooled center for KF5503/33), and baseline pain intensity as covariate. All pair-wise treatment differences were estimated based on the least-square means of the difference (LSD).

Secondary efficacy variables

Distribution of responder rates using pain intensity - Percent improvement from baseline in pain intensity at 48 hours (KF5503/32) and at the end of Day 5 (KF5503/33) was calculated using an 11-point NRS. Subjects without a pain value at these time-points (e.g., subjects who discontinued prior to this assessment) were assigned the worst possible score (0 [i.e., no improvement]). The responder rate for a given percent improvement value was defined as the proportion of subjects who had a value above that threshold value.

Rescue medication usage - For study KF5503/32, rescue medication was defined as new analgesics taken during the double-blind treatment period. For study KF5503/33, rescue medication was defined as new analgesics taken during the double-blind treatment period that were not study drug. Non-opioid analgesics that were started at least 28 days prior to randomization and that remained stable during the double-blind period were not considered rescue medication. If there was a significant increase in the regimen of the stable non-opioid analgesic, that change was also considered as a rescue medication.

Additional pain intensity and pain relief variables - At each analysis time point (for KF5503/32: Hour 12, 24, 48, and 72; for KF5503/33: Day 2, Day 5 and Day 10), TOTPAR, SPID, and SPRID were analyzed separately using ANCOVA model with factors of treatment, center (pooled center for KF5503/33), and baseline pain intensity as the covariate. The least significant difference was used to perform pair-wise treatment comparisons.

Time to perceptible, meaningful, and confirmed perceptible pain relief - The distributions of the time to onset of perceptible pain relief and meaningful pain relief were estimated by the Kaplan-Meier method and compared using log-rank statistics with center as a stratification factor. Time to confirmed perceptible pain relief was equivalent to the stopwatch time of first perceptible pain relief if the subject also experienced meaningful pain relief.

Patient global impression of change – The assessments were summarized and compared with placebo (Cochran-Mantel-Haenszel test to control for center (pooled center for KF5503/33)).

Active comparator versus placebo – Comparison of oxycodone HCl IR versus placebo was performed (to validate the sensitivity of the study assays) on SPID (using LOCF, BOCF, and WOCF imputation), TOTPAR, and SPRID over 12, 24, 48, and 72 h for KF5503/32 and 2, 5, and 10 days for KF5503/33 with an analysis of covariance model including factors of treatment, center (pooled center for KF5503/33), and baseline pain intensity as a covariate. Similarly, treatment comparisons based on the time to first rescue medication use and distribution of responder rates were carried out using the log rank, Gehan, and Van Der Waerden tests (for the distribution of responder rates). Analyses were performed for the ITT analysis set at a 2-sided 0.05 alpha level.

Tapentadol IV versus oxycodone IR – Tapentadol IR at doses of 75 mg and 100 mg for KF5503/32 and at doses of 50 mg and 75 mg for KF5503/33 was compared with oxycodone HCl IR 15 mg and 10 mg, respectively, for efficacy while evaluating the corresponding safety profiles at these doses using a stepwise approach. The non-inferiority in analgesic effect of the specified tapentadol IR doses versus oxycodone IR was examined based on the primary endpoint for each study (SPID48 for KF5503/32 and 5-day SPID for KF5503/33).

Results:

The following excerpts are from Dr. Ellen Field's Clinical Review for tapentadol HCl tablet. For final Agency's assessment of efficacy and safety, see Dr. Field's Clinical review. Dr. Field's stated that efficacy was demonstrated for tapentadol IR treatment at doses of 50 mg, 75 mg, and 100 mg using a dosing interval of 4 to 6 hours in two adequate and well-controlled clinical studies.

KF5503/32 Bunionectomy - Tapentadol IR demonstrated statistically superior efficacy compared to placebo treatment based on the primary (regardless of imputation strategy used) and all secondary variables. In addition, there was a numerical trend of increasing efficacy with increasing tapentadol IR doses. Assay sensitivity was confirmed by the separation of the oxycodone HCl IR 15 mg group from placebo in the primary efficacy variable, SPID48 (sum of pain intensity difference at 48 hours).

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Descriptive statistics and pairwise comparison of SPID48 using Hochberg procedure:

	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	43.4	127.6	131.3	158.5	170.6
(Range)	(-278;274)	(-185;402)	(-199;462)	(-94;408)	(-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	

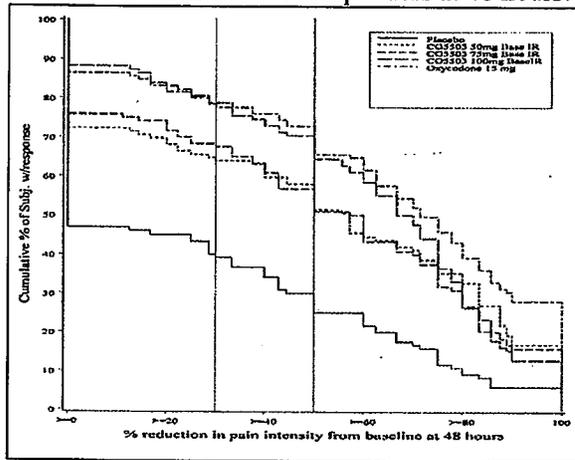
^a Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate. Adjusted p-values using Hochberg procedure. Oxycodone group is not included.

Comparison with Placebo: Bunionectomy (Study KF5503/32: Intent-to-Treat 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 (69.71, 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) ^{b,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 ≥30% improved at Hour 48 ^e	<0.001	<0.001	<0.001	<0.001
Pain assessment ≥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 ^{e,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

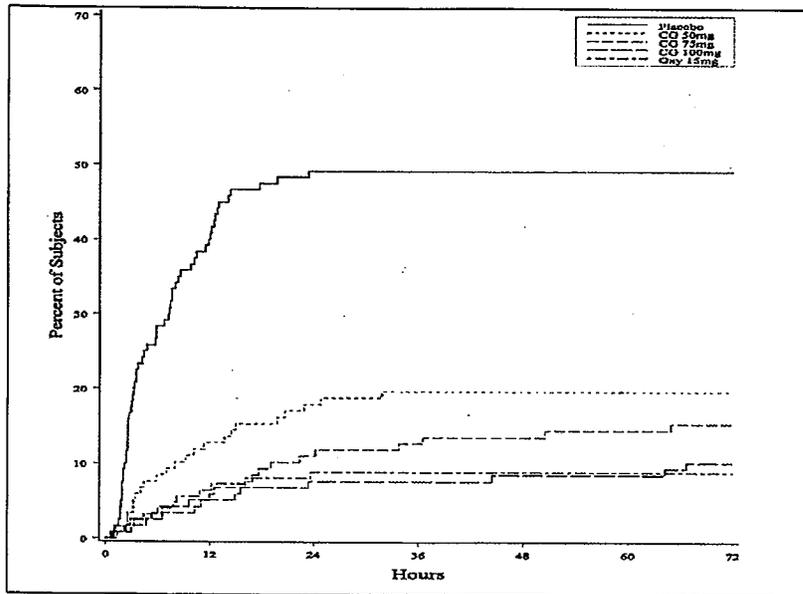
^a Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate.
^b P-values adjusted for multiplicity using Hochberg procedure.
^c P-values for tapentadol groups are adjusted for multiplicity using Hochberg procedure. P-value for oxycodone group 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.
Higher value in SPID indicates greater pain relief.
Higher value in TOTPAR, SPRID indicates greater pain relief.

Cumulative distribution of responders at 48 hours:



Note: the treatment groups are well separated from the placebo group.

Time to rescue medication:



Note: time to rescue was longer for active treatment groups

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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.

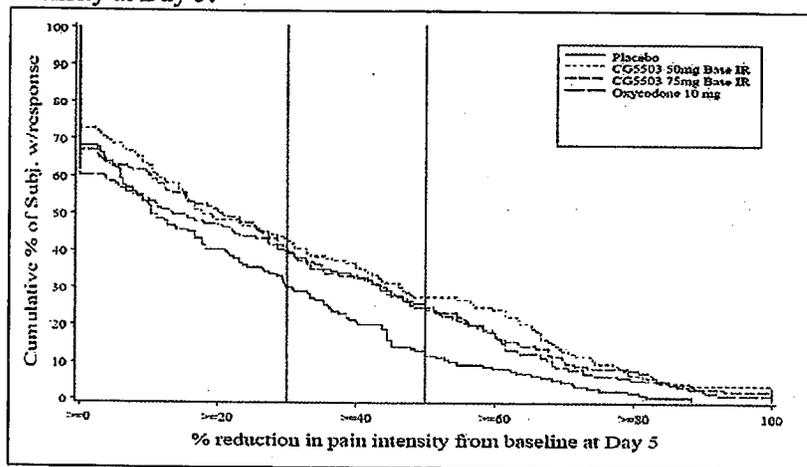
Note: time to meaningful pain relief was shorter for active treatment groups

KF5503/33 End-Stage Degenerative Joint Disease - Tapentadol IR demonstrated superior efficacy compared with placebo treatment on the primary (regardless of imputation strategy used) and most secondary variables. Assay sensitivity was confirmed by the separation of the oxycodone HCl IR 10 mg group from placebo in 5-day SPID.

Descriptive statistics and pairwise comparison of SPID at Day 5: (by LOCF computation);

	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	--

Cumulative distribution of responder rates based on percent change from baseline in pain intensity at Day 5:

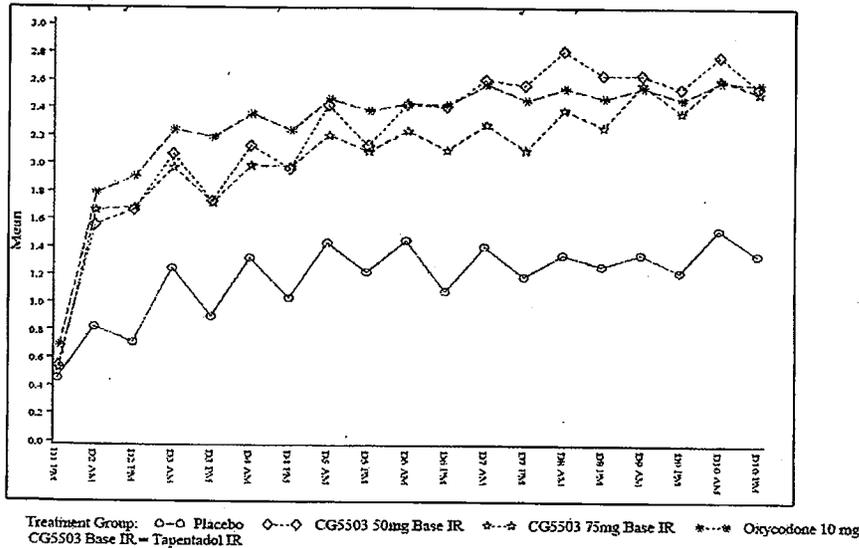


Comparison with Placebo: Degenerative Joint Disease (Study KF5503/33: Intent-to-Treat Analysis Set)

	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) ^d	<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 ^{e, f}	0.626	0.626	0.142
2-day SPID (LOCF) ^g	<0.001	<0.001	<0.001
10-day SPID (LOCF) ^g	<0.001	<0.001	<0.001
5-day TOTPAR (LOCF) ^g	<0.001	<0.001	<0.001
5-day SPRID (LOCF) ^g	<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.

Mean pain intensity difference over time for all treatment groups:



Note: the treatment groups are well separated from the placebo group.

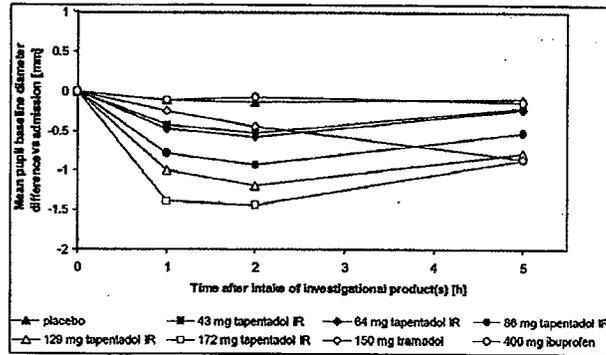
2.2.2 What biomarkers and how are they measured in clinical pharmacology and clinical studies?

Pupillometry was used as a biomarker to test for mu-agonist activity in early studies in the development program. A trend was seen towards decreasing pupil diameter with increasing dose of tapentadol.

A typical biomarker used in opioids is to measure the pupil diameter for mu-agonist activity. The relationship between decrease in pupil diameter with that of pain relief has not been fully explored and understood. Generally, there is decrease in pupil diameter with mu-agonist administration. Study KF5503/02 was a randomized, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group, dose-response study in the treatment of dental pain after third molar surgery. Tapentadol doses were 43, 64, 86, 129 and 172 mg in comparison to oral tramadol 150 mg, ibuprofen 400 mg and placebo.

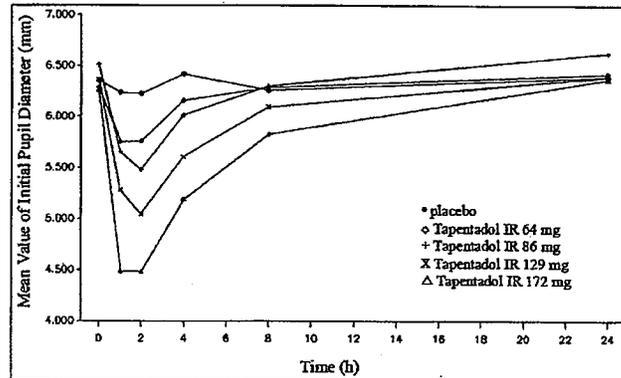
The initial decrease in pupil diameter was most pronounced in the 129 mg and 172 mg tapentadol IR groups and less pronounced in the 150 mg tramadol group. A trend was seen towards decreasing pupil diameter with increasing dose of tapentadol.

Mean Pupil Diameter, Difference Versus Baseline (N = 400) Following Intake of Single-Dose Tapentadol, Tramadol, Ibuprofen or Placebo

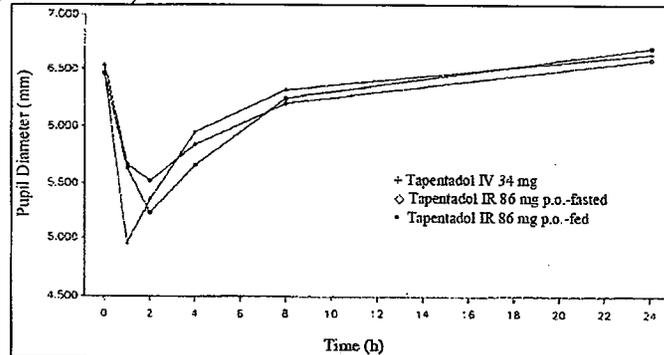


Similar results were obtained from Study HP5503/03 (tapentadol 64, 86, 129 and 172 mg or placebo) and Study HP5503/04 (an i.v. infusion of 34 mg tapentadol over 15 minutes, an oral administration of 86 mg tapentadol IR in the fasted state or an oral administration of 86 mg tapentadol after a continental breakfast).

Effects of Different Doses of Tapentadol and Placebo on Initial Pupil Diameter (Study HP5503/03)



Time Course of Effects on Initial Pupil Diameter After Different Administrations of Tapentadol to Healthy Men (Study HP5503/04)



2.2.3 Are the active moieties in the serum and urine appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, tapentadol is the only active moiety and tapentadol was measured appropriately in serum and urine. Since the metabolites, inactive) are excreted in the urine, glucuronide metabolites were measured in hepatic and renal studies.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

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 Phase 3 studies (KF5503/32 and KF5503/33) based on the following results:

- In a single-dose bunionectomy study KF5503/05, tapentadol HCl 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.

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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.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) from Phase 3 efficacy studies?

In Study KF5503/32, a bunionectomy study, there was a trend of increasing efficacy (SPID48) with increasing tapentadol dose (50mg, 75mg, and 100 mg). In Study KF5503/33, an OA study, it appears that there was no dose related increase in efficacy (SPID at Day 5) from 50mg to 75mg. Nevertheless, both tapentadol doses were found to be efficacious.

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. As stated above, 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. Typically, SPIDs are used frequently and are acceptable for the analysis of analgesic efficacy for acute pain. In Study KF5503/32, a bunionectomy study, there was a trend of increasing efficacy (SPID48) with increasing tapentadol dose (50mg, 75mg, and 100 mg).

Descriptive statistics and pairwise comparison of SPID48 using Hochberg procedure:

	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	43.4	127.6	131.3	158.5	170.6
(Range)	(-278;274)	(-185;402)	(-199;462)	(-94;408)	(-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.

However, in Study KF5503/33, an OA study, it appears that there was no dose related increase in efficacy (SPID at Day 5) from 50mg to 75mg. 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. Nevertheless, both tapentadol doses were found to be efficacious.

Descriptive statistics and pairwise comparison of SPID at Day 5: (by LOCF computation)

	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	--

2.2.4.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The observed treatment emergent adverse events (TEAEs) appear to be dose-related. Common adverse events appear to increase with increase in tapentadol doses.

Tapentadol has a similar safety profile to that of other immediate-release opioid analgesics and tramadol. Common adverse events included nausea, dizziness, vomiting, somnolence, headache, constipation, pruritis, and asthenic conditions. The Applicant presented a composite of adverse events from all of the clinical trials. There was evidence that the incidence of treatment emergent adverse events appeared to be dose-related, as presented below.

Preferred Term	Placebo (n=619) n (%)	Tapentadol IR				Flex (n=679) n (%)
		0-30 mg (n=22) n (%)	>30-60 mg (n=538) n (%)	>60-90 mg (n=607) n (%)	>90-120 mg (n=333) n (%)	
No. (%) of Subjects with TEAEs	289 (47)	13 (59)	372 (69)	466 (77)	282 (85)	518 (76)
Nausea	30 (13)	3 (14)	172 (32)	207 (34)	156 (47)	125 (18)
Dizziness	48 (8)	1 (5)	110 (20)	157 (26)	125 (38)	123 (18)
Vomiting	26 (4)	1 (5)	80 (15)	112 (18)	89 (27)	115 (17)
Somnolence	17 (3)	1 (5)	74 (14)	91 (15)	85 (26)	69 (10)
Headache	66 (11)	3 (14)	63 (12)	59 (10)	36 (11)	78 (11)
Constipation	16 (3)	2 (9)	30 (6)	30 (5)	25 (8)	87 (13)
Pruritus	8 (1)	0	18 (3)	39 (6)	31 (9)	29 (4)
Dry mouth	2 (<1)	0	15 (3)	26 (4)	14 (4)	36 (5)
Fatigue	3 (<1)	0	7 (1)	19 (3)	8 (2)	38 (6)
Diarrhoea	17 (3)	1 (5)	6 (1)	14 (2)	2 (1)	45 (7)
Hyperhidrosis	4 (1)	0	16 (3)	18 (3)	13 (4)	12 (2)
Pruritus generalised	4 (1)	0	13 (2)	14 (2)	23 (7)	4 (1)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31 (excluding site 011006), KF5503/32, KF5503/33, KF5503/34, and KF5503/37

TEAE = treatment-emergent adverse events.
MedDRA version 10.1 was used for coding
Flex = Tapentadol flexible dose of 50 or 100 mg.

There were no deaths attributable to tapentadol IR, and no unexpected or unusual adverse events of interest.

2.2.4.4 What other exposure-response relationship information were presented in the NDA?

The overall information from the population PK model supported the pharmacokinetic findings from the Phase 1 and 2 studies. Additionally, the overall information obtained from the exposure-response model exercise also supported the findings from the Phase 3 studies. It is noted that each of the Phase 2/3 studies used in the modeling had a different study design and duration, inconsistent dosing regimens including flexible dosing schemes, inconsistent rules regarding the supplemental rescue usage, as well as different primary efficacy variables. Therefore, these studies are not pooled and separate analysis was performed for each of the studies. (See Appendix 2 for additional information)

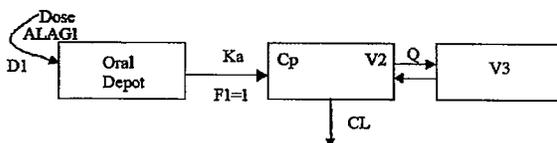
A population PK and exposure-response model was developed using data from Phase 1, renal and hepatic patients and from Phase 2/3 in subjects with moderate to severe acute pain (using sparse PK blood sampling). The primary objectives of these analyses were to assess the PK in the target patient population as well as to evaluate the effects of subject's demographic characteristics and other covariates (e.g., inter- and intra-individual variability) on tapentadol PK and to relate tapentadol exposure to efficacy and safety measures. Four different analyses were conducted to address the primary objectives. (See Appendix 2 for additional information)

POPULATION PK ANALYSIS

The objectives were (1) to estimate typical PK parameters of tapentadol IR in the population and their inter- and intra-individual variability, and (2) to evaluate the effects of subject's demographic characteristics and other covariates on the PK of tapentadol following administration.

The analysis included pooled data from 1,833 subjects from six Phase 1 studies (HP5503/03, PAI-1005/HP5503/13, PAI-1006/HP5503/15, PAI-1002/HP5503/16, PAI-1016/HP5503/24, and PAI-1019/HP5503/30) and six Phase 2/3 studies (KF5503/02, KF5503/04, KF5503/05, PAI-2004/KF5503/21, PAI-2003/KF5503/22, and PAI-3003/KF5503/32). A total of 11,385 PK samples with valid concentration time-points from 1,827 subjects were included in this analysis. Nonlinear mixed effects modeling (NONMEM®) was conducted to develop the population PK model. Various structural models were tested to evaluate their fit to the data. Inter-individual variability (IIV) and inter-occasion variability (IOV), described using an exponential variance model, were explored for each of the PK parameters in the model, as well as various residual error models. The residual error was modeled using an additive error model in the log domain, since the serum concentrations were log-transformed. Using the base (structural) model, the relationships between subject covariates and PK parameters were explored to explain IIVs using a stepwise backward elimination approach. The final model (including all significant subject covariates) was subjected to external validation to assess accuracy and precision of the parameter estimates. The Phase 3 bunionectomy study, PAI-3003/KF5503/32, data was used as an external validation dataset (353 subjects contributed 1,271 serum samples). The final model was re-run on the full dataset to obtain the final parameter estimates.

A two-compartment model with a zero-order release followed by a first order absorption and 1st order elimination best described the PK of tapentadol IR following oral administration:



The parameter estimates of the final model and their precision were obtained after excluding the identified outliers. The final fixed effect parameters were estimated as follows from the final model:

$$CL / F_j = 214 \cdot \left(\frac{WT_j}{71}\right)^{0.996} \cdot \left(\frac{TB_j}{8.04}\right)^{-0.077} \cdot CL_TB50_j \cdot \left(\frac{TP_j}{69.7}\right)^{-0.442} \cdot \left(\frac{FAT_j}{29.8}\right)^{-0.479} \cdot SEX_CL_j \cdot RACE_CL_j$$

where, 214 L/hr is the typical CL/F for a White man with median body weight of 71 kg; TB of 8.04 µmol/L; TP of 69.7 g/L; and FAT of 29.8%, estimated based on BMI, age and gender. CL_TB50j is the shift factor (0.39) for subjects with TB levels greater than 50 µmol/L; and SEX_CLj is the shift factor for women (1.24). The shift factors for Black, Hispanic-Latinos, and other non-White racial groups combined are 0.77, 0.92, and 0.88, respectively. (TB: total bilirubin; TP: total protein; FAT: body fat)

Furthermore, the equation below describes the relationship between the typical values (TV) of apparent volume of distribution of central compartment (V2/F) in the jth subject and covariates:

$$V2 / F_j = 1170 \cdot \left(\frac{WT_j}{71}\right)^{0.96} \cdot \left(\frac{AGE_j}{30}\right)^{-0.209} \cdot \left(\frac{CRCL_j}{101}\right)^{-0.226} \cdot HLTH_V2_j$$

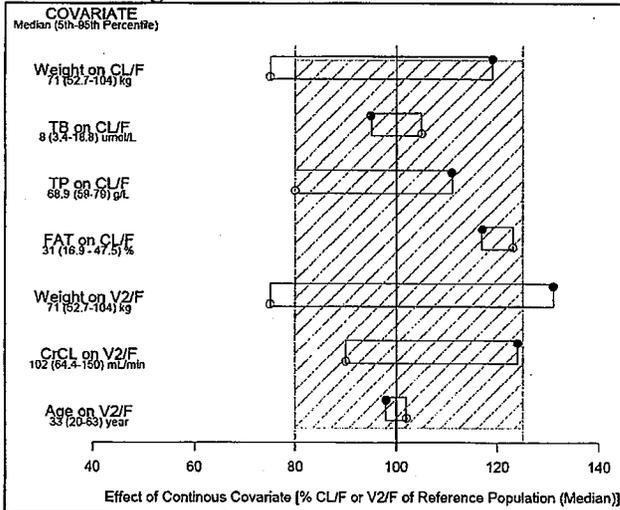
where, 1170 L is the typical value of V2/F for a healthy subject with body weight of 71 kg, age of 30 years, and CRCL of 101 mL/min. HLTH_V2_j is the shift factor (1.11) for bunionectomy and post-surgical dental pain subjects. (HLTH_V2_j: health status indicating healthy subjects or subjects in pain model)

Additionally, the following parameter estimates are obtained: Q/F (L/h) = 24.2; V3/F(L) = 147; KA (h⁻¹) = 2.06; D1 (h) = 0.451; and, ALAG1 (h) = 0.235. (ALAG1: lag time for 1st order absorption process)

Discussion of clinical relevance of covariates identified during the PK modeling

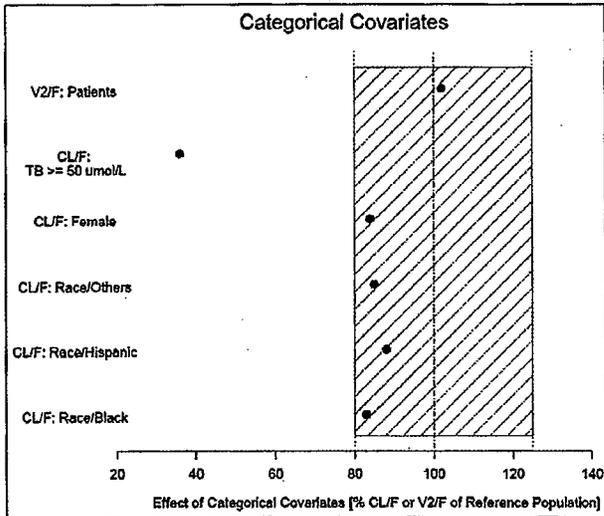
The clearance and volume of distribution are the two pharmacokinetic parameters identified during the modeling as important parameters. The influence of various covariates, such as body weight, hepatic and renal functions, age, health status, body fat, gender, and race, on CL/f and V2F were assessed. These covariate effects were estimated based on the optimized final model (*r602-full-10*). The following figures present the effect of continuous and categorical covariates on CL/F and V2/F.

Estimated Magnitude of Effects of Continuous Covariates in the Final PK Model



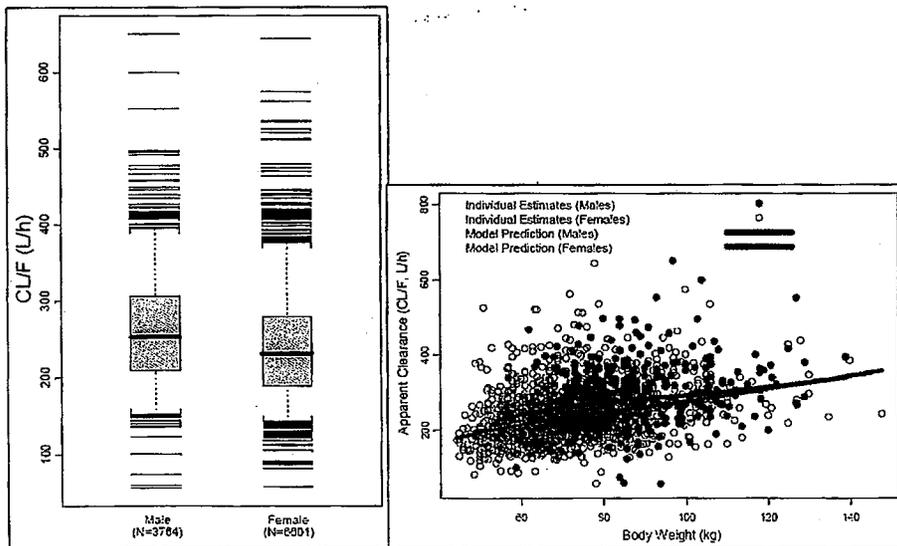
Note: Open circles and solid dots represent point estimates of the covariate effect at the 5th and 95th percentiles of the covariate, respectively, compared to the reference population (median of the covariate). The effect at the 95th percentile value of the covariate is tagged higher in the rectangle relative to the effect at the 5th percentile value of the covariate. The solid vertical line represents the covariate effect for the reference population (median of the covariate), and the shaded area represents the bioequivalence range: 80% - 125%, of this value. The medians, 5th, and 95th percentiles of each covariate are listed on the left. TB – total bilirubin; TP – total protein.

Estimated Magnitude of Effects of Categorical Covariates in the Final PK Model



Note: Solid dots represent point estimates of the covariate effect compared to the corresponding reference populations. The dashed vertical line represents the covariate effects for the reference populations, and the shaded area represents the bioequivalence range: 80% - 125%, of this value. The reference populations are (from top to bottom): healthy volunteers, subjects with TB < 50 $\mu\text{mol/L}$, males, and Caucasians for race.

Body weight and gender: Body weight was found to be a statistically significant covariate on both CL/F and V2/F with a reduction in OFV of more than 100 points. As body weight increased, both CL/F and V2/F increased almost linearly. However, the body weight effect may not be a clinically important due to minimal significance. Gender effect on CL/F was found statistically significant: men appear to have slightly higher apparent oral clearance than women. The model predicted CL/F values for men were about 16% higher than that for women. After body weight was taken into account, the impact of sex on CL/F was small, with women up to approximately 100 kg having a slightly lower CL/F. Again, gender effect may not be a clinically important covariate on the PK of tapentadol.



Note: The post-hoc individual estimates of CL/F from Final PK Model (Model r602-full-10) are plotted by gender (Left Panel) and by body weight (Right Panel). In the right panel, the red dots and black circles are the post-hoc individual estimates of CL/F for males and females, respectively. Description of the boxplot: the upper cap, upper bound of the box, horizontal line in the box, lower bound of the box, and lower cap represent the 95th percentile, 75th percentile, median, 25th percentile, and 5th percentile of the data, respectively.

Age, health status, race, body fat, hepatic and renal functions: Total bilirubin (TB) and total protein (TP) from the subjects, the majority of the subjects were healthy subjects, were identified as statistically significant covariates on CL/F. However, the magnitude of the covariate effects at the 5th and 95th percentiles of the distribution of TP and TB was minimal, as shown in the two figures previously presented titled Estimated Magnitude of Effects of Continuous Covariates in the Final PK Model and Estimated Magnitude of Effects of Categorical Covariates in the Final PK Model.

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Conclusion of the Population PK Analysis of Tapentadol

A two-compartment PK model with zero-order release followed by first-order absorption and first-order elimination described the individual tapentadol PK profiles. The CL/F and V₂/F parameters were identified as parameters which may be affected by various covariates.

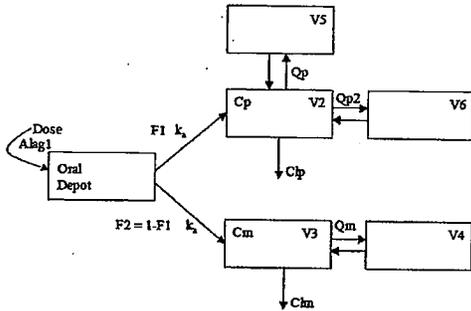
ANALYSIS OF PK OF MAJOR METABOLITE, tapentadol-O-glucuronide, IN RENAL IMPAIRMENT POPULATION

Clinical database - Study HP5503/15 (R331333-PAI-1006)

The database for the population PK analysis of tapentadol and its metabolite tapentadol-o-glucuronide consisted of 40 subjects with varying degree of renal impairment from a single Phase 1 study. From 40 subjects, a total of 460 PK samples for tapentadol and 482 PK samples for tapentadol-o-glucuronide were available for analysis. Serum concentrations of tapentadol and its primary metabolite, tapentadol-O-glucuronide were determined by validated bioanalytical methods. The lower limit of quantification for tapentadol was 0.2 ng/ml and for tapentadol-O-glucuronide 10 ng/ml.

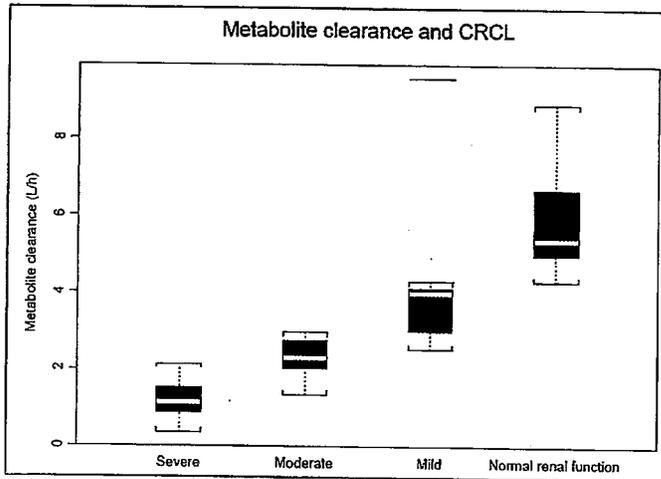
Modeling

The modeling setup was similar to that of the population PK analysis. The CRCL (creatinine clearance) had major influence on the clearance of metabolite. An integrated population PK model was developed for parent and metabolite. A three-compartment model with 1st order elimination best described the PK of tapentadol following oral administration. Schematic Representation of the Structural Model for Tapentadol and its Metabolite Tapentadol-O-Glucuronide:



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Influence of CRCL on the Clearance of Tapentadol-O-Glucuronide



The white line represents the median of the data. The purple box represents the middle 50% of the data. The whiskers represent the maximum and minimum of the data. The black horizontal line represents an outlier.

