CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 200-533	Submission Date: 02/28/11
Submission Type;	Complete Response Resubmission;
Brand/Code Name:	Nucynta™ ER
Generic Name:	Tapentadol HCl Extended Release tablet
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Yun Xu, Ph.D. (acting)
OCP Division:	DCP 2
OND Division:	Division of Anesthesia, Analgesia and Addiction Products
Sponsor:	J&J Pharmaceutical Research and Development, L.L.C., On behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Relevant NDA(s)	22-304
Relevant IND(s):	61,345
Formulation; Strength(s):	Tablet; 50, 100, 150, 200 and 250 mg
Proposed Indication:	Management of moderate to severe chronic pain
Proposed Dosage Regimen:	As with many centrally acting analgesic medications, the dosing regimen of NUCYNTA™ ER should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to follow-up and provide oversight of treatment. The recommended NUCYNTA™ ER total daily dose is 100 mg to 250 mg twice daily approximately every 12 hours with or without food. Patients currently not taking opioid analgesics should begin NUCYNTA™ ER therapy with 50 mg twice a day. Patients receiving NUCYNTA™ (immediate-release formulation) may be converted to NUCYNTA™ ER by administering the same total daily dose. Administer half the total daily dose of NUCYNTA™ ER approximately every 12 hours. Daily doses greater than 500 mg of NUCYNTA™ ER have not been studied and, therefore, are not recommended.

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current Complete Response application. The Applicant submitted bioequivalence information bridging the PR2 Phase 3 clinical and tamper-resistant-formulation (TRF) to-be-marketed (TBM) tapentadol extended-release (ER) formulations.

From clinical pharmacology perspective, the clinical pharmacology information submitted in the Complete Response is acceptable provided a mutual agreement on the labeling language is reached between the Applicant and the Agency, and, the results from the Office of Scientific Investigation (OSI) inspection are acceptable In order to provide adequate information to address the issues stated in the Complete Response respect to clinical pharmacology, the Applicant needed to submit bioequivalence information from two doses, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations along with in vitro dissolution data in support of the biowaiver request for the intermediate strengths. The Applicant submitted bioequivalence information from all available strengths to address the concerns in the current complete response submission.

With respect to Labeling, there are minor changes recommended for the Clinical Pharmacology section of the label. The recommended changes to the package insert are made by striking out the existing texts and adding new texts, in RED fonts, where appropriate (see section 3: Detailed Labeling Recommendations).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tapentadol is a centrally-acting synthetic analgesic. [redacted] The exact mechanism of action is unknown; [redacted]

12.2 Pharmacodynamics

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

Effects on the cardiovascular system: There was no effect of therapeutic and supratherapeutic doses of tapentadol on the QT interval. In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects were administered five consecutive immediate-release formulation doses of tapentadol [redacted] 100 mg every 6 hours, [redacted] tapentadol 150 mg every 6 hours, placebo and a single oral dose of moxifloxacin. Similarly, the immediate-release formulation tapentadol [redacted] had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

[redacted]

12.3 Pharmacokinetics

Absorption

The m~~M~~ean absolute bioavailability after single-dose administration (fasting) of [redacted] NUCYNTA ER is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of NUCYNTA™ ER.

Dose proportional increases for AUC have been observed after administration of NUCYNTA™ ER over the therapeutic dose range.

[redacted]

[redacted]

Food Effect

The AUC and Cmax increased by 6% and 17%, respectively, when NUCYNTA ER [redacted] tablet [redacted] was administered after a high-fat, high-calorie breakfast. [redacted] NUCYNTA™ ER may be given with or without food.

…

Metabolism and Elimination

In humans, [redacted] about 97% of the parent compound is metabolized. Tapentadol is mainly metabolized via Phase 2 pathways, and only a small amount is metabolized by Phase 1 oxidative pathways. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% O-glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. The terminal half-life is on average 5 [redacted] hours after oral administration. The total clearance of tapentadol is [redacted] 1603 +/- 227 [redacted] ml/min.

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In Vivo NUCYNTA™ ER Formulation-Alcohol Interaction

Tapentadol may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

An in vivo study examined the effect of alcohol (240 mL of 40%) on the bioavailability of a single dose of 100 mg and 250 mg of NUCYNTA™ ER tablet in healthy, fasted volunteers. After [redacted] co-administration of 100 mg NUCYNTA™ ER tablet and alcohol, the mean Cmax value [redacted] increased by 48% [redacted] compared [redacted] to control-[redacted]

[redacted] with a range [redacted] of 0.99-fold to 4.38-fold [redacted] The mean tapentadol AUClast and AUCinf were increased by 17%; the Tmax and t½ were unchanged. After [redacted] co-administration of a 250 mg NUCYNTA™ ER tablet and alcohol, [redacted] the mean Cmax value increased by [redacted] 28% [redacted] compared [redacted] to control. [redacted] with range [redacted] of [redacted] -0.90-fold to 2.67-fold. The mean tapentadol AUClast and AUCinf were increased by 16%; the Tmax and t½ were unchanged.