Conclusions on the metabolite analysis

A three-compartment disposition model for tapentadol combined with a two compartment model for tapentadol-o-glucuronide best described the PK of tapentadol and its major metabolite after oral administration in healthy subjects and subjects with renal impairment. The most important covariate was CRCL on the clearance of the metabolite.

Simulations indicate dosing to subjects with mild renal impairment, moderate or severe renal impairment resulted in up to 1.5, 2.5 and 8.7 fold higher exposure to tapentadol-O-glucuronide compared to subjects with normal renal function, while the exposures to tapentadol was not affected.

EXPOSURE-RESPONSE ANALYSIS

Clinical database

Two Phase 3 studies (PAI-3002/KF5503/33 and PAI-3003/KF5503/32) and 2 Phase 2B studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22) were used. Each of these studies had a different study design and duration, inconsistent dosing regimens including flexible dosing schemes, inconsistent rules regarding the supplemental rescue usage, as well as different primary efficacy variables. Therefore, these studies are not pooled and suitable analyses are performed separately for each. The exposure measures used in the exposure-response analysis include randomized doses, subject's average daily doses, and simulated PK exposure measures such as steady-state AUC, or C_{max} , C_{avg} , and AUC over a specific timeframe. The efficacy variables used included primary efficacy variables in all studies and in addition in study PAI-2003/KF5503/22, four secondary efficacy variables. The simulated PK exposure measures were obtained from the population PK analysis. All other data used came from the clinical data bases used for each study's statistical analysis and clinical report.

Modeling

The models built were either linear models or simple E_{max} models.

Linear Model - The linear model fits a linear relationship between the efficacy variable and dependent variables such as dose and other covariates:

$$Y_i = \beta_0 + \beta_1 * Dose_i + \beta_2 * Bpain_i + \epsilon_i$$

where Y_i is the efficacy variable such as SPID 5D or SPID48 for the i -th subject and was assumed to be an independent observation following a normal distribution. $Dose_i$ is the dose or average daily dose for the i -th subject and $Bpain_i$ is the baseline pain intensity score for the i -th subject. $Dose_i$ and $Bpain_i$ were assumed to be fixed effects. ϵ_i is the error term for the i -th subject and follows a normal distribution. β_0 , β_1 , and β_2 are the model parameters to be estimated.

E_{max} - The E_{max} model fits a non-linear relationship between the efficacy variable and an

$$Y_i = E_0 + \frac{E_{max} * Exposure_i}{EC50 + Exposure_i} + \epsilon_i$$

exposure measure:

where Y_i is the efficacy variable such as SPID48 or SPRID12 for the i -th subject and was assumed to be an independent observation following a normal distribution. $Exposure_i$ is an exposure measure for the i -th subject and was assumed to be a fixed effect. ϵ_i is the error term for the i -th subject and follows a normal distribution. E_0 , $EC50$, and E_{max} are the model parameters to be

estimated. E_0 is the effect at zero exposure level, EC_{50} is the exposure level that produces half of the maximum effect, and E_{max} is the maximum obtainable effect when the exposure level approaches infinity.

Exposure-Efficacy Response Summary

Among the selected demographic variables examined (age, body weight, baseline pain, sex, and race), only baseline pain intensity significantly affected the analgesic response profile of tapentadol IR. Subjects with higher baseline pain intensity had higher pain reductions.

In study PAI-3002, which employed a flexible dose design, it was observed that subjects with higher body weight took a higher average number of tablets per day. Since the population PK analysis suggests that the clearance of tapentadol IR increases as the body weight increases, the trend observed between dose intake and body weight could be due to the fact that heavier people eliminates the drug faster, thus requiring a higher dose to achieve adequate analgesia compared to lighter people. From the longitudinal analysis of the Phase 3 studies, it is apparent that the efficacy of tapentadol IR is maintained throughout the study duration.

These studies were not primarily designed to evaluate the conversion ratios between tapentadol IR and oxycodone. Two doses of oxycodone IR, 10 mg and 15 mg, were utilized in these clinical studies to establish assay sensitivity. However, none of the studies evaluated both of the doses in the same clinical study. Therefore modeling techniques were utilized to elucidate the equipotent doses of tapentadol IR and oxycodone IR and hence determine an adequate conversion ratio. The analyses conducted to estimate of the conversion factor are therefore exploratory in nature.

For study PAI-3002/KF5503/33, the estimated conversion ratio between tapentadol IR and oxycodone IR is 8.09 with 95% confidence interval of (6.40, 11.10) based on the dose-response analysis. An alternate method, using a reverse dose-response analysis put the estimate for conversion at 7.17 with 95% confidence interval (6.69, 7.65). In both these methods, SPID 5D with LOCF imputation was used as the response and average daily dose was utilized to construct the dose-response analysis. These analyses were repeated using SPID 5D with BOCF imputation and yielded estimated conversion ratios of 5.99 with 95% confidence interval of (4.54, 7.93) based on the dose-response analysis and 7.17 with 95% confidence interval of (6.70, 7.63) based on the reverse dose-response analysis. For study PAI-3003/KF5503/32, the estimated conversion ratio between tapentadol IR and oxycodone IR is 6.60 with 95% confidence interval of (5.99, 7.40) based on the dose-response analysis; is 5.01 with 95% confidence interval (4.75, 5.27) using the reverse dose-response analysis. In both these analyses SPID₄₈ with LOCF imputation and average daily dose was utilized to construct dose-response analysis. These analyses were repeated using SPID₄₈ with BOCF imputation and nearly identical estimates were obtained: 6.70 with 95% confidence interval of (6.03, 7.61) based on the dose-response analysis; is 5.05 with 95% confidence interval (4.79, 5.31) using the reverse dose-response analysis.

EXPOSURE-ADVERSE EVENT ANALYSIS

There are 6 main adverse events (nausea, vomiting, constipation, dizziness, somnolence, and pruritus) that can occur from taking opioids. These AEs have also been observed in the Phase 2

and 3 studies for tapentadol IR. The objectives of this analysis were (1) to assess the potential relationships between the occurrence of selected adverse events after oral administration of tapentadol IR and the extent of drug exposure, and (2) to identify potential risk factors that influence the occurrence of AEs following tapentadol IR administration. Nausea, vomiting, constipation, dizziness, somnolence, and pruritus were selected for analysis.

Dataset

Subjects with measured tapentadol concentrations from two (2) Phase 2 studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22) and one Phase 3 study (PAI-3003/KF5503/32) were included in the exposure-AE analysis (N=803). The corresponding measures for systemic exposure were estimated from the simulated individual PK profiles generated using the individual Bayesian post hoc parameter estimates from the population PK model, which included: AUC at steady state, calculated as randomized dose divided by individual CL/F estimated from the population PK analysis; Average daily AUC during the study, calculated as total AUC over the study duration divided by the study duration. Total AUC for each individual was estimated from the simulated individual PK profiles using the trapezoidal rule; Average concentration over the study duration estimated from the simulated individual PK profiles; C_{max} during the study: calculated as the maximum concentration for each individual from the simulated individual PK profiles; Randomized dose: dose to which the subjects were randomized; Average daily dose, calculated as total administered dose divided by the dosing duration (day).

Results

Exposure-response relationship was observed for all 3 AEs, except that the men tended to have vomiting episodes only at relatively higher exposure levels of tapentadol than women. Dizziness and nausea were observed more for women, but the differences were not significant.

Conclusion of Exposure-AE Analysis

The results from the exposure-AE analysis include bunionectomy studies with a large number of women (~90%) and refer to the postoperative setting. Clear relationships between appropriate measures of exposure and time to first event were observed for most AEs. Although somnolence occurred more frequently in treatment groups than the placebo groups, the exposure-AE relationship was not apparent. Constipation and pruritus appeared to be associated with average exposure measures (average concentration, average daily dose, and average daily AUC). Dizziness and somnolence tended to be associated with peak exposure (C_{max}).

Onset of somnolence was reported to be rapid, and after 10h very few subjects reported new occurrences. The occurrence of the first incidences of nausea and vomiting was associated with exposure (randomized dose or AUC_{ss} calculated from randomized dose) following the first dose of tapentadol IR.

The time to first event of the three most frequently reported AEs (nausea, dizziness, and vomiting) were analyzed using Cox proportional hazards models. AUC_{ss} and C_{max} were identified as the most relevant exposure measures for these AEs based on both graphical exploration and likelihood evaluation. A sigmoidal E_{max} -type relationship was found between

the occurrence of the first AEs and tapentadol exposure. The estimated maximum risk ratio (E_{max}) values for dizziness, nausea, and vomiting were 59.5 (95% CI: 25.6 – 138), 9.6 (95% CI: 5.97-15.4), and 44.4 (95% CI: 15.2-130), respectively.

Gender difference in the hazard ratio was observed, after accounting for the difference in drug exposure between men and women. For nausea and dizziness, the risk for women was generally higher than that for men and the hazard ratio (HR; or relative risk) ranged from 2 to 3 ($p < 0.01$). A higher HR (~5) was observed for vomiting ($p < 0.001$) for the pooled Phase 2/3 data. However, since no vomiting event was observed in men ($N=61$; 12.9% of the PAI-3003/KF5503/32 study population) in the Phase 3 study, the gender difference in vomiting risk may have been inflated. Due to the imbalance in the ratio of women ($N=929$) versus men ($N=140$) in the entire analysis dataset, the interpretation of these results is rather limited. Body weight was found to be a marginally significant but clinically irrelevant factor affecting vomiting ($p=0.04$; HR: 0.99; 95%CI: 0.98 -1.00). The risk of vomiting declines by 1% when body weight increases by 1 kg. While age was found to have a statistically significant effect ($p=0.01$; HR: 0.99; 95%CI: 0.98-1.00) on nausea when the pooled Phase 2/3 dataset was analyzed, its impact was likely clinically irrelevant because when the Phase 3 (PAI-3003/KF5503/32) data were analyzed alone the age effect was not statistically significant ($p=0.36$; HR: 1; 95%CI: 0.98-1.01). The placebo effect for nausea was significant ($>10\%$), while the placebo effect for vomiting was minimal ($<3\%$). The AUC_{ss} of tapentadol was identified to be a predictor of the multiple events of vomiting. The exposure-multiple vomiting events exhibited an E_{max} -type relationship. Similar to time-to-first-event analysis, sex and body weight were identified as risk factors. Body weight had a borderline effect in determining the risk of vomiting events with an incidence rate ratio of 0.98 (95% CI: 0.97 – 0.99). The effect of body weight was statistically significant ($p < 0.001$), but of little clinical relevance. The higher the tapentadol exposure, the more vomiting events a subject would be expected to experience.

Overall, exposure to tapentadol was identified as the primary risk factor governing the time to first occurrence of nausea, vomiting, and dizziness and the event rate of multiple vomiting episodes. An E_{max} -type relationship was found between the occurrence of the AEs and tapentadol exposure. The estimated maximum risk (E_{max}) to experience these AEs could be more than approximately 10 times greater compared to the placebo groups. Gender difference was identified in the risk of these AEs: a higher risk was observed in women than in men in the analyzed data set. As similar gender difference has been observed for oxycodone and other centrally acting analgesics, the higher rate of the aforementioned adverse events in women can be regarded as a class effect. In placebo groups, women reported more nausea and dizziness incidences than men, which suggests women are more predisposed to these AEs compared to men. The results from the exposure-AE analysis should be interpreted with caution since the data used only include bunionectomy studies with a high predominance (approx. 90%) of women and only refer to the postoperative setting.

2.2.4.5 Does tapentadol prolong the QT interval?

No significant QT prolongation effect of tapentadol was detected.

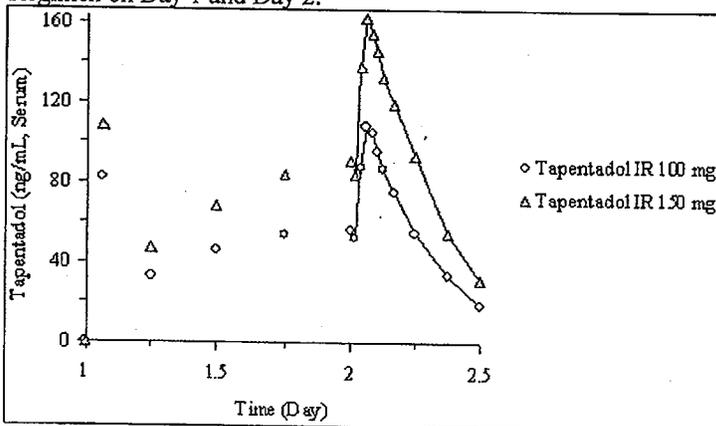
Study HP5503/25 was a single-center, double-blind, randomized, placebo- and 400 mg moxifloxacin positive-controlled, 4-way crossover study in healthy subjects (34 men and 34 women) aged 25 to 64 years, designed to assess the effect of tapentadol on the 12-lead ECG QT interval duration corrected for heart rate (QTc) in healthy men and women receiving multiple dosing (every 6 hours on Day 1 and on Day 2 to achieve steady-state (total of 5 doses each)) of tapentadol IR at therapeutic (100 mg) and suprathapeutic (150 mg) doses. The secondary objectives were to evaluate the incidence of QT/QTc changes from baseline greater than 30 and 60 milliseconds, and of postdose QTc values greater than 450, 480, and 500 milliseconds, to evaluate other ECG intervals (e.g., RR, QRS, PR), and to evaluate the PK of serum tapentadol and serum tapentadol-O-glucuronide. Serial 12-lead ECGs were taken immediately before and up to 12 hours after the last administration of study drug (steady-state) in the morning of Day 2. Blood samples for the determination of tapentadol and tapentadol-O-glucuronide were collected from predose up to 36 hours after the first dose.

PK Parameters of Tapentadol at Steady State (Day 2)(Study HP5503/25)

Parameter	n	Tapentadol IR 100 mg	Tapentadol IR 150 mg
$t_{max,ss}$, h	58	1.45 (0.87-6.00)	1.49 (0.40-6.02)
$C_{max,ss}$, ng/mL	58	129 ± 42.0	197 ± 89.1
C_{trough} , ng/mL	55	55.2 ± 25.2	93.3 ± 50.7
$C_{avg,ss}$, ng/mL	58	78.4 ± 24.3	122 ± 48.0
$AUC_{0-\infty}$, ng·h/mL	58	465 ± 146	729 ± 282
$t_{1/2}$, h	53 ^a	3.7 ± 0.9	3.7 ± 0.9
CL_{ss}/F , mL/min	58	3969 ± 1351	3820 ± 1176

^a tapentadol IR 150 mg, $t_{1/2}$: n=52
Data expressed as mean ± SD, except for t_{max} where median (range) is provided

Mean Tapentadol Serum Concentration-Time Profiles Following 100 or 150 mg Tapentadol IR Dosing Regimen on Day 1 and Day 2.



According to QT-IRT review (Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review, dated 7/17/08), no significant QT prolongation effect of tapentadol was detected. The following paragraphs are excerpted from the QT-IRT review:

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QT prolongation effect of tapentadol HCl (100 mg q6h and 150 mg q6h) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between tapentadol HCl (100 mg and 150 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidance.

This was a Phase 1, single-center, double-blind, randomized, placebo- and positive-controlled, 4-way crossover study to evaluate the electrocardiogram parameters in healthy men and women (n=68) receiving multiple dosing of an immediate-release (IR) formulation of tapentadol HCl at therapeutic and supratherapeutic doses. Overall findings are summarized in Table 1.

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Table 1: The Point Estimates and the 90% CIs corresponding to the Largest Upper Bounds for Tapentadol HCl (100 mg and 150 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time, h	$\Delta\Delta\text{QTcF}$, ms	90%CI, ms
Tapentadol HCl IR 100 mg q6h	26	-0.7	(-3.3, 2.0)
Tapentadol HCl IR 150 mg q6h	26	1.1	(-1.8, 3.8)
Moxifloxacin 400 mg *	1.5	10.2	(6.2, 14.3)

* CIs are adjusted for 11 post-baseline time points. See Table 8.

The suprathreshold dose is only 50% higher than the highest therapeutic dose administered q6h and similar to the expected exposure when 100 mg is administered q4h (assuming an accumulation of 2 based on $T_{1/2}$ of 4 h). The sponsor did not evaluate higher doses of tapentadol HCl because "the results from Study HP5503/13 suggest that higher doses than tapentadol IR 150 mg would lead to an unacceptably high rate of mainly gastrointestinal adverse events in healthy subjects which would not be acceptable for this pharmacodynamic study." To support the suprathreshold dose, the sponsor performed PK simulations in women with mild hepatic impairment and probenecid as concomitant medication, over a range of body-weight observed in the pooled database used to develop the PPK model. According to the simulation, 1 in 1000 patients dose with tapentadol HCl 100 mg are expected to achieve exposures greater than that achieved with tapentadol HCl 150 mg IR.

Moderate hepatic impairment leads to 1.8-fold increase in C_{max} . The sponsor is proposing dose and regimen adjustment for moderate hepatic impaired patients. The proposed dosing in moderate hepatic impaired patients is:

The supra-therapeutic dose of 150 mg q6h covers the range of exposures expected with the modified dosing regimen in moderately hepatic impaired patients.

There was no relationship between tapentadol concentrations and $\Delta\Delta\text{QTcF}$.

b(4)

2.2.5 What are the PK characteristics of the drug and its major metabolite?

The absolute oral bioavailability of tapentadol capsules was 32.0%. Tapentadol protein binding is approximately 20%, mainly to albumin, and protein binding is independent of drug and protein concentration. The main metabolic pathways for the elimination of tapentadol in all species are direct glucuronidation and sulphatation.

Tapentadol is not an inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 in vitro. Tapentadol is not an inducer of CYP1A2, CYP2C9 and CYP3A4 in vitro. More than 95% of the dose was excreted within 24 hours after intake and an average of 99.9% of the dose was recovered after approximately 5 days. Total urinary excretion amounted to 99% of the dose. Only a minor percent (mean: 3%) was excreted as unchanged CG5503 base while

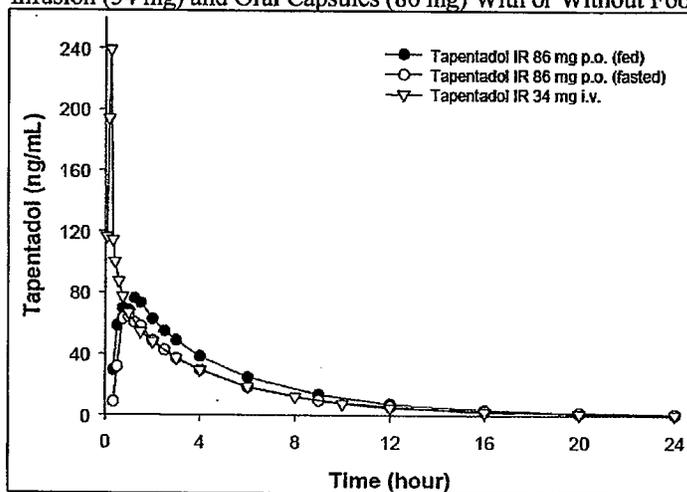
69% was excreted as conjugates. Approx. 27% should be excreted as other metabolites. Fecal excretion amounted to approximately 1%, and excretion in CO₂ was negligible.

2.2.5.1 Absorption

Absolute bioavailability

Study HP5503/04 was a single-center, single-dose, open-label, randomized, 6-sequence, 3-way crossover study in 24 healthy male subjects. Subjects received tapentadol as a 34-mg 15-min i.v. infusion (69 mg/50 mL, batch WMAK01) and as a 86 mg IR dose composed of 4 oral IR capsules of 21.5 mg (batch XDAM04) after an overnight fast (p.o. fasted) and after a standardized continental breakfast (p.o. fed).

Mean Tapentadol Concentration-Time Profiles After Single-Dose Administration as i.v. Infusion (34 mg) and Oral Capsules (86 mg) With or Without Food (Study HP5503/04)



Tapentadol Pharmacokinetic Parameters After Single-Dose Administration of i.v. Infusion, and Oral Capsule With or Without Food (Study HP5503/04)

	34 mg i.v. (batch WMAK01)	4*21.5 mg p.o. Fed (batch XDAM04)	4*21.5 mg p.o. Fasted (batch XDAM04)	Oral Fed/Fasted Ratio, % (90% CI) ^a
C _{max} , ng/mL	243 ± 93.4 [38.4]	101 ± 43.2 [42.8]	78.0 ± 26.9 [34.4]	125.3% (106.9-146.9)
AUC _{last} , ng.h/mL	374 ± 41.0 [11.0]	406 ± 105 [25.8]	310 ± 91.5 [29.5]	132.4% (123.3-142.2)
AUC _∞ , ng.h/mL	379 ± 42.2 [11.2]	411 ± 105 [25.7]	314 ± 91.6 [29.1]	131.9% (123.0-141.4)
t _{max} , h	0.23 (0.17-0.58)	1.25 (0.50-3.00)	1.00 (0.75-3.00)	
t _{1/2} , h	4.09 ± 0.70 [17.0]	4.57 ± 0.68 [14.9]	4.86 ± 0.72 [14.8]	
CL (CL/F), mL/min	1531 ± 177 [11.6]	3763 ± 1233 [32.8]	5007 ± 1820 [36.3]	
V _{dz} (V _{dz} /F), L	540 ± 98 [18.2]	1489 ± 564 [37.9]	2127 ± 970 [45.6]	
F, % (95% CI) ^a	-	42.2 (38.8-45.8)	32.0 (29.4-34.8)	

Data expressed as mean ± SD [% CV], except for t_{max} where median (range) is provided.
^a after dose-normalization, based on log-transformed data.

The absolute oral bioavailability of tapentadol capsules was 32.0% in the fasted state and 42.2% in the fed state.

2.2.5.2 Protein binding, metabolism, enzyme induction/inhibition and mass balance

Protein Binding:

Protein binding in human plasma showed that tapentadol protein binding is approximately 20%, mainly to albumin, and protein binding is independent of drug and protein concentration.

Metabolism:

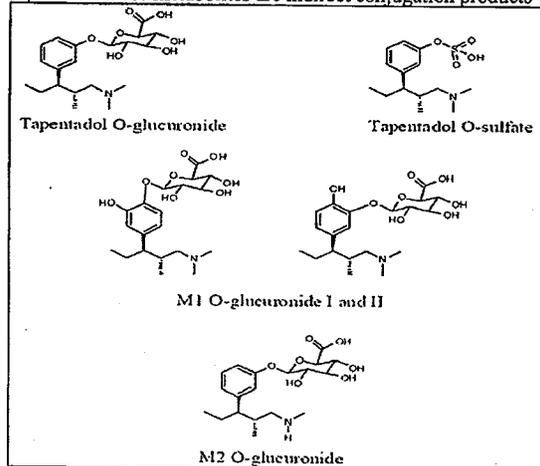
Overall metabolism information: After intravenous and oral administration, the serum concentrations of tapentadol base could be measured in most cases until 24 h after administration. Cleavage with β -glucuronidase/sulfatase revealed high concentrations of the respective conjugates, mainly the glucuronide of tapentadol in serum and urine.

In urine approximately 48% and 59% of the administered dose after i.v. and oral administration, respectively, are excreted via urine in the conjugated form. Only 8% and 3% of unchanged tapentadol base were found in urine after i.v. and oral administration, respectively. In serum, the conjugates exceeded the unconjugated tapentadol base by a factor of 6 and 20 for the i.v. and p.o. administrations, respectively.

Only small amounts of metabolites generated by oxidative pathways (e.g. N-demethylated tapentadol base) were found in urine of humans. The main metabolic pathways for the elimination of tapentadol in all species are direct glucuronidation and sulphatation and these metabolites are shown below:

Molecular Structures of the Major Metabolites of Tapentadol in Humans:

Tapentadol-O-glucuronide and tapentadol-O-sulfate are direct conjugation products; M1-O-glucuronide refers to the glucuronide of the hydroxy-tapentadol, and M2-O-glucuronide refers to the glucuronide of N-desmethyl tapentadol these metabolites are indirect conjugation products



Enzyme Induction and Inhibition:

The *in vitro* potential of tapentadol to inhibit the cytochrome P450 (CYP) isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 was assessed in human liver microsomes. No CYP inhibition was observed. However, at high concentration, there was some inhibition of CYP2D6 by tapentadol. The determined K_i 's were 181 μM (competitive) and 1410 μM (noncompetitive inhibition) and these are 200 to 1400 times higher than maximum therapeutic tapentadol serum concentrations (approximately 1 μM) observed in humans. This inhibition may not be clinically relevant.

The potential of tapentadol to induce CYP1A2, CYP2C9 and CYP3A4 was investigated *in vitro* with freshly isolated human hepatocytes. The results strongly suggested that tapentadol is not a CYP inducer at concentrations that may be achieved at the expected therapeutic doses of 50 to 100 mg.

As noted above, the metabolic clearance of tapentadol in humans is primarily due to glucuronidation. Uridine diphosphate (UDP)-glucuronosyl transferase are considered as a high capacity enzymes. Tapentadol concentration at which half maximum rate (K_m) of drug glucuronidation reactions occurs is much higher than the drug concentrations found at therapeutic doses. For tapentadol, the K_m is estimated at 390 μM or higher, which is approximately 400-fold the maximum clinical serum concentration of around 1 μM . Therefore, limitation of this metabolic elimination route by direct drug-drug interactions during treatment is considered to be unlikely.

Mass Balance:

A single 100 mg capsule of ^{14}C -labelled CG5503 was administered to 4 healthy male subjects for assessment of mass balance. Concentration-time profiles of radioactivity in whole blood and serum (collected up to 14 days), radioactivity in urine (collected up to 14 days), feces and expired carbon dioxide (collected up to 24 h) were collected. Pharmacokinetic parameters from serum profile of CG5503 base and its conjugates, excretion kinetics of CG5503 base and its conjugates in the urine were obtained.

The peak radioactivity in serum was achieved 1.25 to 1.5 hour after administration and it averaged 2.45 $\mu\text{g-eq}$ base /g. In serum, CG5503 was mainly present as the conjugated metabolite [metabolite ratio (conjugated / unconjugated) = 24]. The sum of the parent and its conjugates' AUC_{0-t} accounted for approximately 64% of the total radioactivity, indicating the presence of other metabolites in serum.

More than 95% of the dose was excreted within 24 hours after intake and an average of 99.9% of the dose was recovered after approximately 5 days. Total urinary excretion amounted to 99% of the dose. Only a minor percent (mean: 3%) was excreted as unchanged CG5503 base while 69% was excreted as conjugates. Approx. 27% should be excreted as other metabolites. Fecal excretion amounted to approximately 1%, and excretion in CO₂ was negligible.

Table 4: Main pharmacokinetic parameters for radiocarbon in serum

Parameters	Subjects				Mean	SD
	1	2	3	4		
Cmax ($\mu\text{g-eq base/g}$)	2.63	2.30	1.85	3.01	2.45	0.49
tmax (h)	1.25	1.50	1.50	1.25	1.38	0.14
AUC0-t ($\mu\text{g-eq base.h/g}$)	11.4	10.7	11.1	13.3	11.6	1.2
t _{1/2} , η_z (h)	3.89	3.66	4.10	4.05	3.93	0.20

Table 6: Summary Main pharmacokinetic parameters for radiocarbon and total (unconjugated + conjugated) CG5503 in serum

Parameters	Subjects				Mean
	1	2	3	4	
Radioactivity					
Cmax ($\mu\text{g-eq base/g}$)	2.63	2.30	1.85	3.01	2.45
AUC0-t ($\mu\text{g-eq base.h/g}$)	11.4	10.7	11.1	13.3	11.6
Total CG5503 (unconjugated and conjugated)					
Cmax ($\mu\text{g-eq base/g}$)	1.88	1.58	1.36	2.16	1.74
AUC0-t ($\mu\text{g-eq base.h/g}$)	6.77	6.56	7.56	8.90	7.45
Ratio (unconjugated+conjugated)/radioactivity					
Cmax	71%	69%	74%	72%	71%
AUC0-t	59%	61%	68%	67%	64%

Radiocarbon in red blood cells

Radioactivity possibly bound to blood cells was estimated from the concentration in whole blood and the corresponding serum concentration taking into account the haematocrit value. The calculated concentration of radiocarbon in blood cells was most often positive but did not exceed 5 to 10% of the serum level.

Radiocarbon in urine

The cumulative urinary excretion up to 120 h represented on average 98.6% of the dose (range: _____)

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The urinary excretion of radiocarbon was very rapid since, in all subjects, more than 50% of the dose was excreted after 4 hours and more than 95% after 24 hours. After 48 hours, the excretion rate became negligible with less than 0.25% of the dose per day.

Parameters	Subjects				Mean	SD
	1	2	3	4		
Ae ($\mu\text{g-eq-base}$)	_____				84666	
Ae (% dose)	_____				98.6	0.3
t _{1/2} (h)	_____				23.4	7.3

b(4)

Unconjugated-, conjugated-, and total-CG5503 in urine

Parameter	Subjects				mean	SD
	1	2	3	4		
<i>Unconjugated-CG5503</i>						
Ae (µg-eq-base)					2734	1454
Ae (% dose)					3.18%	1.69%
t1/2,z (h)					5.17	0.36
<i>Conjugated-CG5503</i>						
Ae (µg-eq-base)					58363	2842
Ae (% dose)					68.0%	3.3%
t1/2,z (h)					11.86	10.50
<i>Total-CG5503</i>						
Ae (µg-eq-base)					61098	3450
Ae (% dose)					71.2%	4.0%
t1/2,z (h)					11.28	9.79

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Parameters	Subjects				Mean
	1	2	3	4	
Total-CG5503 Ae (µg-eq-base)					61098
Radiocarbon Ae (µg-eq-base)					84666
Ratio (tot. Ae / radiocarb. Ae)					72%

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Excretion balance for radiocarbon [% of dose]

Subjects	1	2	3	4	Mean	SD
Urine					98.6	0.3
Feces					1.24	0.57
Expired CO2					0.035	0.015
Total					99.9	0.52

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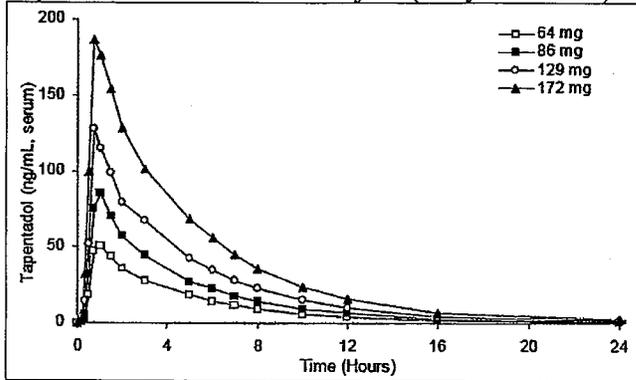
2.2.5.3 What are the single dose and multiple dose PK parameters?

Tapentadol was dose linear from 50 to 150 mg.

Several studies were conducted to assess dose linearity.

1) Study HP5503/03 was a single-center, single-dose, double-blind, placebo-controlled, randomized, dose-escalation study in 33 healthy subjects (16 men and 17 women). Thirty-two subjects completed the study. Subjects received tapentadol 64, 86, 129 and 172 mg or placebo as a 21.5-mg IR capsule formulation (batch XDAM04).

Mean Tapentadol Concentration-Time Profiles After Single-Dose Administration of Tapentadol IR Capsules to Male and Female Subjects (Study HP5503/03)

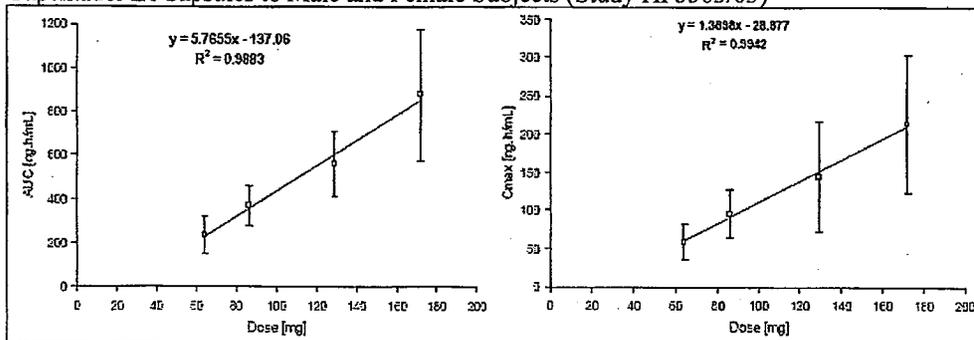


Pharmacokinetic Parameters After Single-Dose Administration of Tapentadol 21.5-mg IR Capsules to Male and Female Subjects (Study HP5503/03)

n=24	64 mg (3*21.5 mg)	86 mg (4*21.5 mg)	129 mg (6*21.5 mg)	172 mg (8*21.5 mg)
C_{max} , ng/mL	58.6 ± 23.8 [40.6]	95.7 ± 31.5 [32.9]	144 ± 72.7 [50.5]	213 ± 91.2 [42.9]
AUC_{last} , ng.h/mL	235 ± 83.9 [35.7]	371 ± 92.2 [24.9]	560 ± 148 [26.4]	873 ± 300 [34.3]
AUC_{∞} , ng.h/mL	238 ± 84.2 [35.4]	373 ± 92.0 [24.6]	563 ± 148 [26.4]	878 ± 301 [34.2]
t_{max} , h	1.00 (0.75-3.00)	1.00 (0.68-1.50)	1.00 (0.50-3.00)	0.88 (0.50-1.50)
$t_{1/2}$, h	5.22 ± 1.02 [19.6]	5.07 ± 1.05 [20.7]	4.68 ± 0.58 [12.5]	4.75 ± 0.64 [13.5]
DN C_{max} , ng/mL	91.5 ± 37.1 [40.6]	111 ± 36.6 [32.9]	112 ± 56.4 [50.5]	124 ± 53.0 [42.9]
DN AUC_{last} , ng.h/mL	368 ± 131 [35.7]	431 ± 107 [24.9]	434 ± 115 [26.4]	508 ± 174 [34.3]
DN AUC_{∞} , ng.h/mL	372 ± 132 [35.4]	434 ± 107 [24.6]	437 ± 115 [26.4]	511 ± 175 [34.2]
Dose-normalized (to 86 mg) ratio of 64-, 129- and 172-mg dose vs. 86-mg dose (%) (90% CI)				
AUC_{∞} (n=16)*	84.5 (77.2-92.6)	-	104.1 (98.4-110.2)	108.7 (100.6-117.6)
C_{max} (n=16)*	80.4 (68.6-94.1)	-	95.6 (81.9-111.5)	97.8 (84.5-113.1)
$t_{1/2}$ (n=16)*	102.7 (88.6-119.0)	-	95.2 (89.6-101.8)	90.3 (84.8-96.1)

* Only subjects receiving active drug in both treatments.
Data expressed as mean ± SD [%CV], except for t_{max} median (range). DN=dose-normalized to 100 mg.

Plot of Mean AUC_{∞} and C_{max} Values With SD vs. Dose After Single-Dose Administration of Tapentadol IR Capsules to Male and Female Subjects (Study HP5503/03)



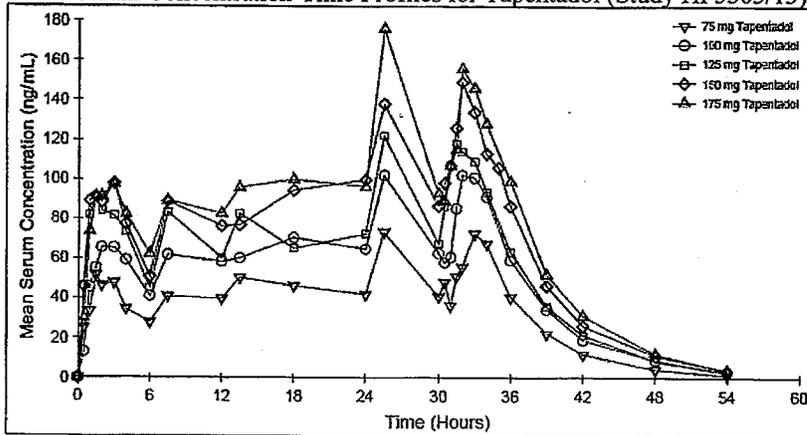
AUC or C_{max} values increased linearly with increase in doses.

2) Study HP5503/07 was a single-center, single-dose, open-label, randomized, 4-way crossover study in 16 healthy male subjects. All subjects completed the study. The objective was to determine the relative bioavailability of tapentadol 21.5 mg (batch AEAM06) and 86 mg (batch AEFD04) IR capsules, and 86 and 172 mg extended release tablets. - This study was not reviewed in detail since Study HP5503/03 contained a broader dosing range.

3) Study HP5503/13 was a single-center, single- and multiple-dose, double-blind, placebo-controlled, parallel-group, dose-escalation study in healthy subjects. Sixteen male and 16 female subjects were included and 22 subjects completed until the study was terminated for operational reasons. There were two treatment arms: Treatment 1 - 75, 125, 175 and 225 mg tapentadol; Treatment 2 - 100, 150, 200 and 250 mg tapentadol.

All subjects received multiple doses (6 doses; 1 every 6 hours) of 3 dose levels and 1 course of placebo. Tapentadol capsules of 25 mg (batch PD1428), 50 mg (batch PD1471) and 100 mg (batch PD1470), and matching placebos were used. The highest dose administered in the study was 175 mg due to premature termination.

Mean Serum Concentration-Time Profiles for Tapentadol (Study HP5503/13)



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Pharmacokinetic Parameters of Tapentadol After First and Repeated Dose Administration of Tapentadol IR Capsules (Study HP5503/13)

	75 mg ^a (n=10)	100 mg (n=12)	125 mg ^a (n=11)	150 mg ^a (n=11)	175 mg ^a (n=10)
First dose					
C _{max} , ng/mL	72.7 ± 36.3	95.1 ± 21.3	124 ± 40.7	135 ± 45.0	125 ± 37.3
AUC _{0-6h} , ng.h/mL	229 ± 90.3	299 ± 87.5	413 ± 132	439 ± 121	446 ± 126
t _{max} , h	1.50 (0.52-3.00)	1.75 (1.00-4.00)	1.50 (0.50-5.95)	1.50 (1.00-3.00)	2.00 (0.50-3.00)
DN-C _{max} , ng/mL	96.9 ± 48.4	95.1 ± 21.3	99.2 ± 32.6	90.0 ± 30.0	71.4 ± 21.3
DN-AUC _{0-6h} , ng.h/mL	305 ± 120	299 ± 87.5	330 ± 106	293 ± 80.7	255 ± 72.0
DN-C _{max} ratio (90% CI)	reference	105.01 (83.19-132.56)	98.63 (80.88-120.27)	98.37 (77.60-124.70)	76.83 (62.54-94.38)
DN- AUC _{0-6h} ratio (90% CI)	reference	100.38 (81.30-123.94)	100.91 (88.01-115.70)	103.64 (83.73-128.29)	84.78 (73.50-97.78)
Repeated doses (steady state)					
	(n=10)	(n=10)	(n=10)	(n=9)	(n=9)
C _{max,ss} , ng/mL	76.2 ± 31.0	118 ± 33.1	138 ± 64.6	160 ± 61.0	162 ± 42.2
AUC _τ , ng.h/mL	324 ± 143	494 ± 123	567 ± 199	675 ± 225	737 ± 166
t _{max} , h	2.95 (1.93-3.98)	2.95 (0.88-5.98)	2.08 (0.92-3.97)	2.03 (0.98-6.00)	2.00 (1.42-3.13)
t _{1/2} , h	3.9 ± 0.4	4.4 ± 0.6	4.0 ± 0.3	4.2 ± 0.7	4.0 ± 0.4
DN-C _{max,ss} , ng/mL	102 ± 41.3	118 ± 33.1	110 ± 51.7	107 ± 40.7	92.6 ± 24.1
DN-AUC _τ , ng.h/mL	432 ± 191	494 ± 123	454 ± 159	450 ± 150	421 ± 94.9
DN-C _{max,ss} ratio (90% CI)	reference	118.11 (91.68-152.14)	105.00 (87.14-126.52)	104.36 (80.61-135.09)	88.63 (72.90-107.75)
DN-AUC _τ ratio (90% CI)	reference	118.94 (94.53-149.66)	108.05 (91.38-127.75)	111.28 (88.05-140.64)	103.01 (86.43-122.77)
^a Administered as a combination of 25, 50 and 100 mg capsules (batches PD1428, PD1471 and PD1470). Data expressed as mean ± SD, except for t _{max} median (range). DN=dose normalized to 100 mg (post-hoc analysis; in the study report dose-normalization to 75 mg was used); τ=dosing interval (6 hours).					

Data shows that there is dose-linearity in the tested dose range.

2.2.5.4 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Based on cross study comparison of PK parameters for tapentadol, C_{max} of tapentadol dose-normalized to 100 mg, the inter subject CV was estimated at 39% and the intra-subject CV was estimated at 20%. For the AUC of tapentadol, dose-normalized to 100 mg, the inter-subject CV was estimated at 34%, whereas the intra-subject CV was estimated at around 13% (n=376).

A cross Study Mean Pharmacokinetic Parameters After a Single Dose of Tapentadol IR, Dose – Normalized to 100 mg Tapentadol (Dataset for cross-study comparison)

Parameter	n	Mean ± SD	%CV
t _{max} , h	631	1.25 (0.50-6.27)	
C _{max} , ng/mL	631	90.1 ± 36.2	39
AUC _∞ , ng.h/mL	576	417 ± 143	34
t _{1/2} , h	576	4.3 ± 0.8	16
CL _R , mL/min	78	99.0 ± 37.3	38
Data expressed as mean ± SD, except for t _{max} where median (range) is provided; n: number of observations. * more than 90% of observations was below or equal to 3 hrs. Cross-reference: post-hoc analysis, data on file			

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

2.3.2 Is dosage adjustments needed in the following populations?

2.3.2.1 What is the status of pediatric studies and/or any pediatric plan for study?

Pediatric data has not been submitted seeking approval of pediatric indications at this stage. Instead, the Applicant requested a 'staged' deferral of the requirement to conduct pain studies in the pediatric population. The Applicant proposed that trials be conducted in a step-wise manner to gather adequate pharmacokinetic, safety and efficacy information in the older children before exposing younger age groups. Adequacy of this plan is currently ongoing discussion in the review team.

The Applicant proposed to begin clinical studies in the 7 to less than 7 years of age group approximately 7 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 post-marketing database.

conducted:

The following studies will be

1

2.

3.

b(4)

b(4)

The following table provides the overview of the age breakdown:

Age group name ^a	Age span (years)	Rationale
Adolescents		
Children		
Children		
Term newborn infants, infants, and toddlers		

b(4)

The following table contains proposed timelines for the pediatric plan:

Step	Type of measure	Expected start	Anticipated duration	Expected finalization (report available)
1				
2				
3				
4				
5				
6				
7				
8				

b(4)

Q: Quarter

Adequacy of this plan is currently ongoing discussion in the review team.

2.3.2.2 Gender differences

Men and women showed that women in general had about 20% higher Cmax and AUC values. After bodyweight correction in this pooled analysis (men had about 20% higher body weight), the mean oral clearance was very similar between men and women.

No specific study was performed to investigate the effect of sex on the PK of tapentadol. However, gender based sub-group analysis performed in study KF5503/08 yielded information on the PK differences between men and women.

Study KF5503/08 was a randomized, double-blind, parallel group, single- and multiple-dose Phase 2 study to assess the safety, tolerability and PK of tapentadol following single- and multiple doses in patients with chronic non-malignant pain.

During the single-dose treatment period, patients received a single dose of 21.5 or 43 mg tapentadol IR. Thirty-six hours after the administration of the single-dose, subjects started taking

the same dose of tapentadol IR Q6H for 5 days. Serum concentrations of tapentadol were determined from blood samples collected at regular time points up to 36 hours in the single-dose period, and up to 48 hours after the last dose in the multiple-dose period.

Pharmacokinetic Parameters After Single- or Multiple-Dose Administration of Tapentadol

Parameter	Tapentadol IR 21.5 mg		Tapentadol IR 43 mg	
	(n=22)		(n=23)	
Single Dose				
t _{max} , h	2.3 (0.8–4.0)		2.0 (1.0–4.0)	
C _{max} , ng/mL	17.1 ± 6.7		30.1 ± 10.4	
AUC _{0-6h} , ng·h/mL	90.5 ± 36.3		169 ± 58.9	
AUC _{0-24h} , ng·h/mL	57.5 ± 23.3		106 ± 37.5	
t _{1/2} , h	4.6 ± 1.3		4.4 ± 0.6	
Multiple dose				
t _{max} , h	1.5 (1.0–4.0)		2.0 (1.0–5.0)	
C _{avg,ss} , ng/mL	16.3 ± 7.3		30.6 ± 9.1	
C _{max,ss} , ng/mL	26.5 ± 12.6		46.6 ± 13.8	
C _{min,ss} , ng/mL	10.3 ± 4.6		20.4 ± 7.2	
AUC _{τ,ss} , ng·h/mL	97.8 ± 44.0		184 ± 54.7	
t _{1/2} , h	4.9 ± 1.1		5.0 ± 1.1	
Acc Ratio	1.8 ± 0.7		1.9 ± 0.6	
Data expressed as mean ± SD, except for t _{max} where median (range) is provided.				

Concentration parameters and AUC's increased with increasing dose. The parameters t_{max} and t_{1/2} were similar for both doses (21.5 and 43 mg tapentadol) following single- and multiple-dose administration.

A sub-analysis was performed to assess potential differences in PK parameters in men versus women. Mean values of AUC and C_{max}/C_{max,ss} were consistently slightly higher (about 20%) for women compared to men after single and multiple doses of tapentadol 21.5 mg and 43 mg.

Pharmacokinetic Parameters for Women and Men After a Single Dose and After the Last Multiple Dose of Tapentadol (Study KF5503/08)

Parameter	Tapentadol IR 21.5 mg		Tapentadol IR 43 mg	
	women (n=14)	men (n=8)	women (n=14)	men (n=9)
Single Dose				
C _{max} , ng/mL	18.4 ± 7.7	14.6 ± 3.8	33.1 ± 11.2	25.6 ± 7.4
AUC _{0-6h} , ng·h/mL	63.5 ± 26.0	47.0 ± 13.3	117.5 ± 40.0	87.4 ± 25.3
AUC _{0-24h} , ng·h/mL	99.9 ± 39.4	73.9 ± 23.8	184 ± 61.8	145 ± 47.8
Multiple Dose				
C _{max,ss} , ng/mL	28.5 ± 14.4	23.0 ± 8.4	48.8 ± 14.7	43.1 ± 12.3
C _{min,ss} , ng/mL	11.6 ± 4.9	8.0 ± 2.7	21.1 ± 8.0	19.2 ± 6.0
C _{avg,ss} , ng/mL	18.1 ± 8.0	13.2 ± 5.1	32.5 ± 9.3	27.7 ± 8.4
AUC _{τ,ss} , ng·h/mL	108 ± 47.8	79.2 ± 30.8	195 ± 56.1	166 ± 50.5
Data expressed as mean ± SD.				

Pooled analysis of all available PK data in men and women showed that women in general had about 20% higher C_{max} and AUC values. After bodyweight correction in this pooled analysis (men had about 20% higher body weight), the mean oral clearance was very similar between men and women.

2.3.2.3 Race

No separate studies were conducted to evaluate the effects of race on the PK of tapentadol. However, comparison of PK data obtained in Japanese subjects in study R331333-PAI-1027 to historical data shows that PK is similar in Japanese subjects as compared to non-Japanese subjects.

Study R331333-PAI-1027 was a single-center, randomized, double-blind, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, PK and PD of tapentadol IR at doses of 10, 20 and 40 mg in 12 healthy Japanese men.

PK Parameters After Single-Dose Administration of Tapentadol IR 10, 20 or 40 mg in Japanese Healthy Men (Study R331333-PAI-1027)

Parameter	Tapentadol Dose		
	10 mg (n=7)	20 mg (n=8)	40 mg (n=8)
t_{max} , h	1.00 (1.00–2.03)	1.50 (0.50–2.00)	1.25 (1.00–3.00)
C_{max} , ng/mL	9.53 ± 3.82	20.5 ± 4.58	44.3 ± 18.0
$AUC_{0-\infty}$, ng·h/mL	43.2 ± 9.84	91.5 ± 17.4	184 ± 48.5
$t_{1/2}$, h	3.4 ± 0.6	3.9 ± 0.9	3.8 ± 0.6
<u>Dose-normalized to 10 mg</u>			
C_{max} , ng/mL	9.53 ± 3.82	10.3 ± 2.29	11.1 ± 4.49
$AUC_{0-\infty}$, ng·h/mL	43.2 ± 9.84	45.7 ± 8.69	45.9 ± 12.1

Data expressed as mean ± SD, except for t_{max} where median (range) is provided.

Maximum serum concentrations were obtained within 1 to 1.5 hours after dosing. The average half-life of tapentadol ranged from 3.4 to 3.9 hours across doses. The C_{max} and AUC values increased with an increase in tapentadol dose in this study. The observed apparent dose-proportionality of tapentadol is in-line with findings in non-Japanese subjects. Based on population PK analysis, compared to White subjects, sub groups of Black subjects, Hispanics, and other combined non-white racial groups had a lower clearance of approximately 17%, 11%, and 15%, respectively. Overall, these differences are not clinically significant and no dosage adjustment is needed based on race.

2.3.2.4 Elderly

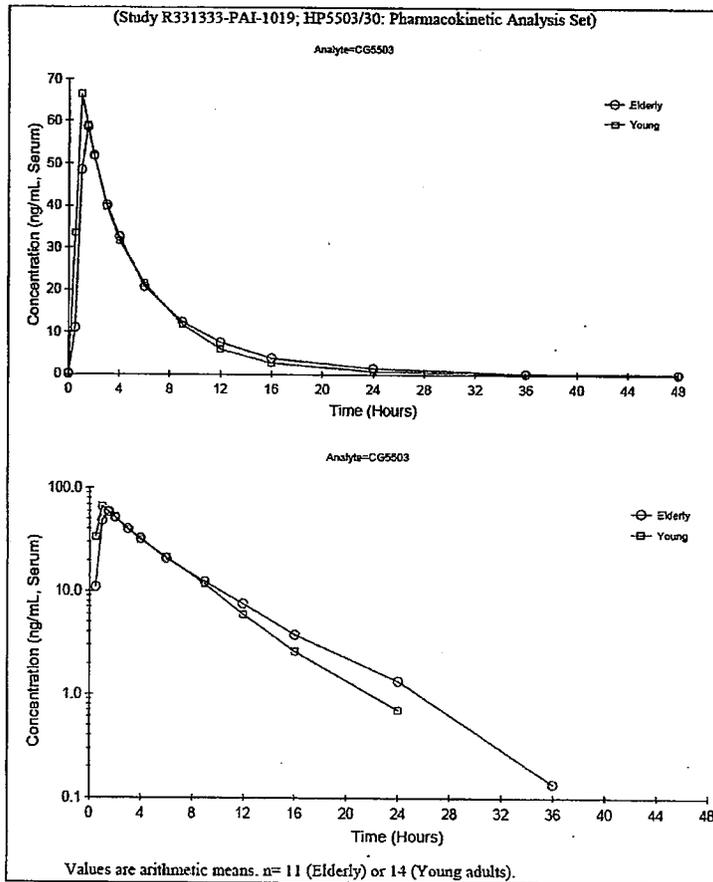
PK characteristics for tapentadol were similar in elderly and healthy subjects, suggesting that age has no impact on the PK of tapentadol. The Applicant proposes to there is no dose adjustment for elderly; however, due to the fact that elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended.

The PK of tapentadol in the elderly subjects was assessed in study HP5503/30. This was a parallel-group, single-center, open-label, single-dose study to compare the 80 mg single-dose PK of tapentadol and its metabolite tapentadol-O-glucuronide between healthy elderly (65 to 78

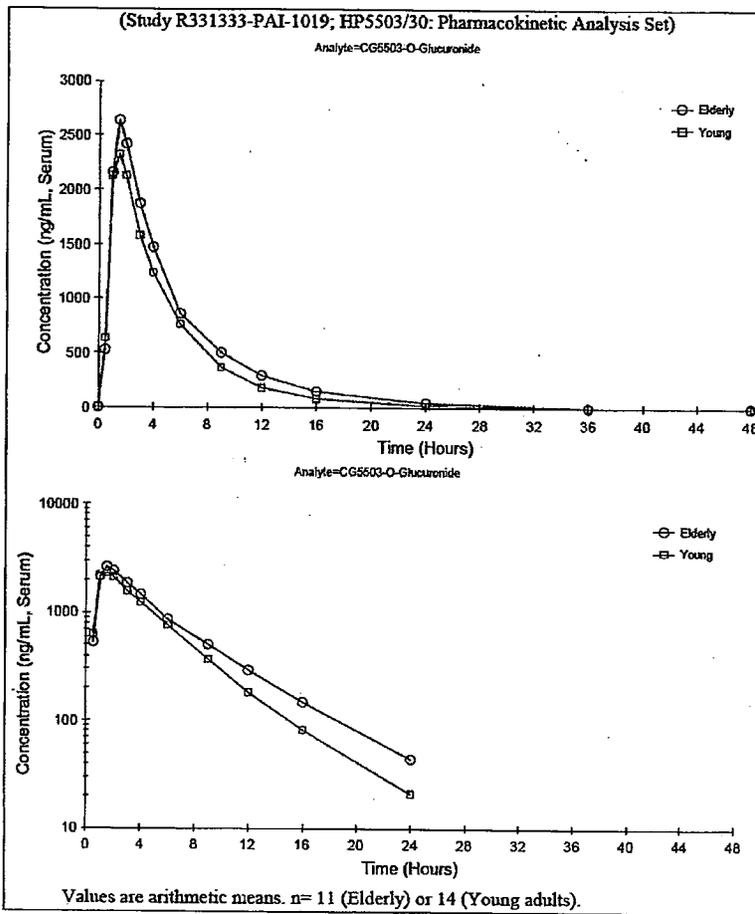
years of age) and young adult (19 and 43 years of age) men and women (16 subjects per age group, 8 men/8women). Thirty-two subjects received a single dose of 80 mg tapentadol.

The mean C_{max} for tapentadol in elderly subjects was 62.6 ng/mL compared to 78.3 ng/mL in young adults. The mean AUC values were 348 and 337 ng.h/mL, and mean AUClast values were 344 and 334 ng.h/mL for elderly and young adult subjects, respectively. Mean t_{1/2}, was 4.6 hours in elderly subjects and 3.6 hours in young adults. Renal clearance was lower in elderly subjects (75.5 mL/min) than in young adult subjects (99.4 mL/min).

PK parameters of the elderly group were compared to young age group using an ANOVA model. Overall, PK characteristics for tapentadol were similar in both age groups, suggesting that age has no impact on the PK of tapentadol.



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Summary of Statistical Comparison of PK Parameters of Tapentadol Between Healthy Elderly and Young Subjects (Study HP5503/30)

Parameter	Ratio, % (Elderly/Young)	Inter-Subject CV (%)	90% CI
AUC _∞ , ng·h/mL	103.29	30.4	(83.74–127.40)
AUC _{last} , ng·h/mL	103.02	30.7	(83.37–127.31)
C _{max} , ng/mL	83.54	35.5	(65.36–106.79)

Data analyzed on log scale, but statistics transformed back to original scale
 Due to vomiting within 2 times median t_{max} after tapentadol administration, only 11 elderly subjects and 14 young adult subjects were included in the analysis.

In the population PK analysis, age was not identified as a significant covariate. Overall, no dose adjustment is needed in the elderly based on the PK of tapentadol.

2.3.2.5 Renal impairment

Total exposure to tapentadol was not different between normal and subjects with renal impairment, indicating that a reduced renal functioning does not influence the single-dose PK of orally administered tapentadol.

Data for tapentadol-O-glucuronide demonstrate that Cmax increased 1.2-, 1.3-, and 1.4-fold for mild, moderate, and severe renal impairment subjects, respectively, compared with healthy subjects. The AUC data showed a 1.5-, 2.5-, and 5.5-fold increase for mild, moderate, and severe renal impairment subjects, respectively, compared with healthy subjects. The mean terminal half-life of tapentadol-O-glucuronide increased 3.3-fold in subjects with severe renal impairment compared to subjects with normal renal function.

Because of the significant accumulation potential of tapentadol-O-glucuronide in severe renal impairment group, the sponsor proposed that tapentadol use is not recommended in this group. However, this metabolite is inactive and not recommending the use of tapentadol based on accumulation potential of an inactive metabolite is not justified.

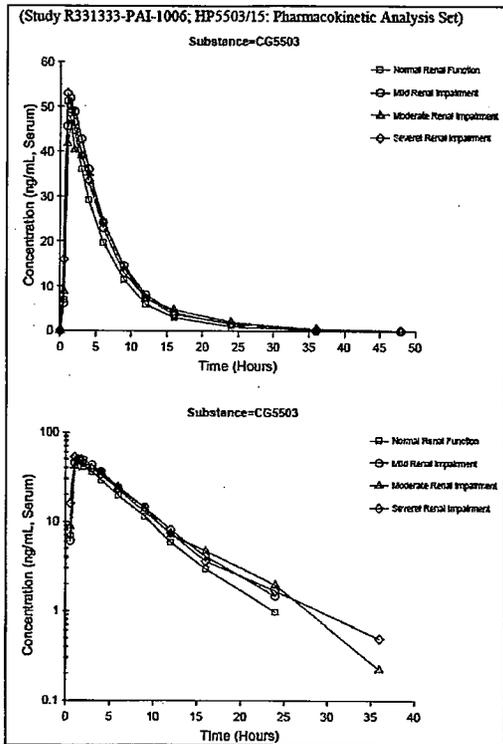
b(5)

Effect of mild, moderate, and severe renal impairment on the PK of tapentadol was assessed in study HP5503/15. This was a single-center, open-label, parallel-group study to evaluate the PK of a single 80 mg oral dose of tapentadol IR in subjects with varying degrees of renal impairment (mild (a creatinine clearance (CLCR)=50 to <80 mL/min), moderate (CLCR=30 to <50 mL/min) or severe (CLCR<30 mL/min) compared to subjects with normal renal function (CLCR≥80 mL/min). Forty subjects (28 men and 12 women, 7 men and 3 women per renal function group) were enrolled. The estimation of CLCR was performed according to the Cockcroft-Gault formula using serum creatinine measurements obtained during screening. Excretion of tapentadol and its main metabolite in urine were determined for up to 48 hours postdose.

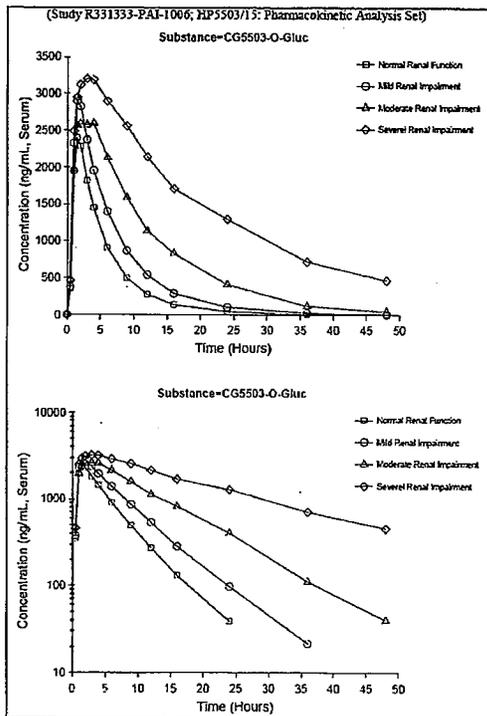
The mean PK parameters of tapentadol in serum after a single oral dose of 80 mg tapentadol IR were very similar in subjects with normal renal function or varying degrees of renal impairment.

Total exposure to tapentadol was not different between normal and subjects with renal impairment, indicating that a reduced renal functioning does not influence the single-dose PK of orally administered tapentadol.

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Pharmacokinetic Parameters of Tapentadol and Tapentadol-O-Glucuronide After Intake of 80 mg Tapentadol IR in Subjects With Varying Degrees of Renal Impairment (Study HP5503/15)

Parameter	Normal Renal Function (n = 9)	Mild Renal Impairment (n = 10)	Moderate Renal Impairment (n = 10)	Severe Renal Impairment (n = 10)
Tapentadol				
C _{max} , ng/mL	58.8 ± 20.4	65.0 ± 20.7	56.5 ± 14.1	59.2 ± 31.8
t _{max} , h	1.00 (1.00–1.50)	1.50 (1.00–4.00)	1.50 (1.00–4.02)	1.00 (1.00–4.00)
AUC _{0-∞} , ng·h/mL	301 ± 53.0	364 ± 120	353 ± 122	354 ± 189
t _{1/2} , h	4.7 ± 0.5	5.4 ± 2.0	5.1 ± 0.7	8.2 ± 2.9
CL/F, mL/min	4579 ± 919	4025 ± 1308	4432 ± 2243	4447 ± 1603
V _d /F, L	1874 ± 487	1819 ± 718	1944 ± 924	3000 ± 1319
CL _R , mL/min	105 ± 32.5	78.6 ± 57.0	60.7 ± 37.3	29.3 ± 21.2
CL/F _{NR} , mL/min	4473 ± 903	3946 ± 1308	4371 ± 2251	4418 ± 1591
A _e , %dose (0-48h)	2.33 ± 0.596	2.12 ± 1.80	1.71 ± 1.49	0.651 ± 0.381
Tapentadol-O-Glucuronide				
C _{max} , ng/mL	2428 ± 624	3134 ± 1094	3180 ± 875	3472 ± 734
t _{max} , h	1.50 (1.00–2.00)	1.50 (1.00–2.02)	1.51 (1.00–6.00)	3.50 (1.50–9.00)
AUC _{0-∞} , ng·h/mL	13916 ± 3123	21258 ± 6486	36191 ± 11874	84942 ± 52258
t _{1/2,z} , h	4.3 ± 0.2	5.1 ± 1.6	6.7 ± 2.0	14.2 ± 8.0
CL _R , mL/min	78.8 ± 32.0	50.0 ± 26.7	31.3 ± 14.2	12.6 ± 7.47
A _e , %dose (0-48h)	44.7 ± 17.2	39.2 ± 8.6	41.9 ± 7.47	33.3 ± 8.58
Data expressed as mean ± SD, except for t _{max} where median (range) is provided.				

Data for tapentadol-O-glucuronide demonstrate that C_{max} increased 1.2-, 1.3-, and 1.4-fold for mild, moderate, and severe renal impairment subjects, respectively, compared with healthy subjects. The AUC data showed a 1.5-, 2.5-, and 5.5-fold increase for mild, moderate, and severe renal impairment subjects, respectively, compared with healthy subjects. The mean terminal half-life of tapentadol-O-glucuronide increased 3.3-fold in subjects with severe renal impairment compared to subjects with normal renal function.

Because of the significant accumulation potential of tapentadol-O-glucuronide in severe renal impairment group, sponsor proposed that tapentadol use is not recommended in this group. However, this metabolite is inactive and not recommending the use of tapentadol based on accumulation potential of an inactive metabolite is not justified.

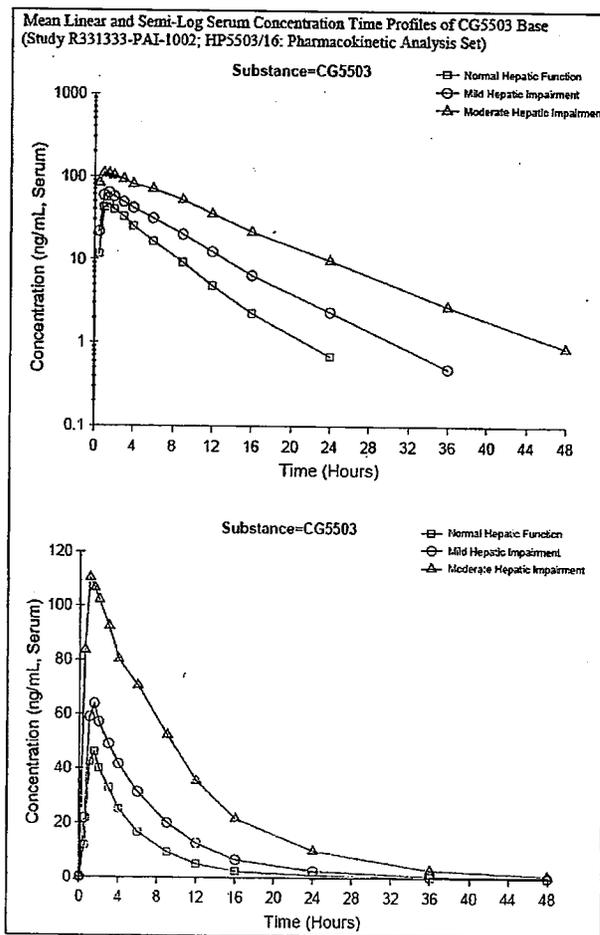
2.3.2.6 Hepatic impairment

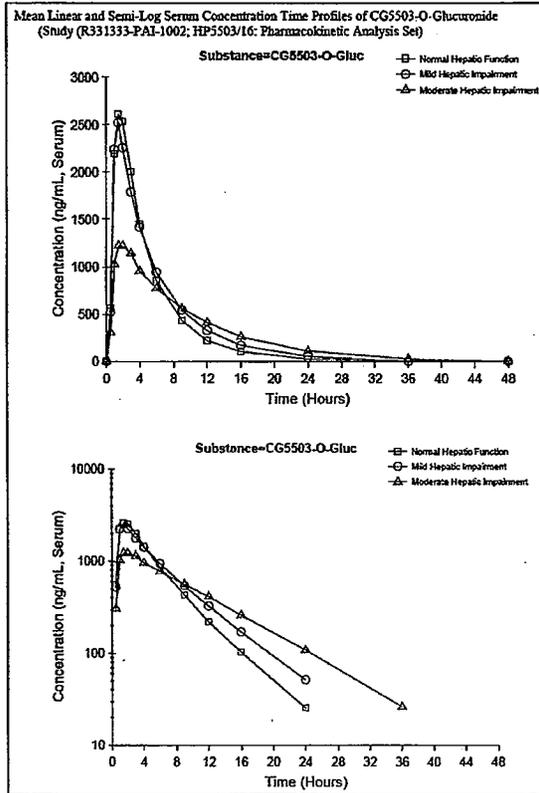
The tapentadol C_{max} values increased 1.4- and 2.54-fold in subjects with mild or moderate hepatic impairment, respectively, versus subjects with normal hepatic function. The AUC of tapentadol was increased 1.7- and 4.2-fold in subjects with mild and moderate hepatic impairment, respectively, versus subjects with normal hepatic function. Severe impairment subjects were not tested. The terminal elimination half-life of tapentadol was increased 1.4-fold in subjects with moderate hepatic impairment, compared to healthy subjects. The mean CL/F of tapentadol decreased 3.6-fold (ratio of arithmetic means) in subjects with moderate hepatic impairment, compared to healthy subjects, but the amount excreted over 48 hours remained below 5% of the total dose.

The serum tapentadol-O-glucuronide AUC values were comparable for all subjects.

The Applicant proposes no dose adjustment in mild impairment subjects. In moderate impairment, the Applicant proposes that tapentadol should be used with caution and should be initiated at 50 mg every 8 hours followed by either shortening or lengthening the dosing interval for further treatment. Tapentadol has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended.

Effect of mild and moderate hepatic impairment on the PK of tapentadol was assessed in study HP5503/16. This was a single-center, open-label, parallel-group study to evaluate the PK of a single 80 mg oral dose of tapentadol IR in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. Subjects were classified into 1 of 3 hepatic-function groups based on the degree of individual hepatic function using the Child-Pugh classification. Subjects with normal hepatic function were matched for body weight, age range, sex and ethnicity. Thirty subjects (15 men and 15 women) were enrolled.





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Pharmacokinetic Parameters of Tapentadol and Tapentadol-O-Glucuronide After Intake of 80 mg Tapentadol IR in Subjects With Varying Degrees of Hepatic Function (Study HP5503/16)

Parameter	Normal Hepatic Function (n=10)	Mild Hepatic Impairment (n=10)	Moderate Hepatic Impairment (n=10)
<u>Tapentadol</u>			
C _{max} , ng/mL	50.9 ± 23.3	66.9 ± 22.4	132 ± 58.6
t _{max} , h	1.50 (1.00-3.00)	1.50 (0.50-2.00)	1.28 (0.50-6.00)
AUC _{last} , ng·h/mL	253 ± 75.8	472 ± 265	1160 ± 509
AUC _∞ , ng·h/mL	257 ± 77.3	477 ± 266	1171 ± 516
t _{1/2} , h	4.3 ± 0.6	5.1 ± 0.9	6.2 ± 1.5
CL/F, mL/min	5602 ± 1521	3539 ± 1641	1536 ± 1154
CL _R , mL/min	97.0 ± 39.8	95.3 ± 30.5	65.5 ± 40.5
CL/F _{NR} , mL/min	5505 ± 1518	3444 ± 1642	1470 ± 1116
Ae, %dose (0-48h)	1.84 ± 0.768	3.36 ± 2.10	4.47 ± 1.52
<u>Tapentadol -O-Glucuronide</u>			
C _{max} , ng/mL	2856 ± 570	2561 ± 755	1424 ± 765
t _{max} , h	1.50 (1.00-3.00)	1.50 (1.00-4.00)	2.50 (1.00-12.00)
AUC _{last} , ng·h/mL	13684 ± 2494	14858 ± 1777	12732 ± 2502
AUC _∞ , ng·h/mL	13828 ± 2546	15020 ± 1752	12888 ± 2498
t _{1/2} , h	3.8 ± 0.3	4.7 ± 0.9	5.9 ± 1.4
CL _R , mL/min	77.8 ± 9.67	70.8 ± 19.1	75.6 ± 19.3
Ae, %dose (0-48h)	44.4 ± 7.95	43.8 ± 10.3	39.3 ± 7.57

Data expressed as mean ± SD, except for t_{max} where median (range) is provided.

Tapentadol serum concentrations increased in subjects with impaired hepatic function, and were highest in subjects with moderate hepatic impairment. The C_{max} values of tapentadol increased 1.4- and 2.54-fold in subjects with mild or moderate hepatic impairment, respectively, versus subjects with normal hepatic function. The AUC of tapentadol was increased 1.7- and 4.2-fold in subjects with mild and moderate hepatic impairment, respectively versus subjects with normal hepatic function. The terminal elimination half-life of tapentadol was increased 1.4-fold in subjects with moderate hepatic impairment, compared to healthy subjects. The mean CL/F of tapentadol decreased 3.6-fold (ratio of arithmetic means) in subjects with moderate hepatic impairment, compared to healthy subjects, but the amount excreted over 48 hours remained below 5% of the total dose.

The serum tapentadol-O-glucuronide AUC values were comparable for subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment. The percentage of the dose excreted into the urine as tapentadol-O-glucuronide and renal clearance were comparable in all subjects.

The Applicant proposes no dose adjustment in mild impairment subjects. In moderate impairment, the Applicant proposes that tapentadol should be used with caution. Furthermore, moderate subjects should be initiated at 50 mg every 8 hours (maximum of three doses in 24 hours). Additional treatment should be achieved by either shortening or lengthening the dosing interval. Tapentadol has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

2.4.1.1 Effects of Other Drugs on Tapentadol

Metoclopramide, omeprazole, naproxen, acetylsalicylic acid and acetaminophen did not affect tapentadol pharmacokinetics. However, the serum C_{max} and AUC levels of tapentadol were elevated in the presence of probenecid, approximately 30% and 57%, respectively, as compared with the control. The elimination half-life of tapentadol in the control was 4.1 hours and was 4.4 hours when tapentadol IR was co-administered with probenecid. The tapentadol-O-glucuronide C_{max} and AUC values were reduced in the presence of probenecid.

Metoclopramide - Metoclopramide affects the GI transit time and this pharmacological effect may have an impact on the PK of tapentadol. Study HP5503/19 was a randomized, open-label, 2-way-crossover, drug-drug-interaction study in healthy men and women to determine the effect of multiple doses (Q6h) of 20 mg metoclopramide on the PK of tapentadol and tapentadol-O-glucuronide. Tapentadol 80 mg was either administered alone or one hour after the 5th dose of metoclopramide (6 doses of 20 mg, Q6h).

PK Parameters of Tapentadol and Tapentadol-O-Glucuronide With and Without Co-Administration of Metoclopramide (Study HP5503/19)

Parameter	Tapentadol IR alone (n=22)	Tapentadol IR + metoclopramide (n=23)
Tapentadol		
t _{max} , h	1.00 (0.75–1.50)	1.00 (0.50–3.00)
C _{max} , ng/mL	87.4 ± 25.6	88.3 ± 34.7
AUC _{last} , ng·h/mL	315 ± 94.7	311 ± 107
AUC _∞ , ng·h/mL	319 ± 95.6	314 ± 107
t _{1/2} , h	4.3 ± 0.7	4.2 ± 0.6
Tapentadol -O-Glucuronide		
t _{max} , h	1.50 (1.00–2.03)	1.50 (1.00–3.00)
C _{max} , µg/mL	2.88 ± 0.59	2.87 ± 0.65
AUC _{last} , µg·h/mL	13.0 ± 2.23	12.5 ± 2.26
AUC _∞ , µg·h/mL	13.1 ± 2.26	12.7 ± 2.28
t _{1/2} , h	3.9 ± 0.4	4.0 ± 0.5

Data expressed as mean ± SD, except for t_{max} where median (range) is provided.

Summary of Statistical Analysis for PK Parameters of Tapentadol in Presence or Absence of Metoclopramide (Study HP5503/19)

(Tapentadol IR + metoclopramide / Tapentadol IR alone)		
Parameter	Ratio, %	90% CI
C _{max} , ng/mL	95.83	80.16–114.55
AUC _{last} , ng·h/mL	95.40	86.74–104.92
AUC _∞ , ng·h/mL	95.25	86.58–104.78

The C_{max} and AUCs were comparable between the two treatments for both tapentadol and tapentadol-O-glucuronide.

Difference in exposure to tapentadol between the treatments was evaluated using an ANOVA model on the 22 subjects who completed both treatment periods and did not vomit within 2 hours (2 times median t_{max}) after tapentadol administration. The 90% CI for the ratio of geometric means were contained within the commonly used range of 80 to 125% for C_{max} and AUCs.

Omeprazole - Omeprazole may increase the pH in the stomach, which may affect the permeability of the tertiary amine tapentadol, due to the fact that such pH change may alter the charge on the molecule. Study HP5503/20 was a single-center, randomized, open-label, 2-way crossover, drug-drug interaction study to determine the effect of omeprazole on the PK of tapentadol and tapentadol-O-glucuronide. Tapentadol IR (80 mg) was administered either alone or 2 hours after the last administration of omeprazole once daily for 4 days.

PK Parameters of Tapentadol and Tapentadol-O-Glucuronide in Presence or Absence of Omeprazole (Study HP5503/20)

Parameter	Tapentadol alone (n=30)	Tapentadol + omeprazole (n=26)
Tapentadol		
t_{max} , h	1.00 (1.00–4.00)	1.50 (1.00–4.00)
C_{max} , ng/mL	79.8 ± 31.3	72.4 ± 27.8
AUC _{last} , ng·h/mL	332 ± 122	336 ± 114
AUC _∞ , ng·h/mL	336 ± 122	340 ± 115
$t_{1/2}$, h	4.5 ± 0.9	4.0 ± 0.5
Tapentadol-O-glucuronide		
t_{max} , h	1.50 (1.00–4.00)	1.50 (1.00–4.00)
C_{max} , ng/mL	3097 ± 772	3102 ± 967
AUC _{last} , ng·h/mL	14374 ± 2946	14883 ± 3476
AUC _∞ , ng·h/mL	14521 ± 2950	15035 ± 3506
$t_{1/2}$, h	4.2 ± 0.7	3.8 ± 0.4
Data expressed as mean ± SD, except for t_{max} where median (range) is provided.		

The mean serum drug concentration time profiles were very similar following a single dose of 80 mg tapentadol administered alone or with 40 mg omeprazole. Overall, serum PK parameters of tapentadol and tapentadol-O-glucuronide were similar when tapentadol IR was administered either alone or with omeprazole.

Summary of Statistical Analysis on the PK Parameters of Tapentadol in Presence or Absence of Omeprazole (Study HP5503/20)

Parameter	Tapentadol IR + omeprazole / Tapentadol IR alone	
	Ratio, %	90% CI
C_{max} , ng/mL	88.51	78.30–100.04
AUC _{last} , ng·h/mL	98.54	91.67–105.92
AUC _∞ , ng·h/mL	98.64	91.75–106.06

After statistical evaluation utilizing a mixed-effect model, no clinically relevant effect of omeprazole was observed on the C_{max} and AUCs of tapentadol. All 90% CIs of PK parameters for the treatment ratios of tapentadol IR with omeprazole versus tapentadol IR were contained within the 80% to 125% confidence intervals, except for the lower limit of C_{max} , which was 78.30%. These results indicate that there is good similarity for the tapentadol PK after both treatment regimens.

Probenecid - Study HP5503/21 was a single-site, randomized, open-label, 2-way crossover, drug-drug interaction study that evaluated the effect of probenecid on the PK of tapentadol and tapentadol-O-glucuronide when administered to 28 healthy men and women. Tapentadol IR (80 mg) was administered either alone or together with the third administration of probenecid 500 mg b.i.d. for 2 days.

PK Parameters of Tapentadol in Presence or Absence of Probenecid (Study HP5503/21)

Parameter	Tapentadol + probenecid (n=24)		Tapentadol alone (n=27)	
	Mean ± SD	%CV	Mean ± SD	%CV
t _{max} , h	1.50 (1.00–2.00)		1.50 (1.00–2.00)	
C _{max} , ng/mL	90.9 ± 33.5	36.9	73.3 ± 28.7	39.1
AUC _{last} , ng·h/mL	550 ± 179	32.6	367 ± 126	34.5
AUC _∞ , ng·h/mL	553 ± 180	32.5	370 ± 126	34.2
t _{1/2} , h	4.4 ± 0.5	10.7	4.1 ± 0.5	11.0

Data expressed as mean ± SD, except for t_{max} where median (range) is provided.

The serum C_{max} and AUC levels of tapentadol were elevated in the presence of probenecid, approximately 30% and 57%, respectively, as compared with the control. The elimination half-life of tapentadol in the control was 4.1 hours and was 4.4 hours when tapentadol IR was co-administered with probenecid.

Summary of Statistical Analysis Results of the PK Parameters of Tapentadol in Presence or Absence of Probenecid (Study HP5503/21)

Tapentadol IR + probenecid / Tapentadol IR alone		
Parameter	Ratio, %	90%CI
C _{max} , ng/mL	130.41	114.64–148.35
AUC _{last} , ng·h/mL	157.29	145.47–170.06
AUC _∞ , ng·h/mL	156.86	145.13–169.53

Comparison of the 90% confidence intervals with the 80% to 125% range commonly accepted for bioequivalence testing showed that C_{max} and all AUC parameters were outside this range.

The tapentadol-O-glucuronide C_{max} and AUC values were reduced in the presence of probenecid, most likely due to the interference of probenecid with the glucuronide conjugation of tapentadol. The average terminal half-life of tapentadol-O-glucuronide was comparable in both treatment periods with 3.9 hours after tapentadol IR alone and 4.5 hours after tapentadol co-administered with probenecid. In both treatments, renal clearance of both the parent compound and the O-glucuronide metabolite were within a similar range.

Urinary Excretion of Tapentadol and its Metabolite Tapentadol-O-Glucuronide in Presence or Absence of Probenecid (Study HP5503/21)

Parameter	Tapentadol IR +probenecid (n=24)	Tapentadol IR alone (n=27)
<u>Tapentadol</u>		
CL _R , mL/min	119 ± 39.7	110 ± 35.3
<u>Tapentadol -O-glucuronide</u>		
CL _R , mL/min	92.6 ± 17.0	88.8 ± 18.6

Naproxen and acetylsalicylic acid (ASA) - Study HP5503/22 was a Phase-1, open-label, 3-way-crossover, drug-interaction study to evaluate the effect of naproxen and acetylsalicylic acid (ASA) on the PK of tapentadol and tapentadol-O-glucuronide following a tapentadol IR administration, in 36 healthy men and women. Subjects received a single oral dose of tapentadol 80 mg alone or in combination with naproxen (together with the third dose of 500 mg b.i.d. for 2

days) and in combination with ASA (together with the second dose of 325 mg ASA once daily for 2 days).

C_{max} and exposure of tapentadol was similar in all treatment groups, indicating that co-administration of either naproxen or ASA has no influence on the oral PK of tapentadol.

PK Parameters of Tapentadol and Tapentadol-O-Glucuronide in the Presence or Absence of ASA or Naproxen (Study HP5503/22)

Parameter	Tapentadol IR alone (n=34)	Tapentadol IR + Naproxen (n=34)	Tapentadol IR + ASA (n=36)
Tapentadol			
t _{max} , h	1.50 (1.00–4.00)	1.50 (1.00–4.00)	1.50 (1.00–3.00)
C _{max} , ng/mL	71.9 ± 22.4	78.7 ± 25.2	76.0 ± 24.3
AUC _{last} , ng·h/mL	410 ± 135	465 ± 150	410 ± 138
AUC _∞ , ng·h/mL	414 ± 135	469 ± 150	415 ± 138
t _{1/2} , h	4.2 ± 0.7	4.2 ± 0.6	4.1 ± 0.7
CL _R , mL/min	105 ± 43.0	106 ± 39.5	114 ± 81.9
Tapentadol-O-glucuronide			
t _{max} , h	1.50 (1.00–4.00)	1.50 (1.00–4.00)	1.50 (1.00–2.00)
C _{max} , ng/mL	2844 ± 583	2601 ± 573	2909 ± 560
AUC _{last} , ng·h/mL	13100 ± 2460	12100 ± 2250	13100 ± 2570
AUC _∞ , ng·h/mL	13300 ± 2530	12300 ± 2270	13200 ± 2580
t _{1/2} , h	3.9 ± 0.7	4.0 ± 0.6	3.8 ± 0.5
CL _R , mL/min	79.6 ± 29.9	82.6 ± 25.0	82.1 ± 42.1
Data expressed as mean ± SD, except for t _{max} where median (range) is provided.			

The 90% CI for the ratio of geometric means of the tapentadol IR with and without concomitant administration of naproxen was contained within the range of 80% to 125% for C_{max}. The upper limits of the 90% CIs for the ratios of geometric means of AUCs were slightly above the 80% to 125% range: i.e. [108.58-126.47] for AUC_{last} and [108.45-126.14] for AUC_∞ with naproxen leading to a mean increase in AUCs of 17%.

All 90% CIs for the ratios of geometric means for the tapentadol IR with ASA versus tapentadol IR alone treatment were included within 80% to 125%, the commonly accepted bioequivalence criteria.

Summary of the Statistical Analysis of Variance by Treatment for Pharmacokinetic Parameters of Tapentadol in the Presence or Absence of Naproxen or Acetyl-Salicylic Acid (n=32) (Study HP5503/22)
Note: Treatment A: tapentadol IR alone. Treatment B: tapentadol IR + naproxen. Treatment C: tapentadol IR + ASA

Parameter	Treatment			Treatment Ratio (%)		90% CI (%)	
	A	B	C	B/A	C/A	B/A	C/A
C_{max} , ng/mL	68.09	76.37	71.08	112.15	104.39	(102.04-123.27)	(94.96-114.75)
AUC_{last} , ng·h/mL	388.85	455.68	384.36	117.19	98.84	(108.58-126.47)	(91.58-106.69)
AUC_{∞} , ng·h/mL	393.45	460.18	388.23	116.96	98.67	(108.45-126.14)	(91.49-106.43)

Results are least-square geometric means.

Log-transformed parameters; ratio: ratio of least-squares geometric means; MSE: mean square error.

Treatment A: tapentadol IR alone. Treatment B: tapentadol IR + naproxen. Treatment C: tapentadol IR + ASA.

Acetaminophen - Study HP5503/23 was a Phase-1, randomized, open-label, 2-way-crossover, drug-drug interaction study that evaluated the effect of acetaminophen (paracetamol) on the PK of tapentadol and tapentadol-O-glucuronide following a single dose of tapentadol IR in 24 healthy men and women. Acetaminophen may be used in subjects in combination with tapentadol. Because interaction between tapentadol and acetaminophen for relevant UGT isoforms may occur, a drug interaction study between acetaminophen and tapentadol was warranted. Subjects received a single oral dose of tapentadol IR 80 mg alone or in combination with acetaminophen (together with the fifth dose of 1000 mg acetaminophen Q6h for 2 days).

Concentrations of tapentadol were similar after administration of tapentadol IR alone and after co-administration with acetaminophen. The terminal half-life was similar for both treatments.

PK Parameters of Tapentadol and Tapentadol-O-Glucuronide in the Presence or Absence of Acetaminophen (Study HP5503/23)

Parameter	Tapentadol IR alone (n=21)	Tapentadol IR + Acetaminophen (N=20)
Tapentadol		
t_{max} , h	1.00 (1.00-4.00)	1.00 (1.00-6.00)
C_{max} , ng/mL	71.4 ± 28.0	67.3 ± 26.9
AUC_{last} , ng·h/mL	313 ± 152	313 ± 138
AUC_{∞} , ng·h/mL	316 ± 152	316 ± 138
$t_{1/2}$, h	4.1 ± 0.6	3.7 ± 0.4
Tapentadol-O-glucuronide		
t_{max} , h	1.50 (1.00-4.00)	1.50 (1.00-6.00)
C_{max} , ng/mL	2619 ± 631	2799 ± 611
AUC_{last} , ng·h/mL	13500 ± 3110	14900 ± 3210
AUC_{∞} , ng·h/mL	13600 ± 3160	15100 ± 3250
$t_{1/2}$, h	3.9 ± 0.4	3.7 ± 0.3

Data expressed as mean ± SD, except for t_{max} where median (range) is provided.

Difference in exposure to tapentadol between the treatments was evaluated using analysis of variance (ANOVA). All 90% confidence intervals for tapentadol IR with acetaminophen treatment versus tapentadol IR alone treatment ratios were included within 80% to 125%, the commonly accepted bioequivalence criteria

Summary of Statistical Analysis of Variance by Treatment for PK Parameters of Tapentadol in Presence or Absence of Acetaminophen (Study HP5503/23)

Parameter	Ratio, % (Tapentadol IR + Acetaminophen / Tapentadol IR alone)	
		90% CI
C _{max} , ng/mL	96.17	84.67–109.24
AUC _{last} , ng·h/mL	100.19	94.39–106.35
AUC _∞ , ng·h/mL	99.92	94.22–105.97

2.5 General Biopharmaceutics

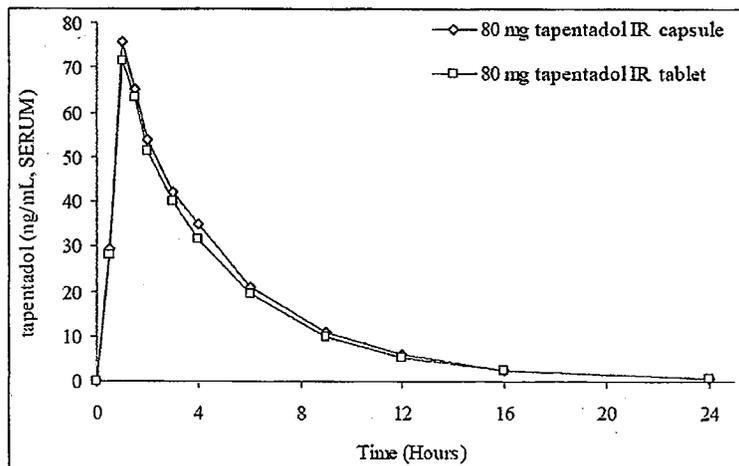
2.5.1 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The Phase 1 and 2 clinical 80 mg and to-be-marketed 80 mg formulations were bioequivalent.

Study HP5503/24 (R331333-PAI-1016) was a single-center, single-dose, open-label, randomized, 2-period, 2-way crossover study in 32 healthy subjects (16 men and 16 women) to assess bioequivalence between the tapentadol IR tablets (80 mg, batch PD1707) and tapentadol IR capsules (80 mg, batch PD1549).

The 90% CIs for these ratios were entirely contained within the bioequivalence range of 80% to 125%. The %CV for C_{max} and AUC were 31% for the IR capsule, compared with 29% and 26% for the IR tablet, respectively.

Mean Tapentadol Serum Concentration-Time Profiles After Single-Dose Administration of Tapentadol IR Tablet and IR Capsule (Study HP5503/24)



Tapentadol Pharmacokinetic Parameters After Single-Dose Administration of Tapentadol IR Tablet and IR Capsule (Study HP5503/24)

	80 mg IR Tablet (PD1707) (n=30)	80 mg IR Capsule (PD1549) (n=30)	Tablet/Capsule Ratio, % (90% CI) (n=30)
C _{max} , ng/mL	76.6 ± 22.5	82.4 ± 25.6	93.77 (85.58 – 102.73)
AUC _{last} , ng.h/mL	322 ± 84.1	345 ± 107	94.48 (89.78 – 99.43)
AUC _∞ , ng.h/mL	326 ± 85.0	349 ± 108	94.41 (89.73 – 99.34)
t _{max} , h	1.00 (0.50 – 4.00)	1.00 (0.50 – 2.02)	
t _{1/2} , h	4.0 ± 0.5	4.0 ± 0.5	

Data expressed as mean ± SD, except t_{max}: median (range).

2.5.2 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification? What data support a waiver of in vivo BE data?

The Applicant wishes to request a waiver to conduct an in vivo bioequivalence study comparing the TBM 100 mg IR tapentadol tablet and the 100 mg IR capsule formulation; the bioequivalence study between IR capsules and tablets was performed at the 80-mg dose strength. In support of the request, the Applicant presented the information regarding the physicochemical properties, the composition, formulation, and pharmacokinetic characteristics of the drug product, the dissolution test results, and the manufacturing method and scale. During the review, additional information regarding the stability of tapentadol in simulated gastric fluid (SGF), USP, and simulated intestinal fluid (SIF) was requested. Overall, adequate information was provided to show that tapentadol is BCS Class I drug and the BCS Committee concurred on the Class I designation.

Background:

A capsule formulation of immediate release (IR) tapentadol was used in Phase-1 and -2 studies, whereas an IR tablet formulation, 50-, 75-, and 100-mg dose strengths, was used in Phase-3 studies and is proposed for marketing. It is noted that 80-mg capsule formulation has been used in several drug-drug interaction and special population studies.

A bioequivalence study was performed in order to bridge the IR capsule to the IR tablet formulation. The results indicated that IR tapentadol 80-mg tablet and the IR 80-mg capsule formulations were bioequivalent (Study HP5503/24).

Discussion:

The Applicant stated that the bioequivalence data obtained for the 80-mg tablet strength can be extrapolated to the 50-, 75- and 100-mg tablets based on the following information:

1. Tapentadol HCl is classified as a BCS class 1 compound. It is highly soluble and highly permeable. The dosage form is an IR formulation.
2. The qualitative composition of the different strengths of IR tablets is identical.

3. ✓

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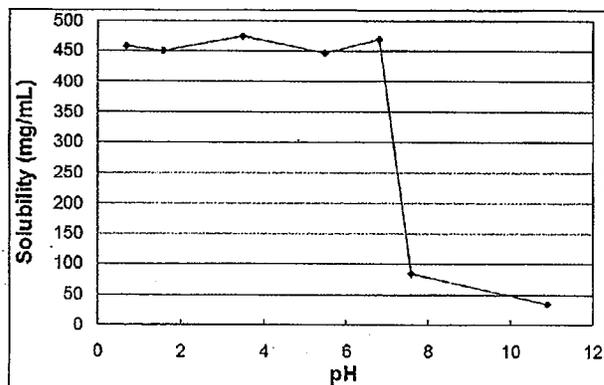
4. The IR tablets for all dose strengths are manufactured by the same manufacturer and process, on the same manufacturing site. The IR tablet formulations used in Phase-3 and proposed for marketing are manufactured using []
5. Based on the same dissolution method, 50-, 80- and 100-mg IR tablet strengths showed similar dissolution results. The dosage form shows rapid dissolution, i.e. more than 85% of the active substance is dissolved within 30 minutes.
6. The pharmacokinetics of IR tapentadol are dose-proportional over the clinical dose range of 50 to 100 mg.
7. Clinical efficacy and safety studies included the 50-, 75- and 100-mg tablet formulation, and these dose strengths were found to be safe and efficacious.

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Solubility

The definition of “highly soluble” is when the highest dose strength dissolves in 250 mL or less of aqueous media over a pH range of 1-7.5 at 37 °C. The highest dose strength of tapentadol tablets (100-mg) met this definition. Solubility data across the pH range from 0.5 to 10.9 in aqueous buffers at 37 °C using the shake-flask method are summarized in the following figure:

Solubility of Tapentadol Hydrochloride at 37°C:



Permeability

Absolute BA study: Study HP5503/04 was a single-center, single-dose, open-label, randomized, 6-sequence, 3-way crossover study in 24 healthy male subjects. Subjects received tapentadol as a 34-mg 15-min i.v. infusion (69 mg/50 mL) and as a 86 mg IR dose composed of 4 oral IR capsules of 21.5 mg after an overnight fast (p.o. fasted) and after a standardized continental breakfast.

Tapentadol Pharmacokinetic Parameters After Single-Dose Administration of i.v. Infusion, and Oral Capsule With or Without Food (Study HP5503/04)

	34 mg i.v. (batch WMAK01)	4*21.5 mg p.o. Fed (batch XDAM04)	4*21.5 mg p.o. Fasted (batch XDAM04)	Oral Fed/Fasted Ratio, % (90% CI) ^a
C _{max} , ng/mL	243 ± 93.4 [38.4]	101 ± 43.2 [42.8]	78.0 ± 26.9 [34.4]	125.3% (106.9-146.9)
AUC _{last} , ng.h/mL	374 ± 41.0 [11.0]	406 ± 105 [25.8]	310 ± 91.5 [29.5]	132.4% (123.3-142.2)
AUC _∞ , ng.h/mL	379 ± 42.2 [11.2]	411 ± 105 [25.7]	314 ± 91.6 [29.1]	131.9% (123.0-141.4)
t _{max} , h	0.23 (0.17-0.58)	1.25 (0.50-3.00)	1.00 (0.75-3.00)	
t _{1/2} , h	4.09 ± 0.70 [17.0]	4.57 ± 0.68 [14.9]	4.86 ± 0.72 [14.8]	
CL (CL/F), mL/min	1531 ± 177 [11.6]	3763 ± 1233 [32.8]	5007 ± 1820 [36.3]	
V _d (V _d /F), L	540 ± 98 [18.2]	1489 ± 564 [37.9]	2127 ± 970 [45.6]	
F, % (95% CI) ^a	-	42.2 (38.8-45.8)	32.0 (29.4-34.8)	

Data expressed as mean ± SD [% CV], except for t_{max} where median (range) is provided.

^a after dose-normalization, based on log-transformed data.

The absolute oral bioavailability of tapentadol capsules was 32.0% in the fasted state.

Mass balance study:

The mass balance study was conducted in healthy adult male subjects with ¹⁴C-labeled tapentadol HCl capsules after a single oral dose (100 mg) (Study HP5503/05). The T_{max} for labeled dose was 1.25 – 1.5 h post dosing. An average of 99.9% of the radioactive dose was recovered after approximately 5 days. More than 95% of the dose was excreted within 24 hours post dosing. Total urinary excretion amounted to 99% of the dose. Fecal excretion amounted to approximately 1% and excretion in CO₂ (as ¹⁴CO₂) was negligible.

Stability of tapentadol in SIG and SIF:

The stability of tapentadol HCl (R331333) in simulated gastric fluid (SGF), USP, and simulated intestinal fluid (SIF), USP, was investigated. Solutions of tapentadol HCl (R331333) at ~ 0.58 mg/ml were incubated at 37 °C. Samples were taken at 0, 1, 3, and 6 hours and analyzed using an HPLC method. The results presented in table below:

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Stability of Tapentadol HCl (R331333) in Simulated Gastric Fluid, USP and Simulated Intestinal Fluid, USP

Time Point	% Recovery of Tapentadol HCl (R331333)	
	Simulated Gastric Fluid (SGF)	Simulated Intestinal Fluid (SIF)
0-hour	100.0	100.0
1-hour	100.0	99.8
3-hour	100.1	100.8
6-hour	100.1	99.4

CACO-2 Cell study:

The transport rate of tapentadol (10 µg/mL) in apical to basolateral direction was $7.4 \cdot 10^{-6} \pm 0.94 \cdot 10^{-6}$ cm/s. As a control, the transport rate of tramadol was tested. A transport rate of $7.74 \cdot 10^{-6}$ cm/s was found. The recovery of tapentadol after passive transport determination on CACO-2 cells was 100 ± 2 %, indicating there was no loss of CG5503 due to unspecific binding at the device or uptake in the cells. The transepithelial electrical resistance (TEER) before and after the test period was 130 and 215 Ohms indicating unchanged integrity of the cell monolayer over the entire test period. The accumulation of the concentration over time was linear with the coefficient of determination (R²) being > 0.99.

The CACO-2 cell study data are inadequate to conclude that tapentadol is a highly permeable drug. — was used as an internal standard and not low and high permeability model drugs.

Dissolution profiles

An IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using USP Apparatus 1 (baskets) at 100 rpm or Apparatus 2 (paddles) at 50 rpm in a volume of 900 mL or less in each of the following media: (1) 0.1 N HCl or Simulated Gastric Fluid USP without enzymes; (2) a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes.

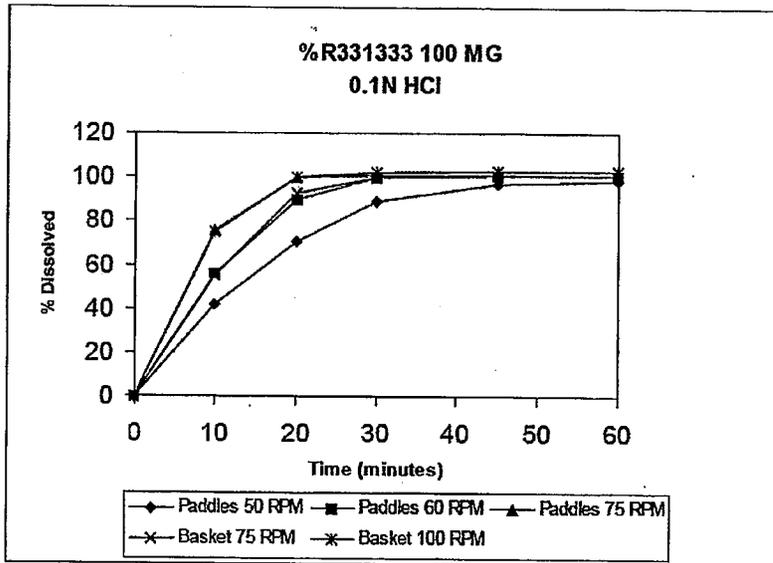
For the 100-mg proposed commercial film-coated tablet, $\geq 85\%$ dissolution was achieved at 30 minutes using USP Apparatus 1 at 100 rpm in at 37 °C in 900 mL of 0.1N HCl, pH 4.5 buffer and pH 6.8 buffer. Dissolution profiles for the 3 pH values are provided in the next figure.

The proposed commercial dissolution method uses USP Apparatus 1 (baskets) at 75 rpm, 900 mL of 0.1N HCl at 37°C, with detection at —

Dissolution profiles were generated for 100- and 50-mg film-coated tapentadol tablets using baskets (USP Apparatus 1) at 75 and 100 rpm and paddles (USP Apparatus 2) at 50, 60 and 75 rpm.

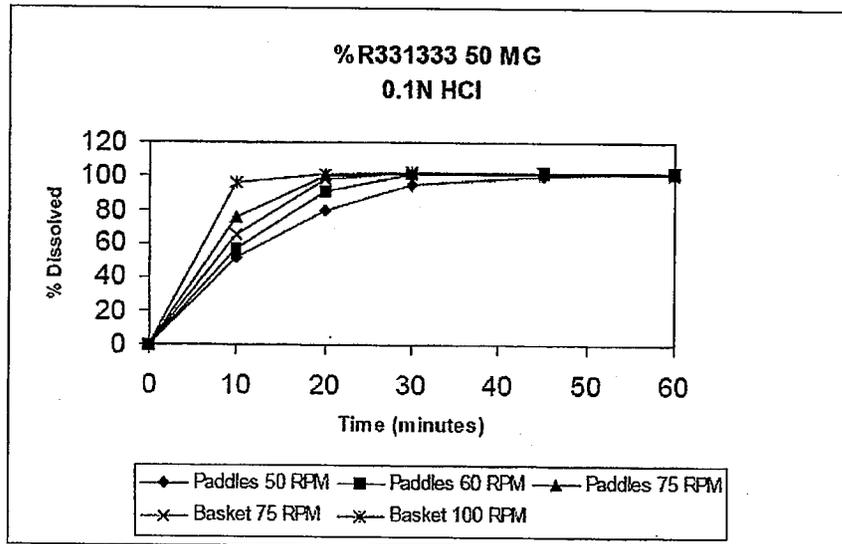
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The Effect of USP Apparatus Type and Rotor Speed on Dissolution Profile of Tapentadol 100-mg Film-Coated Tablets



Note: R331333 is tapentadol

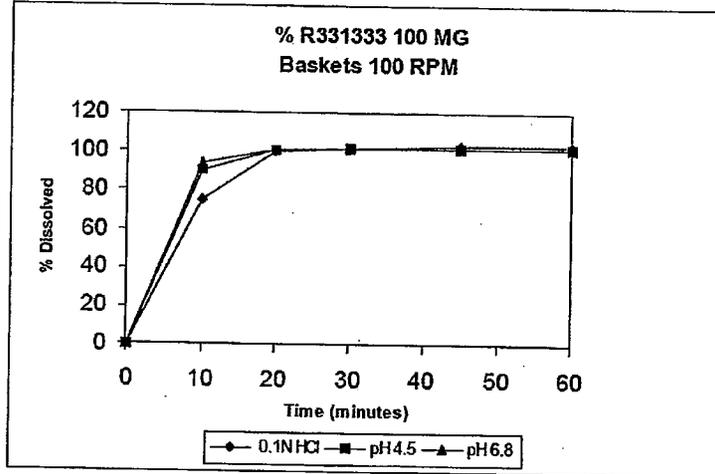
The Effect of USP Apparatus Type and Rotor Speed on Dissolution Profile of Tapentadol 50-mg Film-Coated Tablets



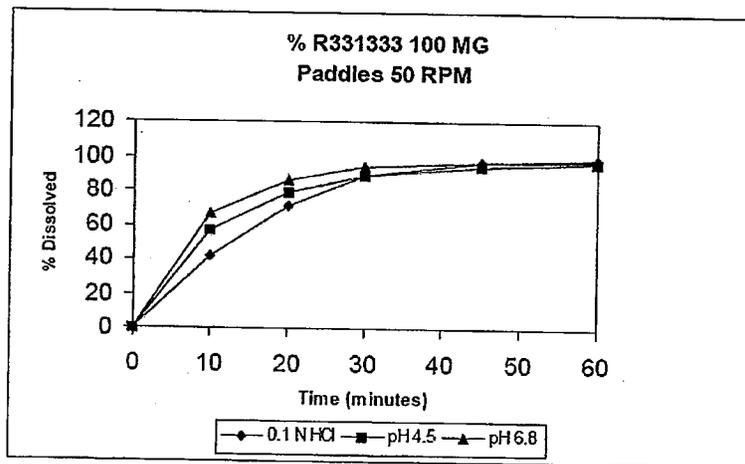
Note: R331333 is tapentadol

The effect of medium pH on drug release was tested at pH 1.2 (0.1N HCl), 4.5 and 6.8. Baskets at 100 rpm and paddles at 50 rpm were used.

The Effect of pH on Dissolution Profiles for Tapentadol 100-mg Film-Coated Tablets using Baskets (USP Apparatus 1)

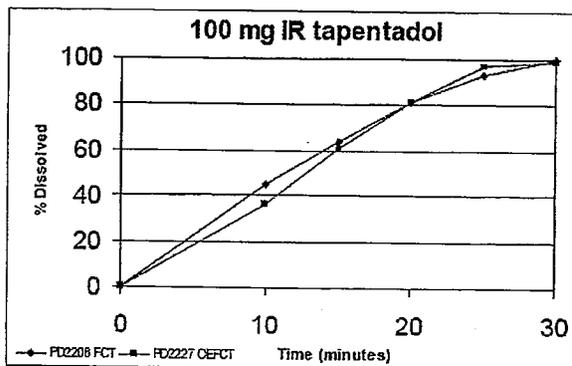
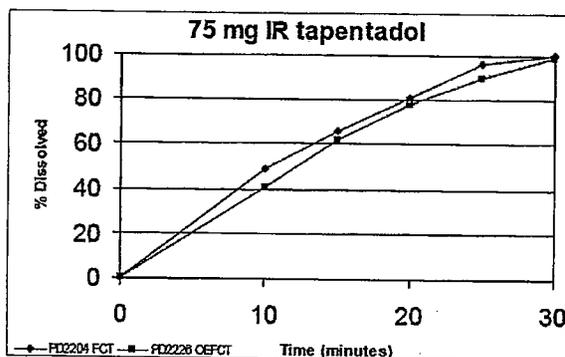
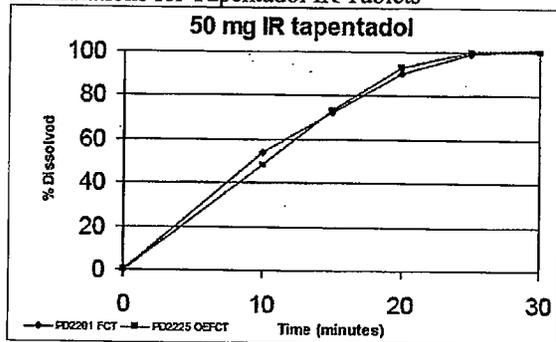


The Effect of pH on Dissolution Profiles for Tapentadol 100-mg Film-Coated Tablets using Paddles (USP Apparatus 2)



Dissolution comparisons between Phase 3 (overencapsulated) and TBM tablets and f2 calculations are presented below.

Dissolution Profiles of Phase 3 Clinical (Overencapsulated, OEFCT-pink line) and TBM (FCT-blue line) Formulations for Tapentadol IR Tablets



Similarity and Difference Factors for the Phase 3 (Overencapsulated) and TBM Formulations of Tapentadol 50-, 75- and 100-mg Tablets

Dose (mg)	f_1 (difference factor)	f_2 (similarity factor)
50	5	70
75	7	62
100	6	64

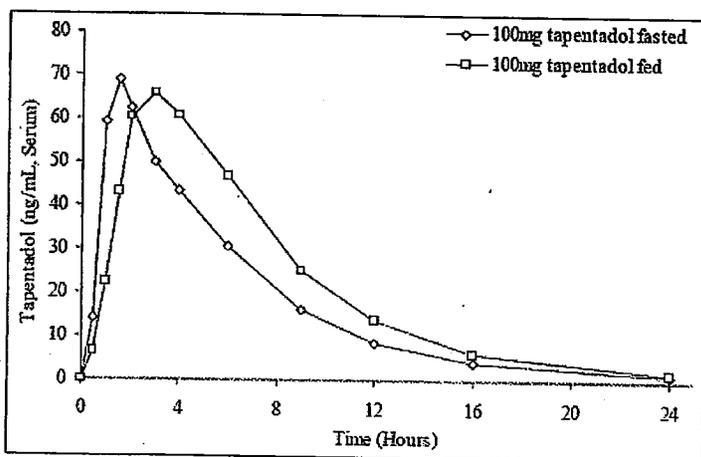
2.5.3 What is the effect of food on the bioavailability (BA) of tablets? What dosing recommendation should be made, if any, regarding administration of tablets in relation to meals or meal types?

C_{max} and AUC increased by 16% and 25% with food, respectively. The t_{max} was prolonged by about 1.5 hours with a median t_{max} of 3.00 hours (range: 1.02-6.00 hours) in the fed state and 1.50 hours (range: 1.00-4.00 hours) in the fasted state. The Applicant discussed the insignificance of food effect during the drug development program and did not restrict the use of tapentadol with respect to meal consumption.

In Phase 3 studies, all doses of study treatment were administered with approximately 120 mL of water, with or without food. Study treatment was swallowed whole and not chewed, divided, dissolved, or crushed.

Study HP5503/34 (R331333-PAI-1014) was a single-center, single-dose, open-label, randomized, 2-way crossover study in 36 healthy subjects (18 males, 18 females) using 100 mg IR tablets (batch PD2213). Thirty-four (17M/17F) subjects completed the study.

Mean Tapentadol Serum Concentration-Time Profiles After Single-Dose Administration of Tapentadol IR Tablet With and Without Food (Study HP5503/34)



Tapentadol Pharmacokinetic Parameters After Single-Dose Administration of Tapentadol IR Tablet With and Without Food (Study HP5503/34)

	100 mg IR Tablet Fed (PD2213) (n=35)	100 mg IR Tablet Fasted (PD2213) (n=34)	Fed/Fasted Ratio, % (90% CI) (n=34)
C _{max} , ng/mL	83.4 ± 28.1 [33.7]	72.8 ± 30.8 [42.4]	115.99 (107.65 - 124.99)
AUC _{last} , ng·h/mL	525 ± 154 [29.2]	421 ± 151 [36.0]	125.18 (119.24 - 131.42)
AUC _∞ , ng·h/mL	536 ± 157 [29.3]	429 ± 154 [35.9]	125.18 (119.26 - 131.40)
t _{max} , h	3.00 (1.02 - 6.00)	1.50 (1.00 - 4.00)	
t _{1/2} , h	3.9 ± 0.4 [10.6]	4.2 ± 0.4 [10.2]	

Data expressed as mean ± SD [%CV], except for t_{max} median(range).

C_{max} and AUC increased by 16% and 25% with food, respectively. The t_{max} was prolonged by about 1.5 hours with a median t_{max} of 3.00 hours (range: 1.02-6.00 hours) in the fed state and 1.50 hours (range: 1.00-4.00 hours) in the fasted state. The Applicant discussed the insignificance of food effect during the drug development program and did not restrict the use of tapentadol with respect to meal consumption.

In Phase 3 studies, all doses of study treatment were administered with approximately 120 mL of water, with or without food. Study treatment was swallowed whole and not chewed, divided, dissolved, or crushed.

2.5.4 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

The Applicant stated that the drug product meets BCS 1 classification. For further discussion, see above section 2.5.3. regarding a request for a biowaiver. ONDQA will assess the acceptance of final dissolution method and specifications for this product.

2.6 Analytical Section

2.6.1 How are tapentadol and its metabolites measured in the serum and urine?

An LC-MS/MS method was used for the quantification of tapentadol and its O-glucuronide and the O-sulfate metabolites in plasma. The method had a validated range of 0.2 to 200 ng/mL, 5.00 to 400 ng/mL and 10.0 to 5,000 ng/mL for tapentadol, tapentadol-O-sulfate and tapentadol-O-glucuronide, respectively. Similarly an LC-MS/MS method was used for the quantification of tapentadol and its O-glucuronide in urine. The method had a validated range of 10 to 10,000 ng/mL and 500 to 100,000 ng/mL for tapentadol and tapentadol-O-glucuronide, respectively.

2.6.1.1 What are the accuracy, precision and selectivity parameters? What is the sample stability under the conditions used in the study?

The following tables show various parameters.

Validation Parameters for Plasma and Serum Methods for Tapentadol and Metabolites

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GRT plasma/serum method (PK534) (Mod5.3.1.4/PK534)	tapentadol	tapentadol
matrix	plasma	serum
validated concentration range	0.5 – 100 ng/ml	0.25 – 100 ng/ml
intra-run accuracy (%)	93.2-104.6	95.8-103.6
intra-run precision (%CV)	≤ 7.4	≤ 8.7
selectivity	no relevant interferences	no relevant interferences
extraction recovery (%)	--	82.0-112.8
extraction recovery IS (%)	--	83.5-87.7
stability in matrix	--	24 freeze-thaw cycles 48 hours at room temperature 24 weeks in a freezer (-20°C and -70°C)
stability of study samples	--	2 years in a refrigerator
processed sample stability	--	48 h at room temperature 24 weeks in a freezer (-20 °C and -70°C)

Validation Parameters for Serum LC-MS/MS Methods for Tapentadol and Metabolites at

serum methods	Tapentadol: validation original method	Tapentadol: re-validation after changes	Tapentadol-O-glucuronide	Tapentadol-O-sulfate
validated concentration range	0.150-100 ng/mL	0.150-100 ng/mL	10.0-5000 ng/mL	5.00-400 ng/mL
inter-run accuracy (%)	96.5-102.6	98.6-109.0	99.2-105.2	96.2-104.2
inter-run precision (%CV)	4.1-6.3	2.9-12.0	4.3-9.7	4.0-11.9
intra-run accuracy (%)	90.8-107.3	89.3-110.1	94.3-108.8	86.4-109.8
intra-run precision (%CV)	1.6-6.8	2.1-12.8	1.2-10.9	2.1-9.3
intra-run accuracy (5 x dilution) (%)	94.4		104.1	100.0
intra-run precision (5 x dilution) (%)	0.9		2.8	2.9
selectivity (interference < 20% of LLOQ)	6 out of 6 sources of serum		6 out of 6 sources of serum	6 out of 6 sources of serum
extraction recovery (%)	107-140		65.3-83.5	63.7-75.4
extraction recovery IS (%)	115-141		67.3-83.3	70.2-85.8
stability in blood ^a	- 120 minutes at room temperature		- 120 minutes at room temperature, no hydrolysis to tapentadol	
stability in serum	- 3 freeze-thaw cycles compared to fresh samples - 24 hours at room temperature - 13 months at -25 ± 5°C ² - 24 hours at 8 ± 5°C		- 3 freeze-thaw cycles compared to fresh samples, no hydrolysis to tapentadol ^a - 24 hours at room temperature, no hydrolysis to tapentadol ^a - 13 months at -25 ± 5°C, no hydrolysis to tapentadol ^a 72 hours at 8 ± 5°C	
processed sample stability	- 24 hours at 8 ± 5°C		no hydrolysis to tapentadol after 192 hours at 8°C ³	
stability in methanol/water (50/50) stock solution	- 6 hours at -25°C, at 5°C and at room temperature		- 7 hours at -25°C, at 5°C and at room temperature - no hydrolysis to tapentadol after 3 days at room temperature in dark and light, 1 month at 5°C and 13 months at -25 °C ³	

b(4)

b(4)

Validation Parameters for Serum LC-MS/MS Methods for Tapentadol and Metabolites at J&JPRD

J&JPRD serum method (BA525; Mod5.3.1.4/BA525)	Tapentadol		Tapentadol-O-glucuronide	
	validation original method	re-validation after method changes	validation original method	re-validation after method changes
validated concentration range	0.200 – 200 ng/mL	0.200 – 200 ng/mL	10.0-10000 ng/mL	10.0-10000 ng/mL
inter-run accuracy (%)	93.5-99.7	101.9-109.8	98.9-101.1	93.0-107.1
inter-run precision (%CV)	2.5-6.9	4.1-9.7	2.7-5.7	3.3-7.5
intra-run accuracy (%)	87.8-104.1	98.1-119.5	92.7-106.0	87.3-111.3
intra-run precision (%CV)	0.8-8.0	0.6-17.4	0.3-7.4	0.3-10.4
intra-run accuracy (10 x dilution) (%)	93.1		101.6	
intra-run precision (10 x dilution) (%)	4.3		2.4	
selectivity (interference < 20% of LLOQ)	5 out of 6 sources of serum	6 out of 6 sources of serum	6 out of 6 sources of serum	6 out of 6 sources of serum
extraction recovery (%)	92.7-98.2		92.3-94.1	
extraction recovery IS (%)	95.6		90.1	
processed sample stability	- 5 days at room temperature	- 6 days at room temperature	- 5 days at room temperature	- 6 days at room temperature
stability in methanolic stock solution	- 3 days at room temperature (dark and light) - 1 month in a refrigerator - 6 months in a freezer		- 3 days at room temperature (dark and light) - 1 month in a refrigerator - 6 months in a freezer	

Validation Parameters for Urine Methods for Tapentadol and Metabolites

Validation parameters for Urine HPLC-fluorescence Method at Grünenthal (GRT)

GRT urine method (PK534; Mod4.2.2.1\PK534)	tapentadol
validated concentration range	0.5 – 100 ng/ml
intra-run accuracy (%)	89.2-101.8
intra-run precision (%CV)	≤ 3.8
selectivity	no relevant interferences
extraction recovery (%)	94.4-129.8
extraction recovery IS (%)	92.9- 95.3
stability in urine	24 freeze-thaw cycles 48 hours at room temperature 24 weeks in a freezer (-20°C and -70°C) refrigerator
processed sample stability	48 h at room temperature 24 weeks in a refrigerator

b(4)

Validation Parameters for Urine LC-MS/MS Methods for Tapentadol and Metabolites at J&JPRD

J&JPRD urine method (BA524; Mod5.3.1.4\BA524)	tapentadol	O-glucuronide
validated concentration range	10.0 – 10000 ng/ml	500-100000 ng/ml
inter-run accuracy (%)	81.5-104.0	95.8-97.0
inter-run precision (%CV)	3.9-8.2	3.2-8.8
intra-run accuracy (%)	88.8-108.3	89.2-105.1
intra-run precision (%CV)	0.7-16.6	0.0-19.2
intra-run accuracy (10 x dilution) (%)	90.7	94.3
intra-run precision (10 x dilution) (%)	5.9	2.1
selectivity (interference < 20% of LLOQ)	6 out of 6 sources of urine	6 out of 6 sources of urine
processed sample stability	5 days at room temperature	5 days at room temperature
stability in urine	3 freeze-thaw cycles compared to reference 72 hours at room temperature	3 freeze-thaw cycles compared to reference 72 hours at room temperature

b(4)

3 Detailed Labeling Recommendations

There are changes recommended for the Clinical Pharmacology section of the label, as below. The package insert is modified by strikeouts of the existing texts and addition of new texts, where appropriate.

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b(4)

19 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

✓ Draft Labeling (b5)

 Deliberative Process (b5)

b(4)

4.2 Individual study review - Population PK/PD study report

Title: Population Pharmacokinetics and Exposure-Response of Tapentadol Immediate Release (IR)

Objectives

The primary objectives of the population pharmacokinetic (PK) analysis of tapentadol were as follows:

- to estimate typical pharmacokinetic parameters of tapentadol in the population and their inter- and intra-individual variability;
- to evaluate the effects of subject's demographic characteristics and other covariates on the pharmacokinetics of tapentadol following oral administration of an IR formulation in healthy subjects and subjects with acute pain.

There are 4 analyses: population PK analysis of tapentadol, analysis of PK of tapentadol-O-glucuronide metabolite in renal impairment patients, exposure-response analysis and exposure-adverse event analysis.

Population PK analysis

Clinical Data

The database available for the population pharmacokinetic analysis of tapentadol consisted of 1,833 subjects; 199 otherwise healthy subjects (10.9%), including 30 subjects with renal impairment and 20 subjects with hepatic impairment, from studies HP5503/03, PAI-1002/HP5503/16, PAI-1005/HP5503/13, PAI-1006/HP5503/15, PAI-1016/HP5503/24, PAI-1019/HP5503/30 and 1,634 subjects with acute pain (89.1%) from studies KF5503/02, KF5503/04, KF5503/05, KF5503/21, PAI-2003/KF5503/22, and PAI-3003/KF5503/32.

For model development, 6 Phase 1 studies and 5 Phase 2 studies were used; there were a total of 10,114 PK samples from 1,474 (80.7%) subjects, which 4824 serum concentration from 198 healthy subjects in the 6 Phase 1 studies aided in the development

of the structural PK model. The model was validated using an external dataset that consisted of data from Study PAI-3003/KF5503/32, which had 353 subjects that contributed 1271 serum samples. Once the population PK model was validated, the entire datasets were combined and the final model was re-run on the full dataset. Including the validation set, the full dataset consisted of 11,385 samples from 1,827 subjects.

Concentration data were not included in the analysis if they met any of the following criteria:

- Concentration was below quantification limit (LLOQ) or NS/NA (no sample or not available)
- When duplicated samples were received, if the difference between the two sample concentrations was within 15%, the average of the two samples was used. If the difference exceeded 15%, both samples were excluded.
- Sample date/time missing
- Discrepancy between sample date from the sample time table and the concentration table
- Quantifiable pre-treatment serum concentration
- Subjects took placebo
- Measured analyte was not tapentadol

Sampling times:

HP5503/03: Blood samples were collected at predose (within 10 min prior to administration), 0.25, 0.33, 0.5, 0.75, 1, 1.5, 2, 3, 5, 6, 7, 8, 10, 12, 16, 24, 28, 32 h after intake of the investigational drug.

PAI-1002/HP5503/16: Blood samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48 h after intake of the investigational drug.

PAI-1005/HP5503/13: Blood samples (4 mL each) for pharmacokinetic analyses were collected on Day 1 just before dosing (predose) and at 0.5, 1, 1.5, 2, 3, 4, 6, 7.5, 12, 13.5, 18, 24, 25.5, 30, 30.5, 31, 31.5, 32, 33, 34, 36, 39, 42, 48, and 54 hours after the first dose.

PAI-1006/HP5503/15: Blood samples were collected on Day 1 at 0 hours (predose) and at 0.5 (30 minutes), 1.0, 1.5 (1 hour and 30 minutes), 2.0, 3.0, 4.0, 6.0, 9.0, 12.0, and 16.0 hours, on Day 2 at 24.0 and 36.0 hours, and on Day 3 at 48.0 hours after administration.

PAI-1016/HP5503/24: Blood samples (4 mL each) were collected on Day 1 at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 16 hours, and on Day 2 at 24 hours after study drug administration.

PAI-1019/HP5503/30: Blood samples (4 mL each) were collected at 0 (predose), 0.5 (30 min), 1, 1.5 (1h30min), 2, 3, 4, 6, 9, 12, 16 (Day 1), 24, 36 (Day 2), and 48 (Day 3) hours after study drug administration.

KF5503/02: A blood sample was taken between 30 min and 5 h after intake of the investigational products

KF5503/04: During the single dose period, blood samples were taken at 1, 2, 4 h (+/- 10 min) after intake of drug. During the multiple-dose phase, blood samples were taken at the following times after the first dose: at predose (-45 to -5 min) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours. Two further samples were taken before (-10 to -5 min) the sixth and seventh dosing. Blood samples were also drawn at the following times after the last dose: at predose (-10 to -5 min) and at 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and between 24 and 36 hours

KF5503/05: Blood samples were taken at 1, 2, 4, 6, 8 h (+/- 10 min) after drug intake.

PAI-2004/KF5503/21: Blood samples were drawn between 10 and 40 minutes, between 45 and 75 minutes, and between 90 and 180 minutes after the first dose and just after each (between 5 and 15 minutes) subsequent dose.

PAI-2003/KF5503/22: Blood samples were drawn at 0 hour (shortly before administration of any of the study drugs) and at 1, 1.5, 4, 8, and 12 hour after the first study medication. The PK samples for the 4- and 8-hour time points were taken shortly before the administration of the 2nd and 3rd doses of study drug, respectively.

PAI-3003/KF5503/32: In total 4 samples were drawn; 2 blood samples were collected on Day 1 at approximately 1 and 3 hours after the first study drug administration and 2 samples were collected before (predose) and approximately 2 hours after the third study drug administration on Day 2.

Sample analysis

Serum samples were separated by centrifugation and frozen at -80°C until analyzed using a validated LC/MS/MS method with a lower limit of quantification (LLOQ) as shown below:

<u>Study</u>	<u>LLOQ in ng/mL</u>
HP5503/03	< 0.24
HP5503/13 (PAL-1005)	0.2
HP5503/15 (PAL-1006)	0.2
HP5503/16 (PAL-1002)	0.2
HP5503/24 (PAL-1016)	0.2
HP5503/30 (PAL-1019)	0.2
KF5503/02	0.25
KF5503/04	< 0.5
KF5503/05	< 0.5
KF5503/21 (PAL-2004)	0.15
KF5503/22 (PAL-2003)	0.2
KF5503/32 (PAL-3003)	0.2

Software and dataset input

Data set was prepared using SAS® Version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Data exploration and visualization was performed using S-PLUS 7 for Windows (Insightful, Seattle, WA). Xpose 3.1 (University of Uppsala, Uppsala, Sweden) was used for covariate screening. Serum concentration-time data were used for non-linear mixed effect modeling by extended least squares regression using the NONMEM package Version V level 1.1, with NM-TRAN version III level 1.1 and PREDPP version IV level 1.1 (ICON, Ellicott City, MD, USA). All model building was performed using NONMEM deployed on the J&J PRD computational GRID, which is based on the United Devices' Metaprocessor product running with an Oracle 9i repository, and a mixture of Intel based processing nodes running Microsoft Windows and Red hat Linux operating systems. The NONMEM GRID solution executes models on the GRID using Intel FORTRAN 9.0.018 for Windows. Measurements below the limit of quantification and missing values were excluded from the analysis. Log-transformed concentrations were used as the dependent variable in the population analysis. The outlier detection in the dense data set was based primarily on visual examination of individual and pooled concentration-time profiles with the same dosing regimen. It is noted that at the final model development stage, 59 model-based outliers ($|WRES| > 5$) from 55 subjects were excluded to derive the final model.

Structural model selection

The entire model building exercise employed the first order conditional estimation (FOCE) method in NONMEM while using log-transformed data. The tapentadol concentration-time data were initially fitted to a 2-compartment model, followed by 1- and 3-compartment models, with different input functions (zero-order absorption first-order absorption, sequential zero order dissolution followed by first order absorption, and parallel zero and first order absorption). Inter-individual (IIV) and inter-occasion (IOV) variability for pharmacokinetic parameters, P, were evaluated using an *exponential error*

model, $P_{j,t} = P^* e^{(\eta_j + \tau_i)}$. The magnitude of residual variability in the log-transformed concentrations was modeled using an *additive* error model and included two random effect parameters to account for the residual variability of intensively sampled PK data and sparsely sampled PK data, separately, $\ln C_{ij} = \ln \hat{C}_{ij} + (1 - SSM) \times \varepsilon_{1ij} + SSM \times \varepsilon_{2ij}$.

For an open two-compartment pharmacokinetic model with first-order elimination, the model was parameterized in terms of clearance (CL/F), volumes of distribution for central and peripheral compartments (V2/F and V3/F, respectively), and inter-compartmental exchange flow rates for the exchange between the central and peripheral volumes of distribution (Q/F). The selection of the final model was based on the following goodness-of-fit (GOF) criteria: closeness of individual fitted curves to observations; the pattern of weighted population and individual residuals plotted against predicted population and individual concentrations, respectively, as well as against the time since the last intake of the study medication (or since the first intake of the study medication), judged from visual exploration; visual inspection of the observed versus predicted concentration values; reduction in OFV (if appropriate for nested models); decrease in the residual error variance.

Building a covariate model

The initial covariate screening was done by graphical assessment as well as different statistical analyses using posterior Bayes estimates of random effects (ETAs) produced by the POSTHOC step of a NONMEM® run to evaluate the relationships between ETAs and covariates: stepwise linear regression within S-PLUS®, generalized additive modeling (GAM implemented in XPOSE), bootstrap GAM (implemented in XPOSE). The covariates included in the analysis (a complete list) are demographic variables (age, weight, gender, race and derived body size variables such as body mass index, body surface area, and percent body fat content), liver enzyme values (i.e. ALT), renal function test (creatinine clearance), health status and co-medications, if appropriate. Total bilirubin and total protein were selected as surrogate markers for hepatic function test. Height was not tested as an independent covariate because of its correlation with weight; it was only used to calculate the derived body size variables. Covariates selected were subsequently incorporated in the population model. Continuous covariates were included

in the model using the following equation: $TVP = \theta_x \left(\frac{Covariate}{Covariate.Median} \right)^{\beta}$ where TVP is typical value of a primary PK parameter, e.g., CL, Vd, and flow rate. Taking into account the additivity of metabolic and renal CL, the model for the effect of creatinine

clearance (CRCL) on the typical value of the drug clearance was as follows: $TVCL = \theta_{CL,1} + \theta_{CL,2} * CRCL$ where, the first ($\theta_{CL,1}$) and the second ($\theta_{CL,2}$) term approximate the metabolic and the renal part of the total clearance, respectively. To stabilize the model, this relationship was approximated by an exponential function: $TVCL = \theta_{CL,1} * \exp[\theta_{CL,2} * (CRCL - \text{median})]$. All categorical covariates including binary covariates like gender (SEX), coded as index variables having values of 0 or 1, were incorporated into the model as follows: $TP = \theta_x * \exp(\text{Covariate} * \theta_y)$. All preliminarily identified statistically significant covariates were included into the final base model. The effects of gender and health status were evaluated after including all other variables into the full model by forward addition.

Forward and backward covariate selection and elimination

Covariates were formally evaluated for statistical significance by including them in the model one at a time. The covariate was included if there was a decrease in the OFV of greater than 6.63 (χ^2 test, $df = 1$, $\alpha = 0.01$). After this initial evaluation, the covariate resulting in the lowest p-value was included into the base structure model. In the next iteration, the remaining covariates were added to the updated model, again one at a time, and the covariate resulting in the lowest p-value was then added to the model. This process was repeated until all the significant covariates were included in the model.

The final significance of each fixed effect was evaluated by deleting it from the full model one at a time. If the exclusion of a fixed effect resulted in an increase in OFV less than 7.88 ($P < 0.005$, χ^2 , 1 df) the covariate was removed from the model.

Model Refinement for Subject Specific Random Effects

The structure of the variance-covariance matrix for the subject-specific random effects was optimized after finalizing the covariate model. The original dimension of the diagonal matrix was reduced by excluding random effects with negligible variance estimates ($\omega_2 < 0.0001$) if necessary. Pair-wise plots of empirical Bayes estimates of η (ETAs) produced by NONMEM runs were examined visually. The cases with the highest correlations were tested for statistical significance by including respective covariance between the subject-specific random effects. The resultant model was called optimized final index model.

External Model Evaluation

The model developed was examined for its predictive ability, and the performance was evaluated on a validation data set that was not used in the model building exercise. Population predictions for all concentrations in the validation data set were obtained using the dosing and necessary covariate information. The diagnostic plots were then examined for bias and scatter. Prediction errors were computed that provide a measure of bias and precision by assessing the differences between the measured and population mean predicted concentrations. The prediction error percents (PE%) were computed for each concentration value using: $PE\%_y = (DV_y - PRED_y) / PRED_y * 100$

Summary statistics of PE% and |PE|% were calculated to assess bias and precision of the model-predicted concentrations relative to the observed concentrations. The distribution of PE% was evaluated as a measure of bias and the distribution of |PE|% was utilized as a measure of precision in the predicted values. The model was considered acceptable, both accurate and precise, (i.e., externally validated) if the median PE% and the median |PE|% were $\leq 15\%$ and 30% , respectively.

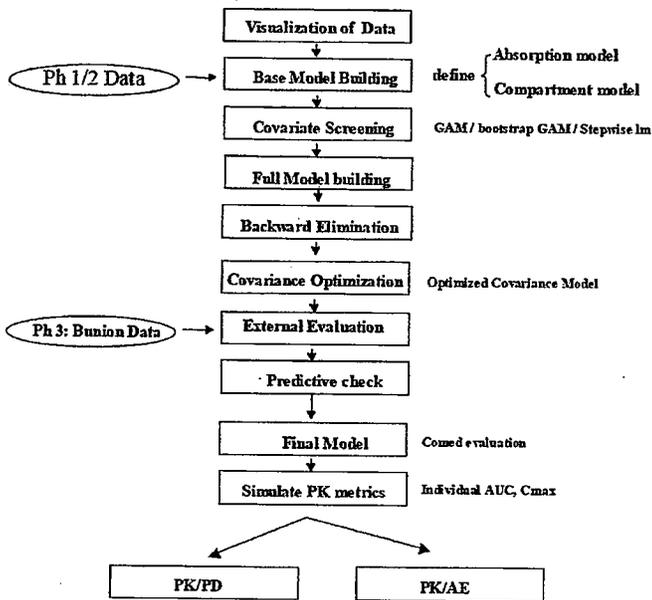
Evaluating the Effect of Concomitant Medications

Among the concomitantly administered drugs, the medications that were administered to more than 10% of subjects were used for the analysis. Usually, more than one concomitant medication was co-administered to the subjects. In subjects receiving concomitant medications, concentrations of tapentadol could only be affected during the periods when the co-medications were actually taken. Therefore, systematically high or low population residuals corresponding to the periods of taking concomitant medications should be considered as indicative of a drug-drug interaction. However, in some cases, it is also possible that a comedication had a prolonged effect on the PK of tapentadol. Since the dosing durations in the studies of acute pain were generally short (i.e., no longer than 72 hours), it was reasonable to assume that the impact of concomitant medication would last until the end of the study once administered. The approach based on population residuals was used to investigate potential pharmacokinetic interactions of tapentadol with concomitant medications. Population residuals were first analyzed graphically. The boxplots of the residuals from the subjects with and without each concomitant medication were compared. The similarity in the distributions of residuals with and without a concomitant medication indicates no influence of the concomitant medication on the PK of tapentadol.

Results

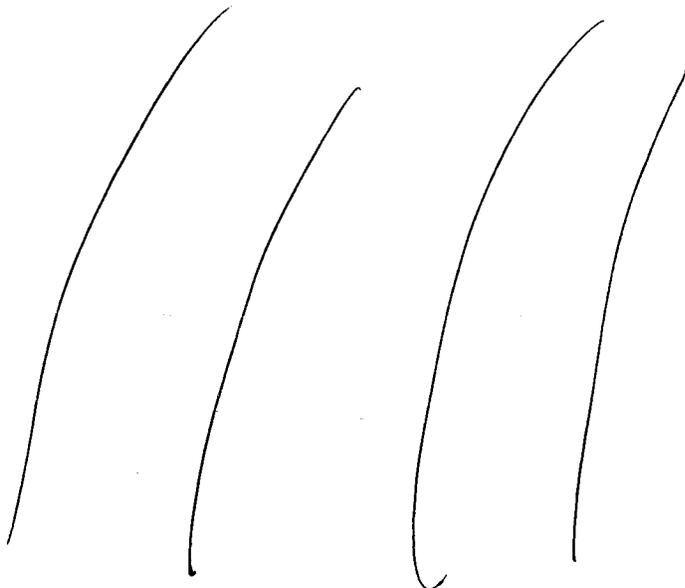
The following flow chart depicts the model development process:

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ON ORIGINAL**



The dataset was visually inspected for the exploratory data analysis.

Visual Inspection of Data:



b(4)

Final Base Model

The characteristic features of the structural models, the objective function values, and the change in objective function values from the reference models are presented below:

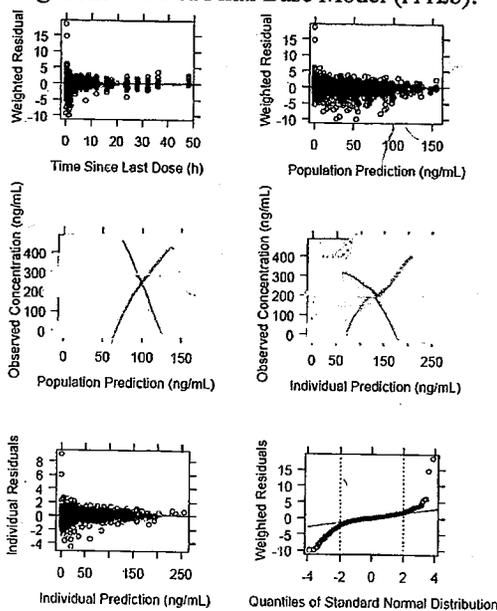
Models Explored to Find the Final Base Model (r112b)

Run	OFV	Delta OFV	MIN	COV	REF	Model
Select absorption model						
Data:						
r100	-455	1359	y	n	r102	2cmt full IIV, 2 residual errors, 0 order absorption
r101	446	2260	y	y	r102	2cmt full IIV, 2 residual errors, 1st order absorption
r102	-1814	0	y	y	NA	2cmt full IIV, 2 residual errors, KOSKA
r103	1382	3196	y	n	r102	2cmt full IIV, 2 residual errors, KOKA model
Refine Inter-Individual variability						
102-1	-1773	41	y	n	r102	deleting ETA on Q
102-3	-1781	33	y	y	r102	deleting ETA on both Q and V3
102-8	-1734.2	79.8	y	y	r102	D1=log2/KA*THETA
r102-10	-1746	NA	n	n	r102	ETA(D1) = THETA*ETA(KA)
r102-11	-1298	NA	n	n	r102	D1 / KA BLOCK
Compartment model						
r104	128	1862.2	y	y	r102-8	1 compartment
r105	-1775	NA	n	n	r102-8	3 compartment
Inter-occasion Variability						
r111b	-1740.8	-6.6	y	y	r102-8	IOV(CL); Lump occasion 4-7 together
r112b	-1834	-99.8	y	y	r102-8	IOV(V2); Lump occasion 4-7 together
r113b	-3229	NA	n	n	r102-8	IOV(KA); Lump occasion 4-7 together
r119b	-1833	1	y	y	r112b	IOV(V2); Lump occasion 5-7 together
r120b	-1834	0	y	y	r112b	IOV on V2, 7 occasions (without lumping)

Note: NA, not applicable

The goodness-of-fit plots to support the appropriateness of the final base model (r112b) are shown below.

Diagnostic Plots of Final Base Model (r112b):



Note: In observed vs. population and individual predictions, the solid line represents the line of identity and the dashed line represents a LOWESS smoother. In all the residual plots, the ordinate value of zero is presented (solid horizontal line) and a LOWESS smoother is also plotted (dashed line). On the bottom right panel the solid line represents the Q-Q normal line and the vertical dashed lines are plotted at -2 and 2.

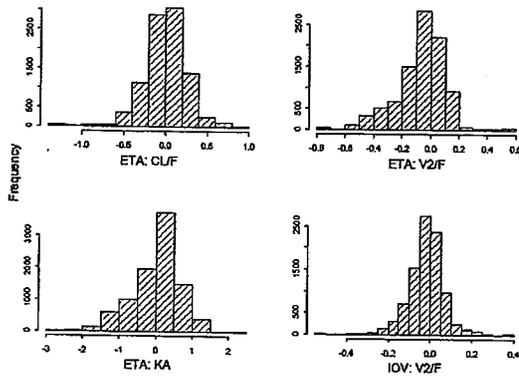
b(4)

There was minor deviation from the unity line in the plot of observed vs. individual predicted concentrations. This deviation diminished considerably by inclusion of covariates during the covariate model building process.

The distributions of the post hoc inter-individual variability and inter-occasion variability are shown below.

Distributions of Inter-Individual Variability (IIV) and Inter-Occasion Variability (IOV) of Final Base Model (r112b):

Empirical distributions (histogram) of IIV for CL/F, V2/F, KA, and IOV for V2/F are plotted.



The population mean parameter estimates and the associated precision (%SE) for the final base model (r112b) are provided in the following table. All model parameters were estimated with reasonable precision.

Parameter Estimates of Final Base Model r112b:

Parameter	Population Mean		Magnitude of Between-Subject-Variability (%CV)	
	Final Estimate	%SE	Final Estimate	%SE
CL (L/hr)	250	1.4	31.6	32.2
V2 (L)	1280	1.99	25.9	45
KA (hr-1)	1.85	4.45	78.5	24.1
D1 (h)	0.6	5.32		
ALAG1 (h)	0.197	1.52		
V3 (L)	191	8.85		
Q (L/hr)	36.1	17.56		
IOV V2			17.4	55.3
Sigma (SD):				
Sparsely sampled	0.485	42.3		
Sigma (SD):				
intensively sampled	0.406	28.3		

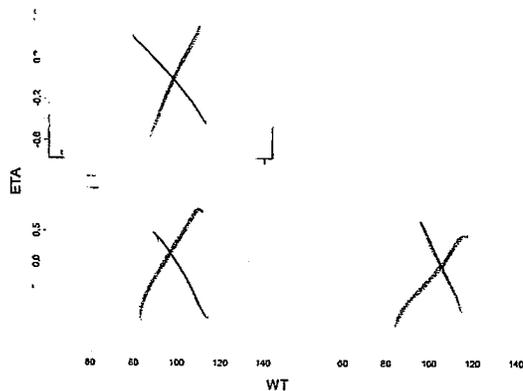
Minimum Value of the Objective Function = -1834

Effects of the covariates

The effects of the selected subject covariates were evaluated on clearance, central volume of distribution, and absorption rate constant. Body weight was initially evaluated as a representative body size related covariate. To assess hepatic function, only bilirubin and total protein were collected in all the studies selected for the population analysis. Therefore, total bilirubin and total protein were chosen as markers of hepatic function. The renal function was evaluated using calculated creatinine clearance (CRCL). The results of the representative covariate graphical approach are presented. A strong correlation was observed between body weight and the IIV of CL/F and V2/F.

Inter-Individual Variability (IIV or ETA) of PK Parameters Versus Body Weight (WT): Graphical inspection of the parameters

ZKA, ZV2, and ZCL represent IIV for KA, V2/F, and CL/F, respectively. A LOWESS smoother is presented in each panel (solid line).



b(4)

A stepwise linear regression approach in S-PLUS®, GAM, and bootstrap GAM as implemented in XPOSE were used to identify the potential covariates to be evaluated in the population model. In the final full covariate model, the following fifteen (15) covariate-parameter combinations were identified (r206):

- CL/F: AGE, WT, CRCL, FAT, TB, TP, SEX and RACE
- V2/F: AGE, WT, CRCL, TB, and Health Status
- KA: AGE and FAT

The following tables contain the covariates identified from the stepwise linear regression approach and the selected full covariate model (r206).

Covariates Identified From GAM, Bootstrap GAM, and Stepwise Multiple Linear Regression

Covariate Tested	GAM	Bootstrap GAM (p=0.5)	Stepwise / Linear Regression*
CL	AGE, WT, CRCL, FAT, TB, TP, RACE	AGE, WT, CRCL, FAT, TB, TP, RACE	AGE, WT, CRCL, FAT, TB, TP, RACE
	AGE, WT, CRCL, FAT, TB, TP, RACE	AGE, WT, CRCL, TB	AGE, WT, CRCL, TB
V2	AGE, WT, CRCL, TB, TP	AGE, WT, CRCL, TB	TB
KA	AGE, FAT, RACE	AGE, FAT, RACE	AGE, FAT

* Significance level: 0.05

Models Explored to Define the Full Covariate Model (r206)

Run	OFV	Delta OFV	MIN	COV	REF	Model
Full model with preliminary covariates						
r201	-2318		y	y		Asian as a separate category
r202	-2318		y	y		Pool Asian, Native Hawaiian, and American Indians
Test Sex and Health Status by forward selection						
Step 1						
r203-1	-2330	-12	y	n	r202	SEX: CL
r203-2	-2319	-1	y	y	r202	SEX: V2
r203-3	-2325	-7	y	n	r202	SEX: KA
r204-1	-2318	0	y	y	r202	HLTH: CL
r204-2	-2401	-83	y	y	r202	HLTH: V2
r204-3	-2326	-8	y	y	r202	HLTH: KA
Step 2						
r205	-2407	-6	y	y	r204-2	HLTH:V2; SEX:KA
r206	-2412	-11	y	y	r204-2	HLTH:V2; SEX:CL
r207	-2403	-2	y	n	r204-2	HLTH:V2; SEX:V2
r208	-2401	0	y	y	r204-2	HLTH:V2 and CL
r209	-2401	0	y	y	r204-2	HLTH:V2 and KA
Step 3						
r210	-2418	-6	y	y	r206	HLTH:V2; SEX:CL/ SEX:KA
r211	-2413	-1	y	y	r206	HLTH:V2; SEX:CL/ SEX:V2
r212	-2412	0	y	y	r206	HLTH:V2; SEX:CL/ HLTH:CL
r213	-2412	0	y	y	r206	HLTH:V2; SEX:CL/ HLTH:KA
Test additional covariates						
r206-1	-2418	-6	y	y	r206	RACE:KA
r206-2	-2412	0	y	y	r206	ALT:CL

After optimizing the covariate model, the Model r602 was identified as the final covariate model and the following tables contain the final modeling steps and the parameter estimates from the Model r602.

List of the Models Used for Refinement to Obtain the Final PK Model for the Index Dataset

Run	TAB-6					
	OFV	Δ OFV	MIN	COV	REF	Model
Test Other Body Size Covariates						
r461-BMI-CLV2	-2217	181	y	y	r461	Replace WT with BMI
r461-BSA-CLV3	-2414	-16	y	n	r461	Replace WT with BSA
Optimize CL/F vs. TB Relationship						
r500	-2448	-50	y	y	r461	Power function (TB ≤ 50); indicator function : TB > 50
Optimize Variance-Covariance Structure						
r600	-2724	-276	y	n	r500	full ETA
Step 1						
r603	-2713	11	y	n	r600	CL/KA block removed
r604	-2718	6	y	n	r600	V2/KA block removed
r605	-2482	242	y	y	r600	CL/V2 block removed
Step 2						
r601	-2713	5	y	n	r604	CL/KA block removed
r606	-2461	257	y	n	r604	CL/V2 block removed
Step 3						
r602	-2712	1	y	y	r601	ZV2 = ZCL*THETA

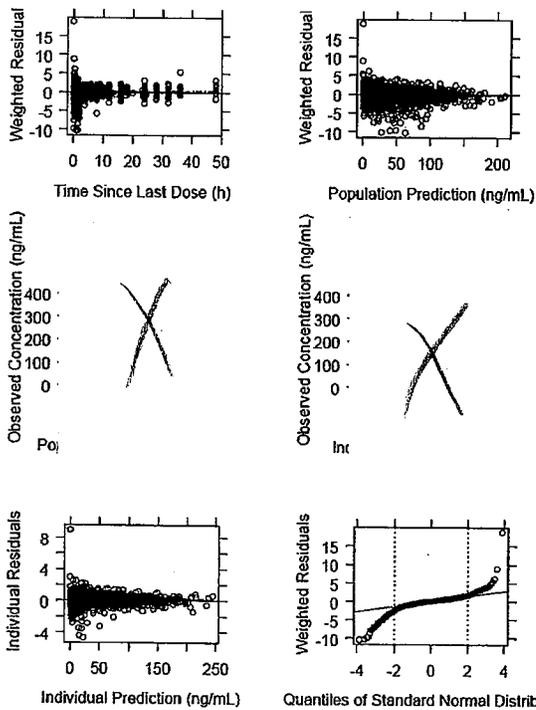
Comparison of the Parameter Estimates of Final Model With Index Dataset, Index Plus Validation Dataset

	Index dataset (r602)		Index + Validation dataset (r602-full)	
	Estimate	SE (%)	Estimate	SE (%)
CL (L/hr)	228	3.2%	219	2.8%
CL: WT power	1	8.1%	0.982	7.2%
CL: TB power (< 50 umol/L)	-0.109	-20.0%	-0.0978	21.5%
CL: shift factor for TB >= 50 umol/L	-1.05	-7.9%	-1.05	6.6%
CL: TP power	-0.544	-19.7%	-0.41	24.9%
CL: FAT power	-0.39	-15.3%	-0.469	11.2%
CL: shift factor for female	0.186	19.9%	0.202	15.9%
CL: shift factor for Black	-0.184	-24.7%	-0.184	13.9%
CL: shift factor for Hispanic	-0.0595	-45.4%	-0.0962	27.1%
CL: shift factor for Other races	-0.074	-122.2%	-0.0732	108.7%
V2 (L)	1090	2.5%	1070	3.0%
V2: WT power	1.01	7.2%	0.964	7.7%
V2: AGE power	-0.145	-26.1%	-0.177	22.5%
V2: CRCL power	-0.22	-18.5%	-0.216	23.3%
V2: shift factor for patients	0.207	12.0%	0.217	12.5%
KA (hr-1)	1.9	4.0%	1.84	4.1%
D1 (h)	0.62	4.6%	0.63	4.7%
ALAG1 (h)	0.171	2.9%	0.171	2.9%
V3 (L)	183	8.2%	192	10.9%
Q (L/hr)	31.2	15.8%	34.1	23.4%
Scaling factor: IIV(V2)	0.9	5.7%	0.9	6.2%
IIV CL (CV%)	26.6%	30.0%	26.2%	31.3%
IIV KA (CV%)	77.5%	24.5%	84.0%	23.5%
IOV V2 (CV%)	16.2%	41.2%	16.9%	44.2%
Sigma sparse sample	0.479	41.7%	0.498	36.4%
Sigma intensive sample	0.399	25.7%	0.400	25.7%
OFV	-2712		-2128	

The goodness-of-fit plots suggested that the model adequately described the observed concentration data:

Diagnostic Plots for Final Index Model (r602):

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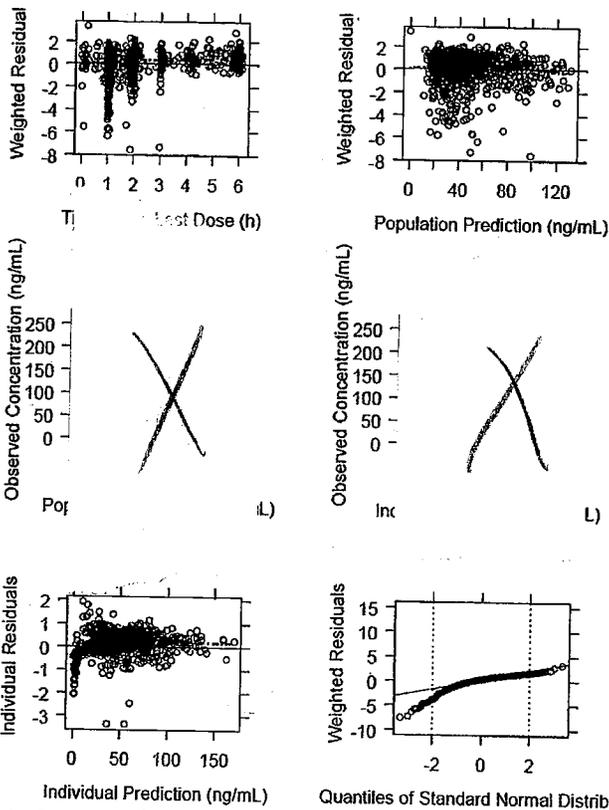
Note: In observed vs. population and individual predictions, the solid line represents the line of identity and the dashed line represents a LOWESS smoother. In all the residual plots, the ordinate value of zero is presented (solid horizontal line) and a LOWESS smoother is also plotted (dashed line). On the bottom right panel the solid line represents the Q-Q normal line and the vertical dashed lines are plotted at -2 and 2.

External Model Evaluation

The external model evaluation was conducted using the test dataset from Study KF5503/32. Overall, the model appeared to adequately predict the PK of tapentadol in Study KF5503/32. The goodness of fit plots for the external validation dataset are provided below.

Diagnostic Plots for External Validation (rr602-EX):

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Note: In observed vs. population and individual predictions, the solid line represents the line of identity and the dashed line represents a LOWESS smoother. In all the residual plots, the ordinate value of zero is presented (solid horizontal line) and a LOWESS smoother is also plotted (dashed line). On the bottom right panel the solid line represents the Q-Q normal line and the vertical dashed lines are plotted at -2 and 2.

Model finalization on the combined dataset

After the external model evaluation, the parameters were re-estimated using the combined dataset of the index and test data. The parameter estimates of the final model and their precision were obtained after excluding the identified outliers. The final fixed effect parameters were estimated as follows from the final model:

$$CL/F_j = 214 \cdot \left(\frac{WT_j}{71}\right)^{0.996} \cdot \left(\frac{TB_j}{8.04}\right)^{-0.077} \cdot CL_TB50_j \cdot \left(\frac{TP_j}{69.7}\right)^{-0.442} \cdot \left(\frac{FAT_j}{29.8}\right)^{-0.479} \cdot SEX_CL_j \cdot RACE_CL_j$$

where, 214 L/hr is the typical CL/F for a White man with median body weight of 71 kg; TB of 8.04 $\mu\text{mol/L}$; TP of 69.7 g/L; and FAT of 29.8%, estimated based on BMI, age and gender. CL_TB50j is the shift factor (0.39) for subjects with TB levels greater than 50 $\mu\text{mol/L}$; and SEX_CLj is the shift factor for women (1.24). The shift factors for Black, Hispanic-Latinos, and other non-White racial groups combined are 0.77, 0.92, and 0.88, respectively. (TB: total bilirubin; TP: total protein; FAT: body fat)

Furthermore, the equation below describes the relationship between the typical values (TV) of apparent volume of distribution of central compartment (V2/F) in the j^{th} subject and covariates:

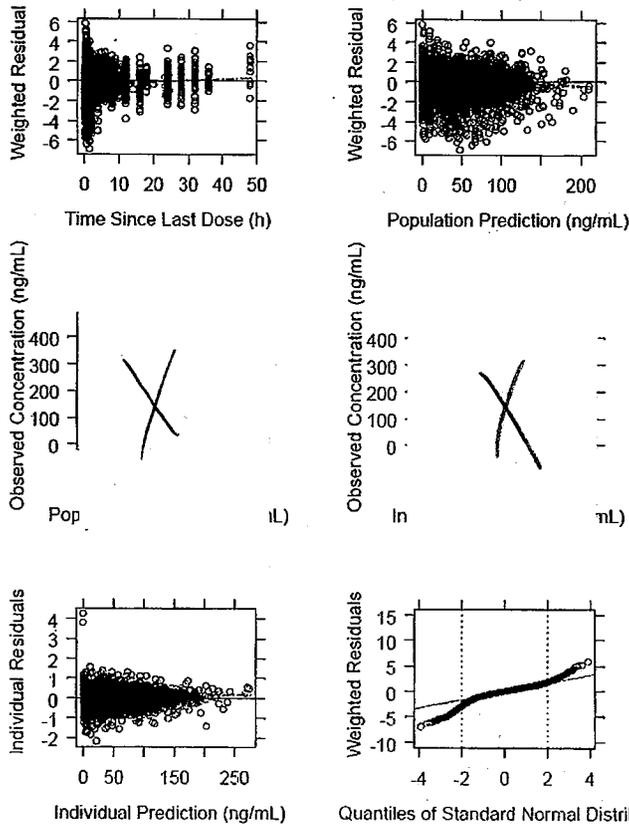
$$V2 / F_j = 1170 \cdot \left(\frac{WT_j}{71}\right)^{0.96} \cdot \left(\frac{AGE_j}{30}\right)^{-0.209} \cdot \left(\frac{CRCL_j}{101}\right)^{-0.226} \cdot HLTH_V2_j$$

where, 1170 L is the typical value of V2/F for a healthy subject with body weight of 71 kg, age of 30 years, and CRCL of 101 mL/min. HLTH_V2_j is the shift factor (1.11) for bunionectomy and post-surgical dental pain subjects. (HLTH_V2_j: health status indicating healthy subjects or subjects in pain model)

Additionally, the following parameter estimates are obtained: Q/F (L/h) = 24.2; V3/F(L) = 147; KA (h⁻¹) = 2.06; D1 (h) = 0.451; and, ALAG1 (h) = 0.235.

Diagnostic plots of the final population PK model (r602-full-10) are shown below. Also, the overall distribution of weighted residuals and the corresponding quantile-quantile plot shows that the weighted residuals have a normal distribution and that there is little bias.

Diagnostic Plots for Final PK Model (r602-full-10)



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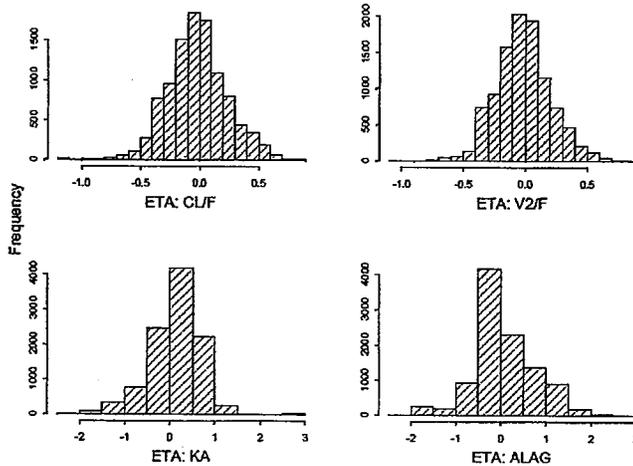
Note: In observed vs. population and individual predictions, the solid line represents the line of identity and the dashed line represents a LOWESS smoother. In all the residual plots, the ordinate value of zero is

presented (solid horizontal line) and a LOWESS smoother is also plotted (dashed line). On the bottom right panel the solid line represents the Q-Q normal line and the vertical dashed lines are plotted at -2 and 2.

The distributions of IIVs of PK parameters are presented below. The distributions of the inter-individual variability of the parameters were centered around zero, as expected.

Distributions of Inter-Individual-Variability (IIV) for the Final PK Model (r602-full-10):

Empirical distributions (histogram) of IIV of CL/F, V2/F, KA, and ALAG are plotted.



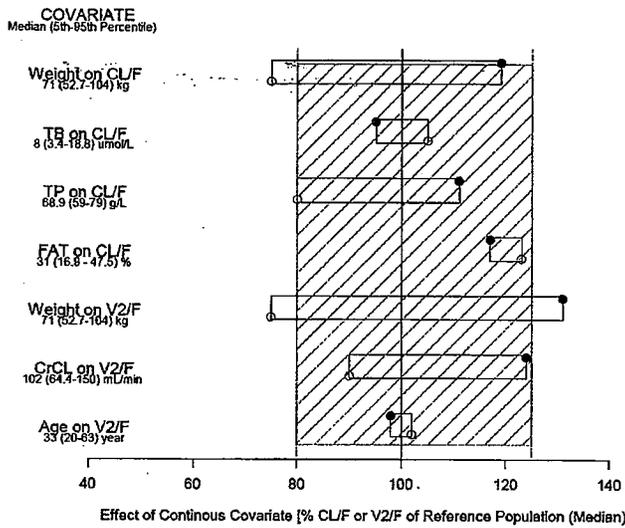
Overall, the final population PK model developed characterized the observed concentrations of tapentadol well with good precision on the parameter estimates.

Discussion of clinical relevance of covariates identified during the PK modeling

The clearance and volume of distribution are the two pharmacokinetic parameters identified during the modeling as important parameters. The influence of various covariates, such as body weight, hepatic and renal functions, age, health status, body fat, gender, and race, on CL/f and V2F were assessed. These covariate effects were estimated based on the optimized final model (r602-full-10). The following figures present the effect of continuous and categorical covariates on CL/F and V2/F.

Estimated Magnitude of Effects of Continuous Covariates in the Final PK Model

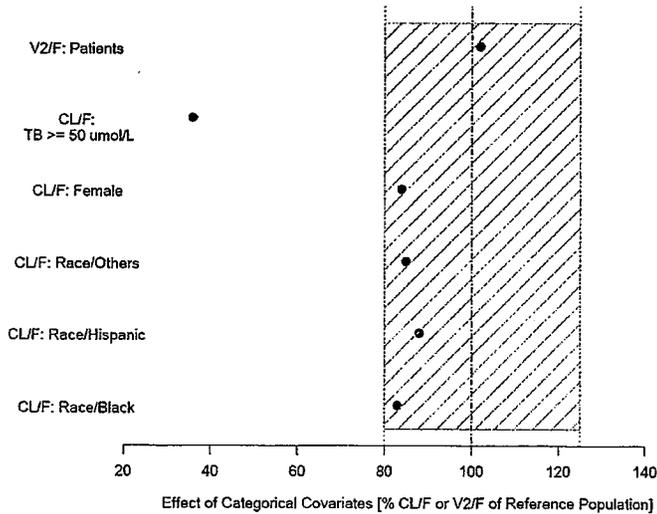
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Note: Open circles and solid dots represent point estimates of the covariate effect at the 5th and 95th percentiles of the covariate, respectively, compared to the reference population (median of the covariate). The effect at the 95th percentile value of the covariate is tagged higher in the rectangle relative to the effect at the 5th percentile value of the covariate. The solid vertical line represents the covariate effect for the reference population (median of the covariate), and the shaded area represents the bioequivalence range: 80% - 125%, of this value. The medians, 5th, and 95th percentiles of each covariate are listed on the left. TB – total bilirubin; TP – total protein.

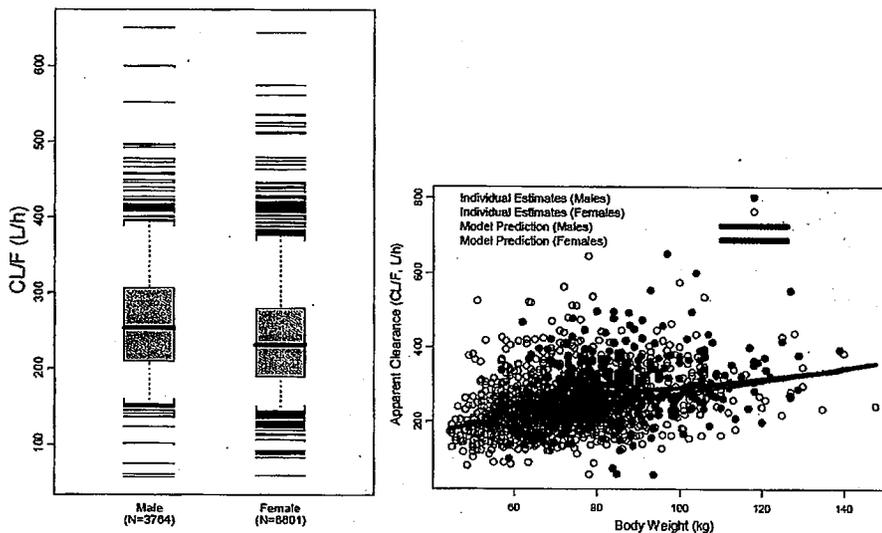
Estimated Magnitude of Effects of Categorical Covariates in the Final PK Model

Categorical Covariates



Note: Solid dots represent point estimates of the covariate effect compared to the corresponding reference populations. The dashed vertical line represents the covariate effects for the reference populations, and the shaded area represents the bioequivalence range: 80% - 125%, of this value. The reference populations are (from top to bottom): healthy volunteers, subjects with TB < 50 $\mu\text{mol/L}$, males, and Caucasians for race.

Body weight and gender: Body weight was found to be a statistically significant covariate on both CL/F and V2/F with a reduction in OFV of more than 100 points. As body weight increased, both CL/F and V2/F increased almost linearly. However, the body weight effect may not be a clinically important due to minimal significance. Gender effect on CL/F was found statistically significant: men appear to have slightly higher apparent oral clearance than women. The model predicted CL/F values for men were about 16% higher than that for women. After body weight was taken into account, the impact of sex on CL/F was small, with women up to approximately 100 kg having a slightly lower CL/F. Again, gender effect may not be a clinically important covariate on the PK of tapentadol.



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Note: The post-hoc individual estimates of CL/F from Final PK Model (Model r602-full-10) are plotted by gender (Left Panel) and by body weight (Right Panel). In the right panel, the red dots and black circles are the post-hoc individual estimates of CL/F for males and females, respectively. Description of the boxplot: the upper cap, upper bound of the box, horizontal line in the box, lower bound of the box, and lower cap represent the 95th percentile, 75th percentile, median, 25th percentile, and 5th percentile of the data, respectively.

Age, health status, race, body fat, hepatic and renal functions: Total bilirubin (TB) and total protein (TP) from the subjects, the majority of the subjects were healthy subjects, were identified as statistically significant covariates on CL/F. However, the magnitude of the covariate effects at the 5th and 95th percentiles of the distribution of TP and TB was minimal, as shown in the two figures previously presented titled Estimated Magnitude of Effects of Continuous Covariates in the Final PK Model and Estimated Magnitude of Effects of Categorical Covariates in the Final PK Model.

Conclusion of the Population PK Analysis of Tapentadol

A two-compartment PK model with zero-order release followed by first-order absorption and first-order elimination described the individual tapentadol PK profiles. The CL/F

and V2/F parameters were identified as parameters which may be affected by various covariates.

ANALYSIS OF PK OF MAJOR METABOLITE, tapentadol-O-glucuronided, IN RENAL IMPAIRMENT POPULATION

The objectives of the population PK analysis for the major metabolite are as follows:

- To describe the PK of a metabolite, tapentadol-O-glucuronide, after oral administration
- To obtain estimates of typical PK parameters and associated inter- and intra-individual variability of tapentadol-O-glucuronide in the target population
- To use simulations for assessing the impact of the statistically significant covariates from the population PK analysis on the overall exposure of tapentadol after oral administration to support the recommended treatment.

Clinical database - Study HP5503/15 (R331333-PAI-1006)

The database for the population PK analysis of tapentadol and its metabolite tapentadol-o-glucuronide consisted of 40 subjects with varying degree of renal impairment from a single Phase 1 study. From 40 subjects, a total of 460 PK samples for tapentadol and 482 PK samples for tapentadol-o-glucuronide were available for analysis. Serum concentrations of tapentadol and its primary metabolite, tapentadol-O-glucuronide were determined by validated bioanalytical methods. The lower limit of quantification for tapentadol was 0.2 ng/ml and for tapentadol-O-glucuronide 10 ng/ml.

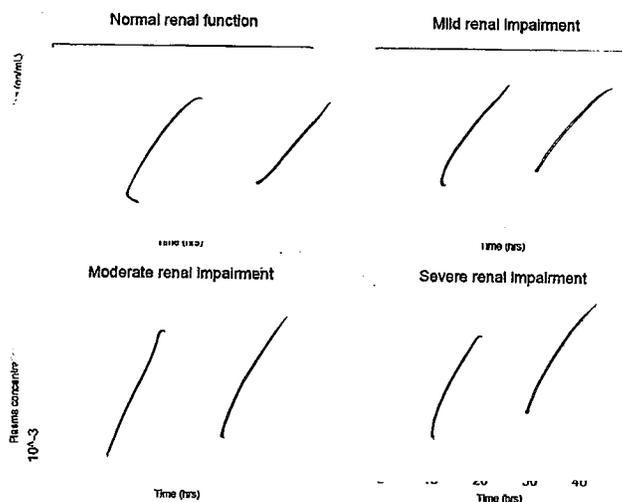
Modeling

The modeling setup was similar to that of the population PK analysis. The CRCL (creatinine clearance) had major influence on the clearance of metabolite. An integrated population PK model was developed for parent and metabolite. A three-compartment model with 1st order elimination best described the PK of tapentadol following oral administration.

Results

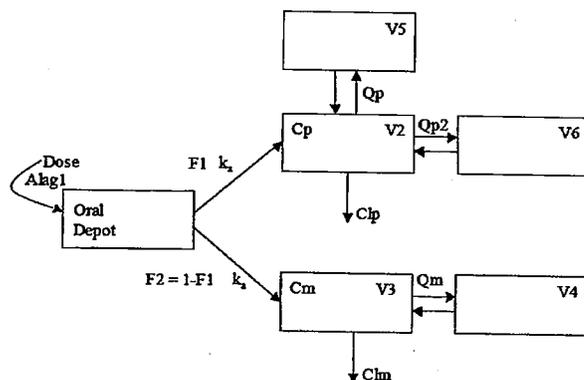
Exploratory Data Analysis: Visual Inspection of Data:

Blue circles represent tapentadol. Red circles represent tapentadol-O-glucuronide.



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Schematic Representation of the Structural Model for Tapentadol and its Metabolite Tapentadol-O-Glucuronide:



Covariate effect

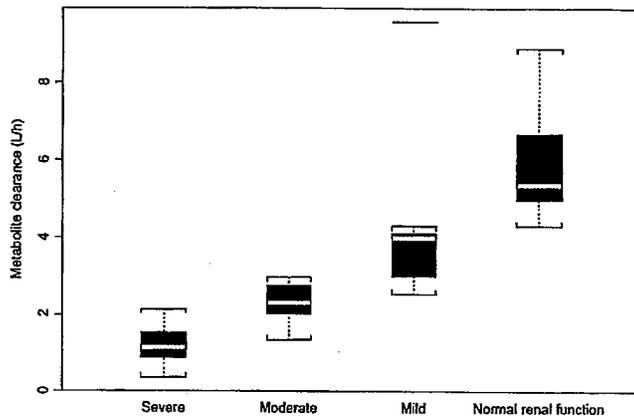
The equation below describes the relationship between covariate and the typical values (TV) of PK parameters in subject j:

$$CL_m / F_j = 3.26 * \left(\frac{CRCL_j}{54.95} \right)^{1.06}$$

where 3.26 L/hr is the TVCLm/F for an individual with CRCL = 54.95 mL/min. The apparent metabolite clearance (calculated from the average post hoc estimates) was 1.19, 2.30, 4.14 and 5.80 L/h in patients with severe, moderate, mild renal impairment and normal renal function, respectively. (note: based on the non-compartmental analysis on urine data, the apparent renal clearance were estimated at 0.76, 1.88, 3.00, 4.68, L/hr in patients with severe, moderate, mild renal impairment and normal renal function, respectively.)

Influence of CRCL on the Clearance of Tapentadol-O-Glucuronide

Metabolite clearance and CRCL



The white line represents the median of the data. The purple box represents the middle 50% of the data. The whiskers represent the maximum and minimum of the data. The black horizontal line represents an outlier.

The parameter estimates from the final joint parent-metabolite model are reported below.

Parameter Estimates From the Final Model of Tapentadol and Tapentadol-O-Glucuronide:

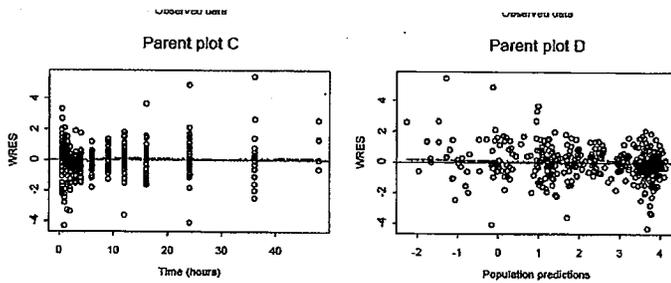
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Parameter	Estimate (SE)	95% CI	%CV
K_a (h^{-1})			
θ_1	0.263 (0.0183)	[0.227; 0.299]	
F1			
θ_2	0.017 (0.00157)	[0.014; 0.020]	
ALAG1 (h)			
θ_3	0.473 (0.0117)	[0.45; 0.496]	
V2/F (L) = θ_4	2.61 (0.356)	[1.921; 3.308]	
Clp/F (L/h) = θ_5	3.90 (0.317)	[3.279; 4.521]	
Clm/F (L/h) = θ_6 * (CRCL/54.95)**			
θ_{11}	3.26 (0.134)	[2.997; 3.523]	
θ_6	1.06 (0.063)	[0.936; 1.184]	
θ_{11}			
Qm/F (h^{-1})			
θ_7	1.91 (0.486)	[0.957; 2.863]	
V _d /F (L)			
θ_8	9.12 (1.43)	[6.32; 11.92]	
Qp/F (h^{-1})			
θ_9	0.175 (0.044)	[0.089; 0.261]	
V _d /F (L)			
θ_{10}	5.95 (0.881)	[4.22; 7.68]	
V _d /F			
θ_{10}	5.95 (0.881)	[4.22; 7.68]	
Qp2/F (h^{-1})			
θ_{12}	0.776 (0.266s)	[0.255; 1.297]	
IV on F1 : ω^2_1	0.0941 (0.029)	[0.037; 0.151]	Sd 0.005
IV on ALAG1 : ω^2_2	0.0386 (0.0212)	[-0.003; 0.08]	20%
IV on V2/F : ω^2_3	0.682 (0.184)	[0.392; 0.972]	83%
IV on Clp/F : ω^2_4	0.0588 (0.019)	[0.022; 0.096]	24%
IV on Clm/F : ω^2_5	0.0515 (0.0159)	[0.02; 0.083]	23%
IV on Qm/F : ω^2_6	0.736 (0.248)	[0.25; 1.22]	86%
IV on V _d /F : ω^2_7	0.274 (0.136)	[0.007; 0.541]	52%
Correlation between Qm/F and V _d /F : ω^2_8	0.412 (0.213)	[-0.005; 0.829]	64%
Residual variability			
σ^2_1 for tapentadol (additive model)	0.0843 (0.0181)	[0.049; 0.12]	Sd 0.29
σ^2_2 for tapentadol-o-glucuronide (additive model)	0.04 (0.016)	[0.009; 0.071]	Sd 0.20

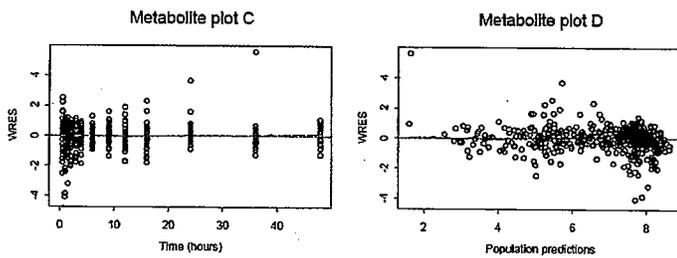
The diagnostic plots are shown below.

Diagnostic Plots of the final model for Parent and Metabolite

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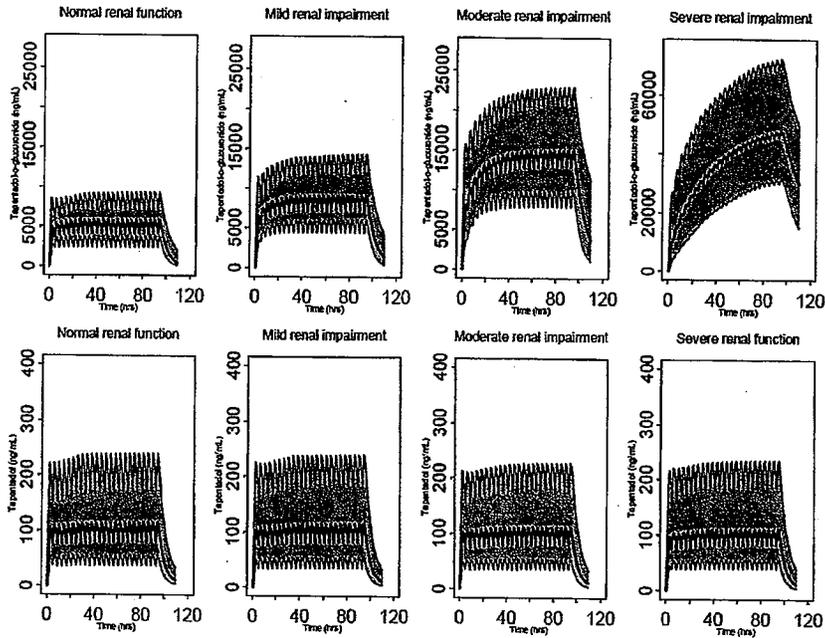


Note: Upper left: Observed data versus population predictions, upper right: Observed data versus individual predictions, lower left: Weighed residuals versus time, lower right: Weighed residuals versus population predictions. Dashed line represents a LOWESS smoother.

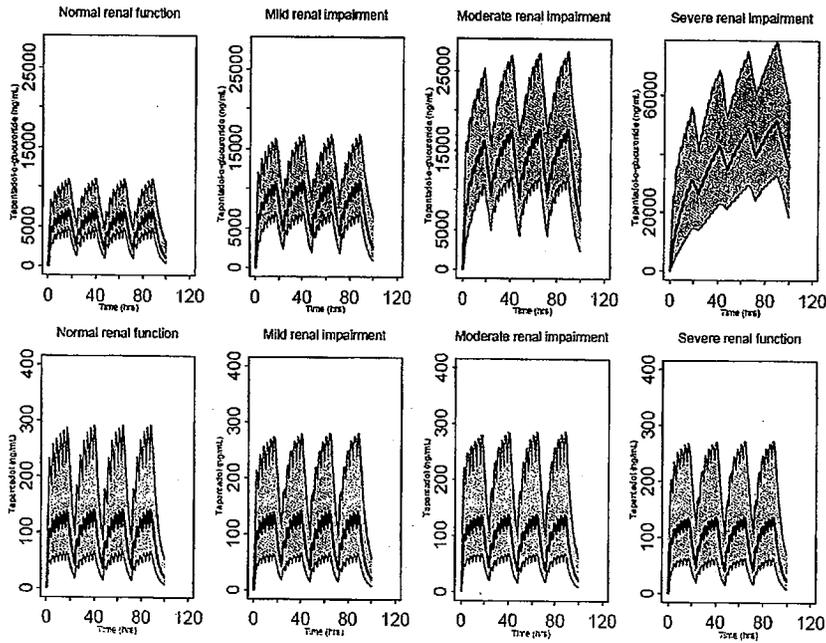
Results of the Simulation Scenarios

Simulations were based on the recommended dosing scenario and also for the one reflecting an overdose scenario:

Simulations Based on Scenario 1 - 100 mg q4h and Second Dose on Day 1, 1H After the First Dose:



Simulations Based on Scenario 2 - 100 mg q3h and Second Dose on Day 1, 1 H After the First Dose:



Conclusions on the metabolite analysis

A three-compartment disposition model for tapentadol combined with a two compartment model for tapentadol-o-glucuronide best described the PK of tapentadol and its major metabolite after oral administration in healthy subjects and subjects with renal impairment. The most important covariate was CRCL on the clearance of the metabolite. Simulations indicate dosing to subjects with mild renal impairment, moderate or severe renal impairment resulted in up to 1.5, 2.5 and 8.7 fold higher exposure to tapentadol-O-glucuronide compared to subjects with normal renal function, while the exposures to tapentadol was not affected.

EXPOSURE-RESPONSE ANALYSIS

The objectives of the exposure-efficacy response analysis were:

- (1) to provide supportive efficacy information through formal exposure-response modeling and to gain better understanding of the efficacious dose ranges of tapentadol IR, and,
- (2) to estimate the conversion ratios between tapentadol IR and oxycodone IR and

Clinical database

Two Phase 3 studies (PAI-3002/KF5503/33 and PAI-3003/KF5503/32) and 2 Phase 2B studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22) were used. Each of these studies had a different study design and duration, inconsistent dosing regimens including flexible dosing schemes, inconsistent rules regarding the supplemental rescue usage, as well as different primary efficacy variables. Therefore, these studies are not pooled and suitable analyses are performed separately for each. The exposure measures used in the exposure-response analysis include randomized doses, subject's average daily doses, and simulated PK exposure measures such as steady-state AUC, or C_{max} , C_{avg} , and AUC over a specific timeframe. The efficacy variables used included primary efficacy variables in all studies and in addition in study PAI-2003/KF5503/22, four secondary efficacy variables. The simulated PK exposure measures were obtained from the population PK analysis. All other data used came from the clinical data bases used for each study's statistical analysis and clinical report.

Modeling

The models built were either linear models or simple E_{max} models.

Linear Model - The linear model fits a linear relationship between the efficacy variable and dependent variables such as dose and other covariates:

$$Y_i = \beta_0 + \beta_1 \square Dose_i + \beta_2 \square Bpain_i + \epsilon_i$$

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where Y_i is the efficacy variable such as SPID 5D or SPID48 for the i -th subject and was assumed to be an independent observation following a normal distribution. $Dose_i$ is the dose or average daily dose for the i -th subject and $Bpain_i$ is the baseline pain intensity score for the i -th subject. $Dose_i$ and $Bpain_i$ were assumed to be fixed effects. ε_i is the error term for the i -th subject and follows a normal distribution. β_0 , β_1 , and β_2 are the model parameters to be estimated.

E_{max} - The E_{max} model fits a non-linear relationship between the efficacy variable and an

$$Y_i = E_0 + \frac{E_{max} * Exposure_i}{EC50 + Exposure_i} + \varepsilon_i$$

exposure measure:

where Y_i is the efficacy variable such as SPID₄₈ or SPRID₁₂ for the i -th subject and was assumed to be an independent observation following a normal distribution. $Exposure_i$ is an exposure measure for the i -th subject and was assumed to be a fixed effect. ε_i is the error term for the i -th subject and follows a normal distribution. E_0 , $EC50$, and E_{max} are the model parameters to be estimated. E_0 is the effect at zero exposure level, $EC50$ is the exposure level that produces half of the maximum effect, and E_{max} is the maximum obtainable effect when the exposure level approaches infinity.

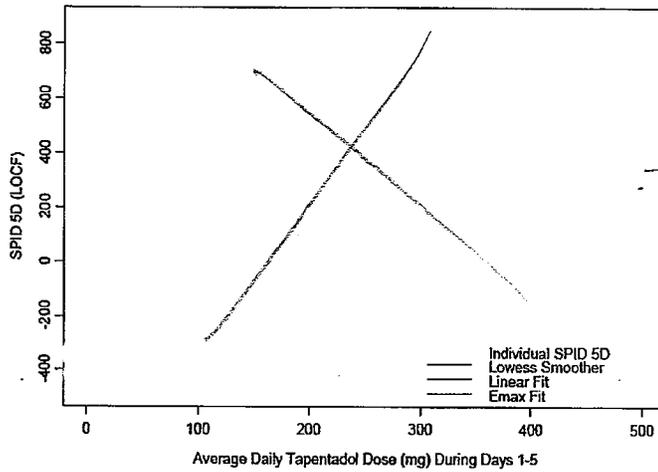
Study PAI-3002/KF5503/33

The primary efficacy end point in this study was the sum of pain intensity differences up to Day 5 (5-day SPID or SPID 5D) using LOCF imputation for missing pain intensity scores after premature discontinuation. The Applicant speculated that SPID did not demonstrate statistical separations among the 3 active randomized doses: 50 mg and 75 mg of tapentadol IR, and 10 mg of oxycodone IR. *It is noted that blood concentrations of study drug were not collected in this study.* Therefore, exposure-response analysis was not conducted using randomized doses or simulated PK measures, but was conducted using each subject's average daily dose, calculated as the total administrated dose (mg) divided by the dosing duration (day). Longitudinal analysis using the repeatedly measured pain intensity scores was also conducted using the average daily dose.

Dose-response using average daily dose and 5-day SPID - Due to the flexible dosing design, the average daily dose per subject varied. The range of the average daily dose for the 75 mg group almost entirely overlapped that of the 50 mg dose group. The average number of tablets taken is calculated as the total number of administrated tablets divided by the dosing duration (day).

Modeling results - SPID 5D (5-day SPID) is plotted against the average daily dose. A nonparametric Loess smoother, a linear regression line, and an E_{max} model were fitted.

Dose Response of SPID 5D (LOCF), Study PAI3002

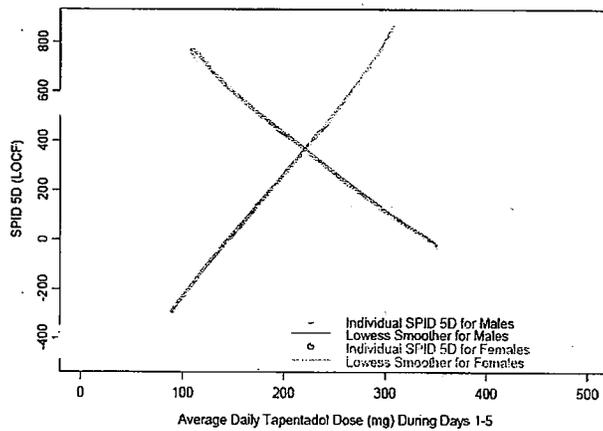


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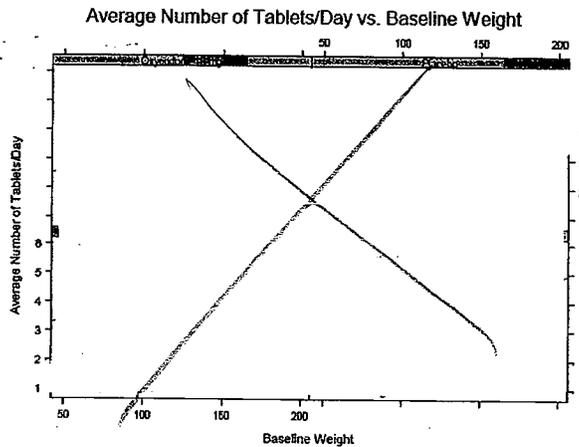
There were no apparent differences in the three model fits. For simplicity, the linear model was chosen to describe the relationship between average daily dose and SPID 5D.

Modeling and covariate influences – No gender effect was observed. It was observed that subjects with higher body weight took more average number of tablets per day.

Dose Response of SPID 5D (LOCF) by Gender, Study PAI3002



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Note: It seems that subjects self-adjusted the number of tablets taken based on baseline weight.

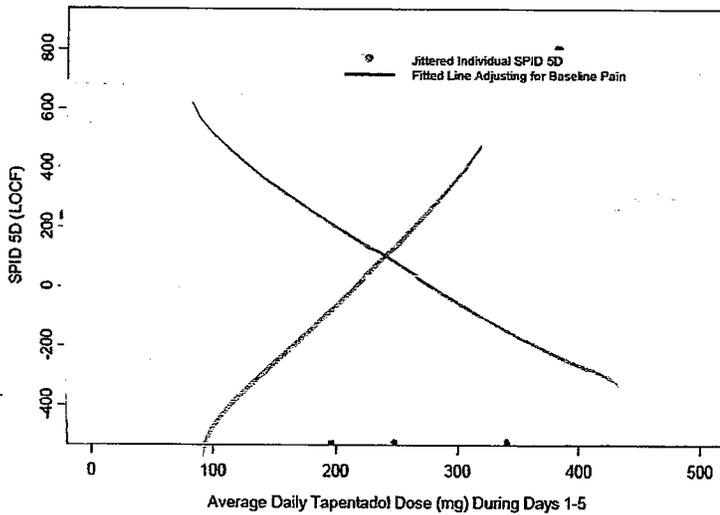
Results of dose-response of oxycodone IR using average daily dose and 5-Day SPID – A similar dose-response curve for Oxycodone IR, adjusting for baseline pain was built. The conversion ratio between tapentadol IR and oxycodone IR was estimated.

Approach 1 - Based on Dose-Response of Tapentadol IR - The average SPID 5D for oxycodone IR 10 mg group was 236.5 (± 222.82). Based on the final dose-response model for tapentadol IR obtained above, an equivalent tapentadol IR average daily dose to that of the randomized oxycodone IR 10 mg was estimated by setting the functional form of the equation describing the dose-response relationship of tapentadol IR equal to that observed for the oxycodone IR 10 mg group and solving the equation for the equivalent dose for tapentadol IR. Confidence intervals for the estimated equivalent dose were obtained in a similar manner from the 95% confidence bounds of the dose-response curve (see below). The estimated equivalent average daily dose of tapentadol IR to the randomized oxycodone IR 10 mg group was 248.3 mg with a 95% confidence interval (196.5, 340.8) mg. The estimated conversion ratio was 8.1 with 95% confidence interval of (6.4, 11.1), conditioned on the observed mean average daily dose of 30.7 mg for the oxycodone IR 10 mg group.

Dose Response of SPID 5D (LOCF), Study PAI3002

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Dose Response of SPID 5D (LOCF), Study PAI3002

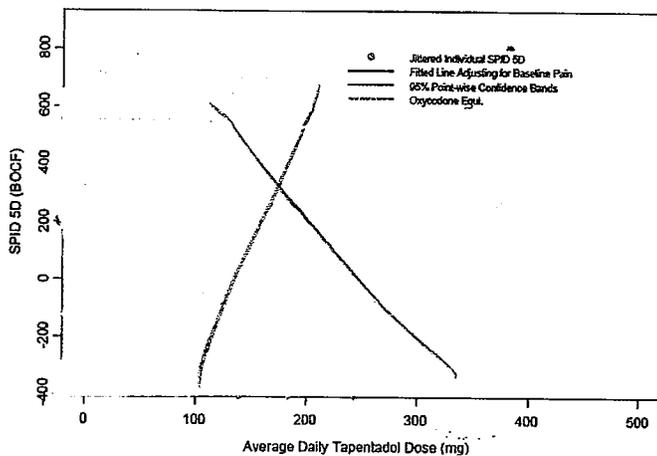


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Note: Conversion ratio between Oxycodone and Tapentadol was estimated based on the fitted dose-response linear model of Tapentadol IR.

Approach 2 - Based on Reverse Dose-Response of Both Tapentadol IR and Oxycodone IR Using 5-Day SPID - This approach reverses the dose-response relationship and builds linear models to describe average daily dose as functions of SPID 5D. This was done for both tapentadol IR and oxycodone IR. Due to the flexible-dosing design, both the average daily dose and SPID 5D can be viewed as random variables. This model assumed they jointly follow a bivariate normal distribution, then the conditional distribution of either one of the two follows a normal distribution when conditioned on the other. Within the observed dose ranges for tapentadol IR (37.5 mg to 420 mg) and oxycodone IR (10 mg to 60 mg), two linear models were built linking their respective average daily doses to SPID 5D. For each observed SPID 5D, the corresponding doses for both tapentadol IR and oxycodone IR was obtained from these models and a conversion ratio and a 95% confidence interval for this ratio were calculated. The standard error for this ratio was calculated based on the estimated standard errors for both the numerator and denominator using the first-order Taylor approximation of the ratio as a linear function of the numerator and denominator. These ratios were calculated for all values within the range of observed average daily doses and varied smoothly between 7.05 and 7.32. At the mean SPID 5D level of 204.4 and mean baseline pain level of 6.7 on the NRS scale, for the study population as a whole, the estimated conversion ratio was 7.17 (± 0.244) with 95% confidence interval (6.69, 7.65).

Dose Response of SPID 5D (BOCF), Study PAI3002



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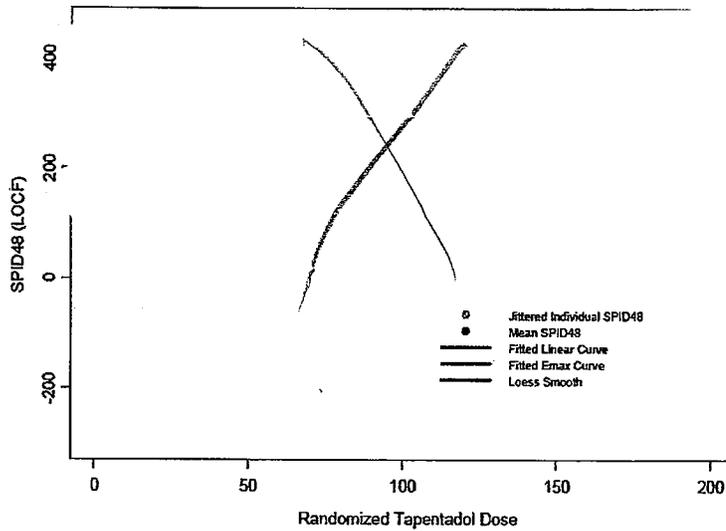
Note: Conversion ratio between Oxycodone and Tapentadol was estimated based on the fitted dose-response linear model of Tapentadol IR.

Study PAI-3003/KF5503/32

Similar methodologies were used as for study PAI-3002/KF5503/33. The primary efficacy end point in this study was the sum of pain intensity difference at Hour 48 (SPID₄₈) using LOCF imputation for missing pain intensity scores after premature discontinuation. The study demonstrated clear dose-response among the three tapentadol IR doses: 50 mg, 75 mg, and 100 mg. Sparse sampling of blood concentrations of study drug was performed in this study. Therefore, exposure-response analysis was conducted using each subject's randomized daily dose, average daily dose, calculated as the total administrated dose (mg) divided by the dosing duration (day), and simulated PK measures such as steady-state AUC, or C_{max}, C_{avg}, and AUC over 48 hours. Longitudinal analysis using the repeatedly measured pain intensity scores was conducted using the average daily dose.

Dose-Response of Tapentadol IR Using SPID₄₈ and Randomized Dose - SPID₄₈, the sum of pain intensity difference at Hour 48, was plotted against the randomized dose. A nonparametric Loess smoother, a linear regression line, and an E_{max} model were fitted. There were no apparent differences among the three model fits. For simplicity again, the *linear model* is chosen to describe the relationship between average daily dose and SPID₄₈.

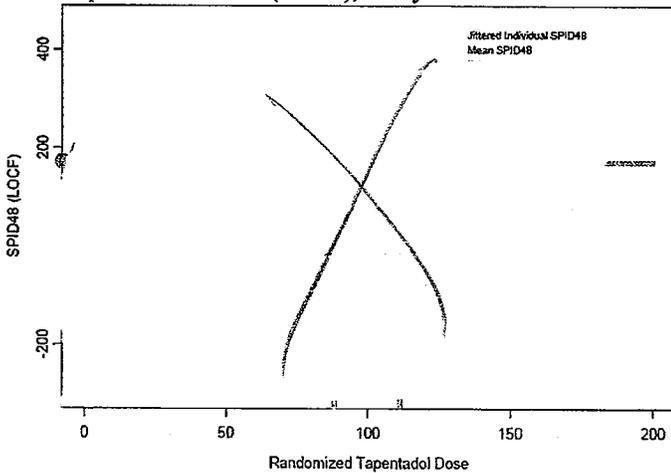
Dose Response of SPID₄₈ (LOCF), Study PAI3003



b(4)

Modeling and results - The parameter estimates for the linear model suggest that for a 10 mg increase in tapentadol IR, there will be an increase of 14.28 units in SPID₄₈. The estimated mean SPID₄₈ for the placebo group was 32.19 (± 9.716).

Dose Response of SPID48 (LOCF), Study PAI3003



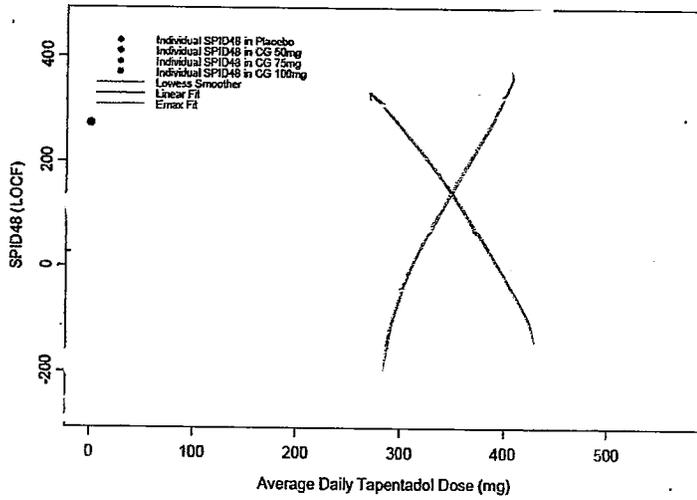
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Note: Conversion ratio between Oxycodone and Tapentadol was estimated based on the fitted dose-response linear model of Tapentadol IR using the randomized doses.

Dose-Response of Tapentadol IR Using SPID₄₈ and Average Daily Dose – SPID₄₈ was plotted against the average daily dose (see below). The nonparametric Loess smoother, a linear regression line, and an E_{max} model were fitted. There were no apparent differences among the three model fits. For simplicity, the linear model was chosen to describe the

relationship between average daily dose and SPID₄₈. These results show that for every 100 mg increase in tapentadol IR, there will be an increase of 31.8 units in SPID₄₈.

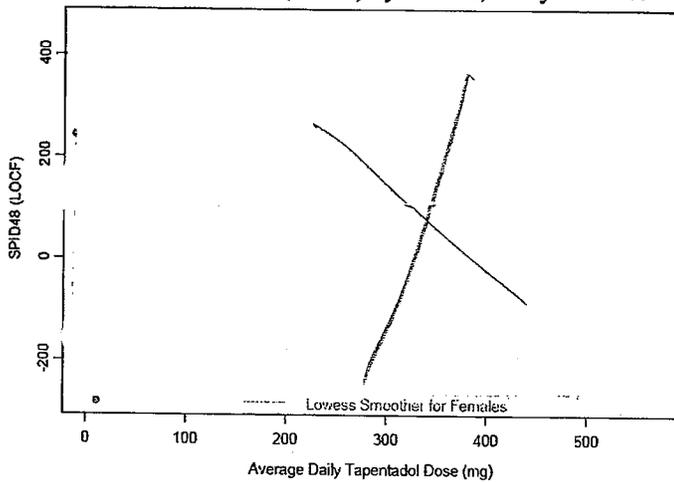
Dose Response of SPID₄₈ (LOCF), Study PAI3003
Dose Response of SPID₄₈ (LOCF), Study PAI 3003



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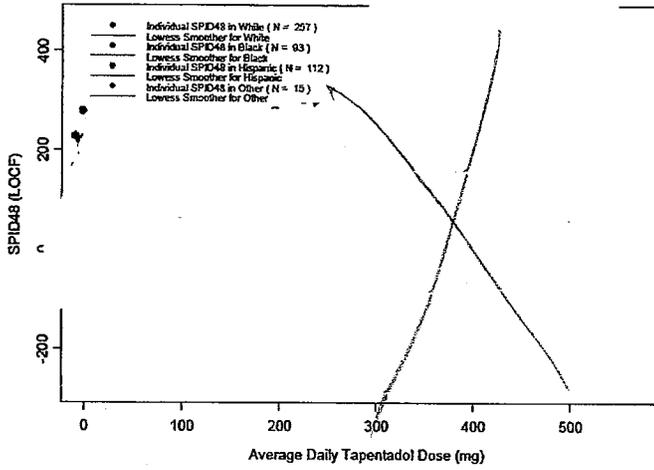
The effects of demographic variables such as sex, race, age, weight, and baseline pain was examined graphically. There were no apparent differences observed.

Dose Response of SPID₄₈ (LOCF) by Gender, Study PAI3003



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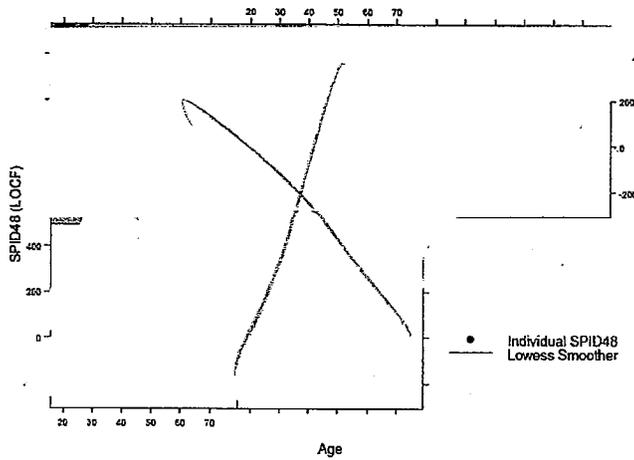
Dose Response of SPID₄₈ (LOCF) by Race, Study PAI3003



b(4)

Note: The race group "OTHER" only has 15 subjects. There are no apparent differences in dose-response among the different race groups.

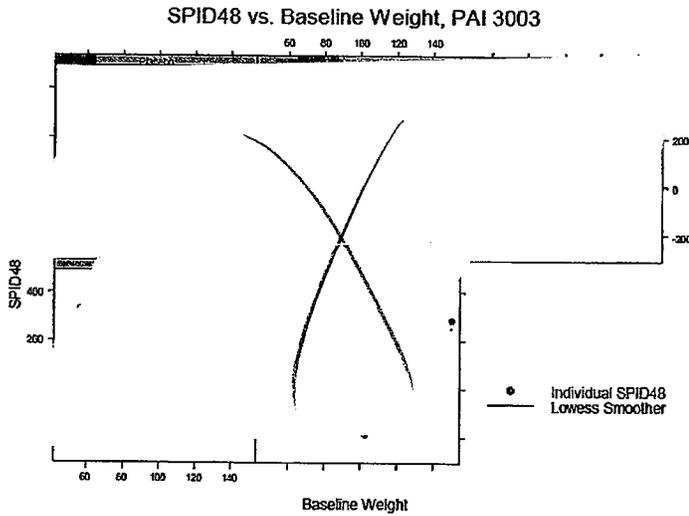
SPID48 vs. Age, PAI3003



b(4)

Note: There are no consistent influences of age on SPID₄₈

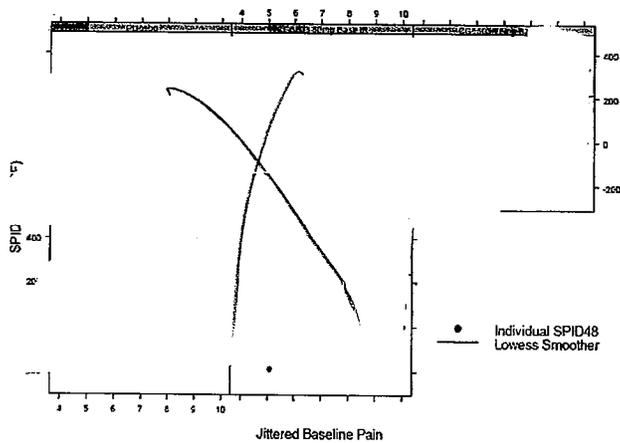
SPID48 vs. Baseline Weight, PAI3003



b(4)

Note: There are no consistent influences of weight on SPID₄₈.

SPID48 vs. Baseline Pain, PAI3003
SPID48 vs. Baseline Pain, PAI 3003



b(4)

Note: There are consistent influences of baseline pain intensity on SPID₄₈ across the groups.

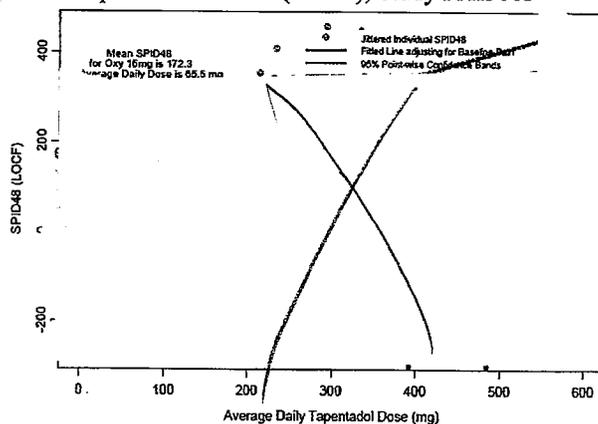
Dose-Response of SPID₄₈ for Oxycodone IR Using Average Daily Dose

A dose-response curve for Oxycodone IR adjusting for baseline pain was similarly built.

Approach 1 - Based on Dose-Response of Tapentadol IR Using Randomized Doses – The average SPID₄₈ for oxycodone IR 15 mg group was 172.3 (\pm 110.86). The estimated equivalent dose of tapentadol IR to the randomized oxycodone IR 15 mg group was 98.1 mg with a 95% confidence interval (88.4, 111.3) mg. The estimated conversion ratio was 6.54 with a 95% confidence interval of (5.89, 7.42).

Approach 2 - Based on Dose-Response of Tapentadol IR Using Average Daily Doses - An equivalent tapentadol IR average daily dose to that of the randomized oxycodone IR 15 mg was estimated by setting the functional form of the equation describing the dose-response relationship of tapentadol IR equal to that observed in the oxycodone IR 15 mg group and solving the equation for the equivalent dose of tapentadol IR. The estimated equivalent average daily dose of tapentadol IR to the randomized oxycodone IR 15 mg group was 432.4 mg with 95% confidence interval (392.4, 484.8) mg. The estimated conversion ratio is 6.6 with 95% confidence interval of (5.99, 7.4), conditioned on the observed mean average daily dose of 65.5 mg for the oxycodone IR 15 mg group.

Dose Response of SPID48 (LOCF), Study PAI3003



b(4)

Note: Conversion ratio between Oxycodone and Tapentadol was estimated based on the fitted dose-response linear model of Tapentadol IR using the average daily doses.

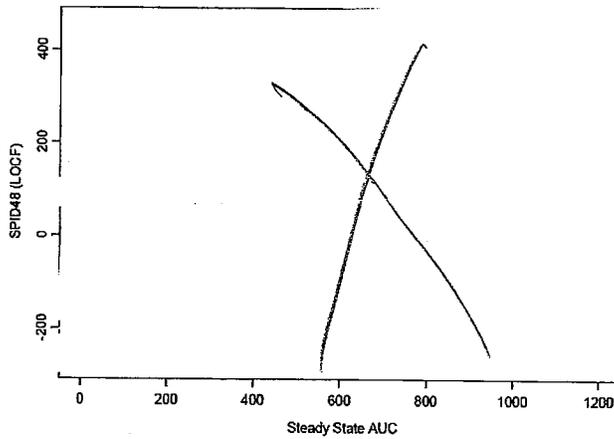
Exposure-Response Using Simulated PK Measures - SPID₄₈ was plotted against simulated PK measures such as steady-state AUC, or C_{max}, C_{avg}, and AUC over 48 hours. *The nonparametric Loess smoothers indicated non-linear relationships; therefore simple E_{max} models were fitted.* The E₀ and E_{max}, (which are the estimated efficacy effect for placebo and the estimated maximum obtainable efficacy effect when exposure approaches infinity,) estimated using all four simulated PK measures are similar and consistent with each other. This is expected because all these PK parameters were highly correlated. The maximum model predicted effect ranged from 216-260 on SPID₄₈ scale. When AUC at steady state was considered, half the maximal effect was observed at AUC_{ss} value of 400 µg.h/mL. It should be noted that this value lies between the observed AUC_{ss} values after multiple doses of 75 and 100 mgs (Study HP5503/13). At AUC_{ss} values of about 500 µg.h/mL, the effect approaches the maximal model predicted effect suggesting that the exposure-response curve is rather flat and therefore is of little consequence.

SPID₄₈ vs. Simulated Tapentadol PK Measures Parameter Estimates for E_{max} Models (Study R331333-PAI-3003; KF5503/32: Intent-to-Treat Analysis Set)

PK Measures	Parameter	Estimate (\pm SE)	95% Confidence Intervals
Steady State	E0	23.27 (\pm 10.49)	(2.71, 43.84)
State	E _{max}	260.75 (\pm 72.48)	(118.69, 402.80)
AUC	ED50 ^a	exp[5.99 (\pm 0.575)]	(128.70, 1227.91)
AUC	E0	11.56 (\pm 9.59)	(-7.22, 30.35)
During	E _{max}	247.08 (\pm 39.02)	(170.61, 323.55)
First 48 hours	ED50 ^a	exp[7.42 (\pm 0.44)]	(705.12, 3951.83)
C _{max}	E0	22.44 (\pm 10.53)	(1.80, 43.08)
During	E _{max}	216.54 (\pm 48.91)	(120.69, 312.40)
First 48 hours	ED50 ^a	exp[4.19 (\pm 0.56)]	(21.88, 198.81)
C _{avg}	E0	11.25 (\pm 9.11)	(-6.60, 29.09)
During	E _{max}	234.11 (\pm 34.37)	(166.75, 301.47)
First 48 hours	ED50 ^a	exp[2.84 (\pm 0.47)]	(6.86, 42.87)

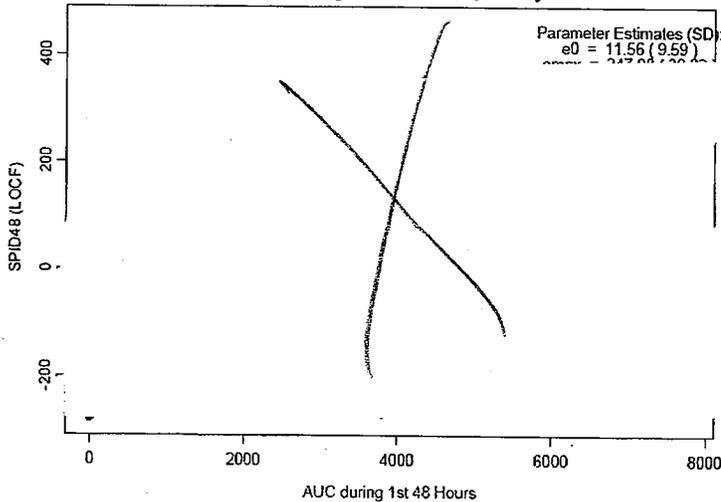
^a A log-normal distribution was assumed.

SPID48 (LOCF) vs. Steady State AUC, Study PAI3003



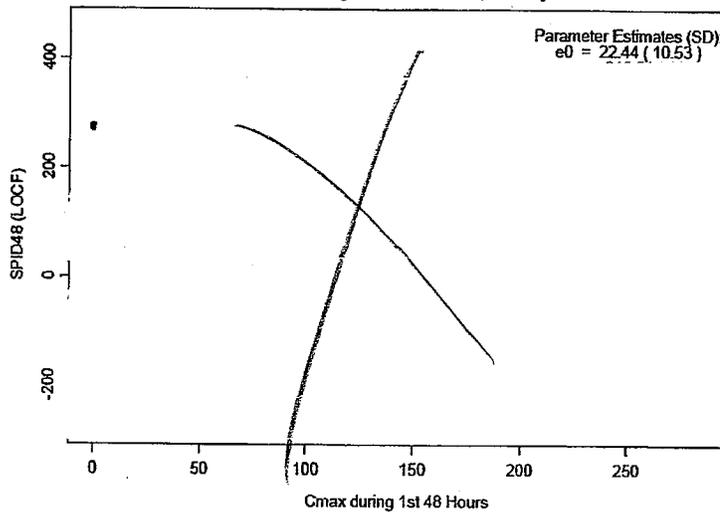
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SPID48 (LOCF) vs. AUC During 1st 48 Hours, Study PAI3003



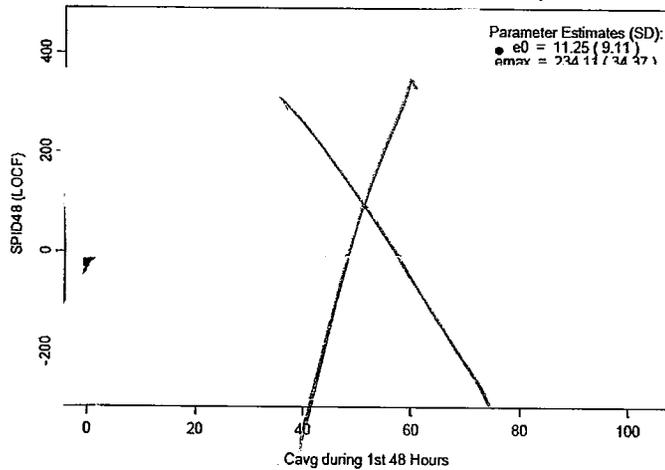
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SPID48 (LOCF) vs. Cmax During 1st 48 Hours, Study PAI3003



b(4)

SPID48 (LOCF) vs. Cavg During 1st 48 Hours, Study PAI3003



b(4)

Exposure-Efficacy Response Summary

Clear exposure-efficacy response relationships were observed for all efficacy variables (e.g. SPID 5D for PAI-3002/KF5503/33). Among the selected demographic variables examined (age, body weight, baseline pain, sex, and race), only baseline pain intensity significantly affected the analgesic response profile of tapentadol IR. Subjects with higher baseline pain intensity had higher pain reductions.

In study PAI-3002, which employed a flexible dose design, it was observed that subjects with higher body weight took a higher average number of tablets per day. Since the

population PK analysis suggests that the clearance of tapentadol IR increases as the body weight increases, the trend observed between dose intake and body weight could be due to the fact that heavier people eliminates the drug faster, thus requiring a higher dose to achieve adequate analgesia compared to lighter people. From the longitudinal analysis of the Phase 3 studies, it is apparent that the efficacy of tapentadol IR is maintained throughout the study duration.

These studies were not primarily designed to evaluate the conversion ratios between tapentadol IR and oxycodone. Two doses of oxycodone IR, 10 mg and 15 mg, were utilized in these clinical studies to establish assay sensitivity. However, none of the studies evaluated both of the doses in the same clinical study. Therefore modeling techniques were utilized to elucidate the equipotent doses of tapentadol IR and oxycodone IR and hence determine an adequate conversion ratio. The analyses conducted to estimate of the conversion factor are therefore exploratory in nature.

For study PAI-3002/KF5503/33, the estimated conversion ratio between tapentadol IR and oxycodone IR is 8.09 with 95% confidence interval of (6.40, 11.10) based on the dose-response analysis. An alternate method, using a reverse dose-response analysis put the estimate for conversion at 7.17 with 95% confidence interval (6.69, 7.65). In both these methods, SPID 5D with LOCF imputation was used as the response and average daily dose was utilized to construct the dose-response analysis. These analyses were repeated using SPID 5D with BOCF imputation and yielded estimated conversion ratios of 5.99 with 95% confidence interval of (4.54, 7.93) based on the dose-response analysis and 7.17 with 95% confidence interval of (6.70, 7.63) based on the reverse dose-response analysis. For study PAI-3003/KF5503/32, the estimated conversion ratio between tapentadol IR and oxycodone IR is 6.60 with 95% confidence interval of (5.99, 7.40) based on the dose-response analysis; is 5.01 with 95% confidence interval (4.75, 5.27) using the reverse dose-response analysis. In both these analyses SPID₄₈ with LOCF imputation and average daily dose was utilized to construct dose-response analysis. These analyses were repeated using SPID₄₈ with BOCF imputation and nearly identical estimates were obtained: 6.70 with 95% confidence interval of (6.03, 7.61) based on the dose-response analysis; is 5.05 with 95% confidence interval (4.79, 5.31) using the reverse dose-response analysis.

EXPOSURE-ADVERSE EVENT ANALYSIS

There are 6 main adverse events (nausea, vomiting, constipation, dizziness, somnolence, and pruritus) that can occur from taking opioids. These AEs have also been observed in the Phase 2 and 3 studies for tapentadol IR. The objectives of this analysis were (1) to assess the potential relationships between the occurrence of selected adverse events after oral administration of tapentadol IR and the extent of drug exposure, and (2) to identify potential risk factors that influence the occurrence of AEs following tapentadol IR administration. Nausea, vomiting, constipation, dizziness, somnolence, and pruritus were selected for analysis.

Dataset

Subjects with measured tapentadol concentrations from two (2) Phase 2 studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22) and one Phase 3 study (PAI-3003/KF5503/32) were included in the exposure-AE analysis (N=803). The corresponding measures for systemic exposure were estimated from the simulated individual PK profiles generated using the individual Bayesian post hoc parameter estimates from the population PK model, which included: AUC at steady state, calculated as randomized dose divided by individual CL/F estimated from the population PK analysis; Average daily AUC during the study, calculated as total AUC over the study duration divided by the study duration. Total AUC for each individual was estimated from the simulated individual PK profiles using the trapezoidal rule; Average concentration over the study duration estimated from the simulated individual PK profiles; C_{max} during the study: calculated as the maximum concentration for each individual from the simulated individual PK profiles; Randomized dose: dose to which the subjects were randomized; Average daily dose, calculated as total administered dose divided by the dosing duration (day).

Analysis of Time to First Event - The relationship between the time to first AE event for the 6 AE variables and the exposure to tapentadol was first subjected to graphical exploration (e.g., Kaplan-Meier plots) followed by modeling. Time to the first occurrence of an AE reflects rate of onset of this adverse event following drug exposure and its distribution was characterized by a survival function that is modeled through its hazard rate function. The Cox Proportional-hazards model implemented in S-PLUS (Version 7, Insightful, Seattle, WA) was used to model the time to first event data. The E_{max} functional form for the exposure measure was also explored.

The AE data were analyzed by pooling the three Phase 2 and 3 studies first. Since different study designs (e.g., duration of dosing) were adopted in the selected Phase 2 and 3 studies (12-h dosing and q4h regimen for PAI-2003/KF5503/22 and 72-h dosing and q4-6h regimen for PAI-2004/KF5503/21 and PAI-3003/KF5503/32), the treatment emergent window for KF5503/22 (60 h) was used to censor the AE data from PAI-2004/KF5503/21 and PAI-3003/KF5503/32. In addition, the AE data from the confirmatory Phase 3 study (PAI-3003/KF5503/32) were analyzed separately.

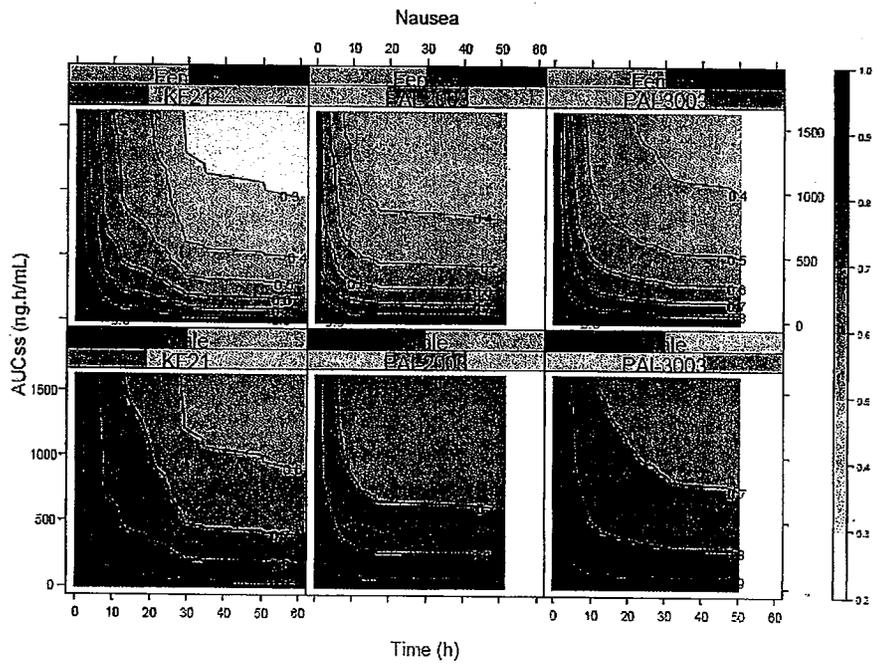
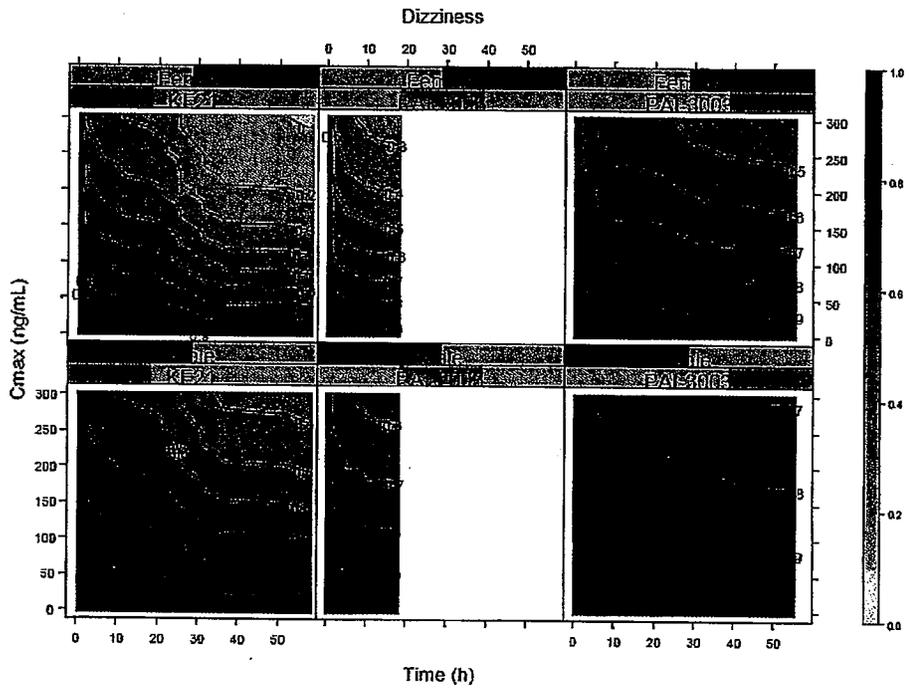
Analysis of Multiple Adverse Events – The relationships between the exposure to tapentadol and multiple events of the 6 selected AEs were also explored graphically.

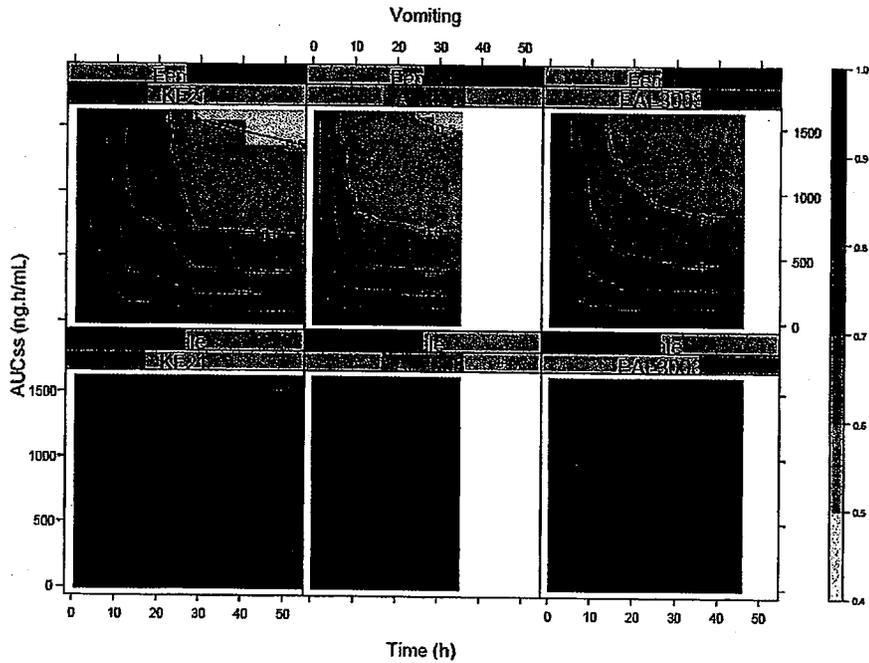
Results

Very clear exposure-response relationship was observed for all 3 AEs, except that the men tended to have vomiting episodes only at relatively higher exposure levels of tapentadol than women. Dizziness and nausea also exhibited unequivocal exposure-response and women seemed to experience more AEs than men.

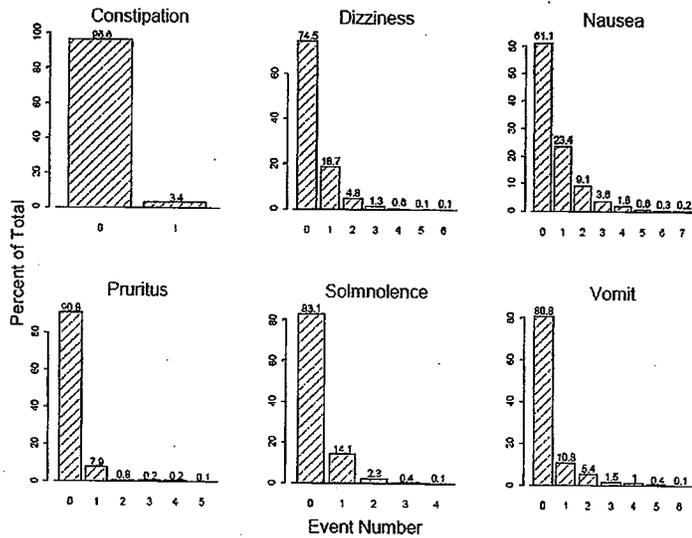
Expected Exposure-AE Response Relationship

The estimated exposure-AE response in male (lower panels) and female (upper panels) subjects for dizziness, nausea, and vomiting based on the final Cox models are presented. The contour lines in each panel represent the probability of survival. KF21 represents KF5503/21



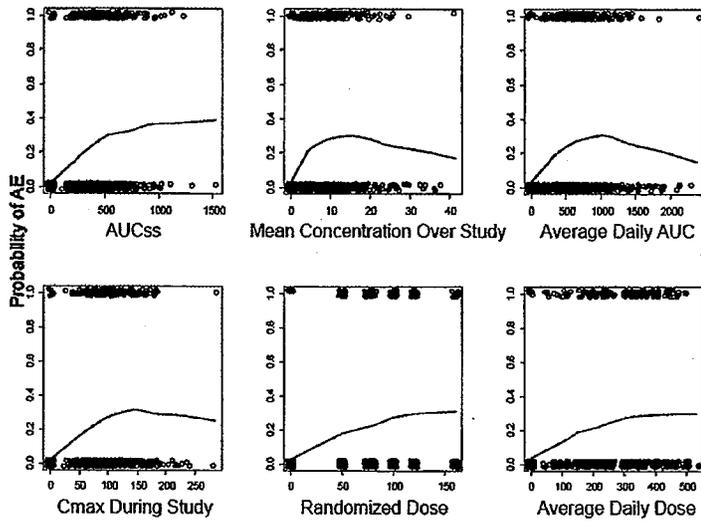


Frequency of Occurrence of AEs

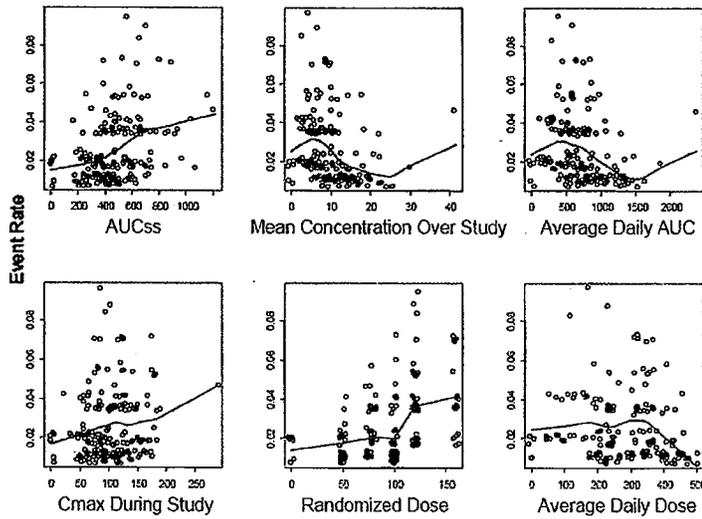


Relationship Between Occurrence of Vomiting and Exposure to Tapentadol

The probability of having vomiting during the study is plotted versus different exposure measures: steady-state AUC (AUCss), average concentration over the study duration, average daily AUC, maximum tapentadol concentration during the study, randomized dose, and average daily dose. The solid line in each panel is the LOWESS smoother.



Relationship Between Multiple Event Rate of Vomiting and Exposure of Tapentadol
 Event rate for multiple vomiting events (≥ 1), calculated by total vomiting count for a subject divided by the corresponding study duration, are plotted versus different exposure measures: steady-state AUC (AUCss), average concentration over the study duration, average daily AUC, maximum tapentadol concentration during the study, randomized dose, and average daily dose. The solid line in each panel is the LOWESS smoother.



Conclusion of Exposure-AE Analysis

The results from the exposure-AE analysis include bunionectomy studies with a large number of women (~90%) and refer to the postoperative setting. Clear relationships

between appropriate measures of exposure and time to first event were observed for most AEs. Although somnolence occurred more frequently in treatment groups than the placebo groups, the exposure-AE relationship was not apparent. Constipation and pruritus appeared to be associated with average exposure measures (average concentration, average daily dose, and average daily AUC). Dizziness and somnolence tended to be associated with peak exposure (C_{max}).

Onset of somnolence was reported to be rapid, and after 10h very few subjects reported new occurrences. The occurrence of the first incidences of nausea and vomiting was associated with exposure (randomized dose or AUC_{ss} calculated from randomized dose) following the first dose of tapentadol IR.

The time to first event of the three most frequently reported AEs (nausea, dizziness, and vomiting) were analyzed using Cox proportional hazards models. AUC_{ss} and C_{max} were identified as the most relevant exposure measures for these AEs based on both graphical exploration and likelihood evaluation. A sigmoidal E_{max} -type relationship was found between the occurrence of the first AEs and tapentadol exposure. The estimated maximum risk ratio (E_{max}) values for dizziness, nausea, and vomiting were 59.5 (95% CI: 25.6 – 138), 9.6 (95% CI: 5.97-15.4), and 44.4 (95% CI: 15.2-130), respectively.

Gender difference in the hazard ratio was observed, after accounting for the difference in drug exposure between men and women. For nausea and dizziness, the risk for women was generally higher than that for men and the hazard ratio (HR; or relative risk) ranged from 2 to 3 ($p < 0.01$). A higher HR (~5) was observed for vomiting ($p < 0.001$) for the pooled Phase 2/3 data. However, since no vomiting event was observed in men (N=61; 12.9% of the PAI-3003/KF5503/32 study population) in the Phase 3 study, the gender difference in vomiting risk may have been inflated. Due to the imbalance in the ratio of women (N=929) versus men (N=140) in the entire analysis dataset, the interpretation of these results is rather limited. Body weight was found to be a marginally significant but clinically irrelevant factor affecting vomiting ($p = 0.04$; HR: 0.99; 95%CI: 0.98 -1.00). The risk of vomiting declines by 1% when body weight increases by 1 kg. While age was found to have a statistically significant effect ($p = 0.01$; HR: 0.99; 95%CI: 0.98-1.00) on nausea when the pooled Phase 2/3 dataset was analyzed, its impact was likely clinically irrelevant because when the Phase 3 (PAI-3003/KF5503/32) data were analyzed alone the age effect was not statistically significant ($p = 0.36$; HR: 1; 95%CI: 0.98-1.01). The placebo effect for nausea was significant (>10%), while the placebo effect for vomiting was minimal (<3%). The AUC_{ss} of tapentadol was identified to be a predictor of the multiple events of vomiting. The exposure-multiple vomiting events exhibited an E_{max} -type relationship. Similar to time-to-first-event analysis, sex and body weight were identified as risk factors. Body weight had a borderline effect in determining the risk of vomiting events with an incidence rate ratio of 0.98 (95% CI: 0.97 – 0.99). The effect of body weight was statistically significant ($p < 0.001$), but of little clinical relevance. The higher the tapentadol exposure, the more vomiting events a subject would be expected to experience.

Overall, exposure to tapentadol was identified as the primary risk factor governing the time to first occurrence of nausea, vomiting, and dizziness and the event rate of multiple vomiting episodes. An E_{max} -type relationship was found between the occurrence of the AEs and tapentadol exposure. The estimated maximum risk (E_{max}) to experience these AEs could be more than approximately 10 times greater compared to the placebo groups. Gender difference was identified in the risk of these AEs: a higher risk was observed in women than in men in the analyzed data set. As similar gender difference has been observed for oxycodone and other centrally acting analgesics, the higher rate of the aforementioned adverse events in women can be regarded as a class effect. In placebo groups, women reported more nausea and dizziness incidences than men, which suggests women are more predisposed to these AEs compared to men. The results from the exposure-AE analysis should be interpreted with caution since the data used only include bunionectomy studies with a high predominance (approx. 90%) of women and only refer to the postoperative setting.

Overall population pharmacokinetics and modeling conclusions

- Pop.PK model - A two-compartment model with zero-order release followed by a first order absorption and first order elimination best described the PK of tapentadol IR following oral administration
 - Body weight might have influence on the PK of tapentadol. As body weight increased, the CL/F and V2/F of tapentadol increased, but the magnitude is small and no dose adjustment is warranted based on body weight.
 - Hepatic function (total bilirubin and total protein serum levels) – TB and TP influenced clearance of tapentadol, which decreased more than 60% in subjects with total bilirubin greater than 50 $\mu\text{mol/L}$, mostly due to moderately impaired patients (n=3). These results confirms the findings of the Phase 1 hepatic impairment study. Tapentadol should be used with caution in subjects with moderate hepatic impairment, and dose adjustment is warranted in this group of subjects.
 - Renal function (creatinine clearance (CRCL)) – CRCL was found not to be a statistically significant factor for the clearance of tapentadol.
 - Age - Age was not considered to be a clinically significant factor for the clearance of tapentadol.
 - Gender - Tapentadol clearance was slightly higher in men than in women after adjusting for all covariates that impact tapentadol clearance.
 - Race - The model predicted clearance of tapentadol in Black subjects, Hispanic-Latinos, and other non-White racial groups combined was approximately 17%, 11%, and 15%, lower respectively, than that of White subjects. The differences are minimal and dose adjustment may not be warranted.
 - There is no evidence that concomitant administration of ibuprofen, combination of hydrocodone and acetaminophen (for e.g. Vicodin), metoclopramide, acetaminophen, and ketorolac influence the PK of tapentadol.
- Renal impairment model - Creatinine clearance significantly influenced the exposure to the major active metabolite tapentadol-O-glucuronide. Tapentadol exposure was

not affected. The clearance of tapentadol-O-glucuronide is approximately 2.5-fold decreased in moderate renally impaired subjects compared to subjects with normal renal function.

- Exposure-response modeling - Based on two Phase 3 studies (PAI-3002/KF5503/33 and PAI-3003/KF5503/32) and two Phase 2 studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22), demonstrated exposure-efficacy relationships for all efficacy variables used in the four studies. These modeling results were used for empirically estimating the conversion ratios (equi-analgesic dose) between tapentadol and oxycodone IR. The point estimates of the conversion ratio ranged between 3.83 and 8.09, varying numerically depending on the endpoint under consideration, the analysis method including the method of imputation, and the study design.
- Exposure-AE modeling - Based on one Phase 3 study (PAI-3003/KF5503/32) and two Phase 2 studies (PAI-2004/KF5503/21 and PAI-2003/KF5503/22), exposure to tapentadol was identified as significant factor that increased the risk of time to first event of dizziness, nausea, vomiting and multiple-event rate for vomiting after oral administration of tapentadol IR. An Emax-type relationship was found between the occurrence of the AEs and tapentadol exposure. The estimated maximum risk (Emax) to experience these AEs could be more than approximately 10 times greater compared to the placebo groups.
 - It is noted that the exposure-AE analysis data included bunionectomy studies with a high predominance (approx. 90%) of women and only refer to the postoperative setting. In addition to tapentadol exposure, a gender difference in risk of time to first event was also identified. For nausea and dizziness, the risk of reporting an adverse event was generally higher in women than in men following treatment of tapentadol IR and the hazard ratio (relative risk) ranged between 2 to 3 ($p < 0.01$). A higher hazard ratio (relative risk) of about 5 for women relative to men was observed for vomiting ($p < 0.001$), possibly inflated by the data from PAI-3003/KF5503/32, where no vomiting was reported in any of the 61 men (12.9% of the PAI-3003/KF5503/32 study population). As a similar gender difference has been observed for oxycodone and other centrally acting analgesics, the higher rate of the aforementioned adverse events in women can be regarded as a class effect. In placebo groups, women reported more nausea and dizziness incidences than men, which suggest women are more predisposed to these AEs compared to men.

4.3 Consult Review (including Pharmacometric Reviews)

Not Applicable.

4.4 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics	
New Drug Application Filing and Review Form	
General Information About the Submission	
Information	Information

NDA Number	22-304	Brand Name	TBD	
OCPB Division (I, II, III)	II	Generic Name	Tapentadol HCl	
Medical Division	HFD-170	Drug Class	Opioid	
OCPB Reviewer	David Lee	Indication(s)	Pain	
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Immediate release tablet	
		Dosing Regimen	Single dose	
Date of Submission	1/2308	Route of Administration	Oral	
Estimated Due Date of OCPB Review	-	Sponsor	J&J	
Medical Division Due Date		Priority Classification	1S	
PDUFA Due Date	11/23/08			
Clin. Pharm. and Biopharm. Information				
	"X" included if filing at	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	x	1	1	
Isozyme characterization:	x			
Blood/plasma ratio:	x			
Plasma protein binding:	x			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	1	1	
multiple dose:	X	1	1	
Patients-				
single dose:	X			
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:	X			
Subpopulation studies -				
ethnicity:	X	1	1	
gender:	X			
pediatrics:				Deferral
geriatrics:	X			
renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD:				

Phase 1:				
Phase 2/3:	X			
PK/PD:				
Phase 1 and/or 2, proof of concept:	X			
Phase 3 clinical trial:				
Population Analyses -		█	█	
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:	X	1	1	
Relative bioavailability - solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1	1	
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS	X	1	1	
BCS class	X	1	1	
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		

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this page is the manifestation of the electronic signature.**

/s/

David Lee
9/30/2008 10:33:40 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
9/30/2008 10:36:34 AM
BIOPHARMACEUTICS