1.2 Phase IV Commitments

Not applicable.

1.3 Summary of Clinical Pharmacology Findings

In the original NDA submission, the Applicant did not submit bioequivalence information bridging the PR2 Phase 3 clinical and tamper-resistant-formulation (TRF) to-be-marketed (TBM) tapentadol extended-release (ER) formulations. Instead, the Applicant utilized in vitro-in vivo correlation (IVIVC) data to bridge the two formulations. This information was reviewed by Dr. Sandra Suarez (Biopharmaceutics Reviewer, Office of New Drug Quality Assessment (ONDQA)). During the assessment of the IVIVC information, there were several deficiencies related to the proposed IVIVC models and the findings were conveyed to the Applicant on April 21, 2010, during a teleconference. The Applicant was asked to 'reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model [redacted].' In response, the Applicant submitted an amendment to pending application on May 13, 2010, proposing to perform new fasted bioequivalence trials between the PR2 Phase 3 clinical and TRF TBM on the 150 mg and 200 mg strengths and proposing to submit the information prior to the end of the 10-month review cycle (See Biopharmaceutics Review dated June 14, 2010). Thus, from clinical pharmacology perspective, since the proposed IVIVC modeling data was not sufficient to adequately bridge the PR2 and TRF TBM formulations, the clinical pharmacology section of the original NDA was not acceptable. In order to provide adequate information, the Applicant was informed to submit bioequivalence information from two doses, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations along with in vitro dissolution data in support of the biowaiver request for the intermediate strengths. This approach was discussed in a teleconference between the Applicant and the Agency on November 9, 2010. The Agency agreed with the proposed approach in general, i.e., conducting new bioequivalence studies, pending on the review of the study results.

In this current Complete Response submission, the Applicant conducted bioequivalence studies for all strengths, 50, 100, 150, 200 and 250 mg. The results indicated that the TRF TBM tablets (100, 150, 200 and 250 mg) were bioequivalent to the PR2 tablets. The 50 mg strength met the bioequivalence criteria in terms of AUC, but the TRF formulation showed slightly higher (about 29%) Cmax compared to the PR2 formulation. However, 50 mg dose will be strictly used for a titration purpose. Therefore, the result is considered acceptable after discussion with the clinical team.

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 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.

Additional information submitted by the Applicant

The Applicant submitted completed clinical studies in the current Complete Response. The following table contains clinical studies which may contain tapentadol exposure information. These studies were not reviewed due to the fact majority of the studies were conducted with other formulations, e.g., i.v., oral solution, IR, PR2, etc., which are not the proposed TRF extended release formulation. An exception was that a cursory review was conducted for Study HP5503/51, a food effect study (with a 'standard Japanese meal - total calories are approximately 700 - 800 kcal; percentages of energy of contents of meal are: carbohydrate 50-70%, protein less than 20%, lipid 20-30%) with 100 mg TRF ER formulation Japanese healthy men (n=12). (b) (4) This study was reviewed briefly since TRF ER formulation was utilized. The results indicated that the geometric means for Cmax and AUC of tapentadol under fed conditions were approximately 54 and 12% higher compared to under fasted conditions (see table below). The observed arithmetic mean Cmax and AUC values for fed and fasted conditions were 65.7 and 42.8 ng/mL, and, 585 and 520 ng·h/mL, respectively. The provided information was considered not to be critical for this application simply because this study utilized a 'standard Japanese meal', not an Agency's recommended high-fat meal, and, the fact that the studied population does not represent the population majority in the US. Additionally, the high-fat food effect information was assessed in the original NDA submission, and, that study was considered as a pivotal food effect study; in that assessment, the AUC and Cmax increased by 6% and 17%, respectively, when TRF ER tablets were administered after a high-fat meal. The tmax was prolonged by about 1 hour with a median tmax of 6.00 hours (range: 2.98-12.0 hours) in the fed state and 5 hours (range: 2.00-12.0 hours) in the fasted state. In Phase 3 studies, tapentadol ER tablets were also administered without restriction to food. Therefore, we recommend that tapentadol ER tablets may be taken without restriction to food.

Summary of Analysis on the Pharmacokinetic Parameters of Tapentadol – Food Effect Assessment in Japanese Healthy Men (Study R331333-PAI-1052; HP5503/51-: Pharmacokinetic Analysis Set)

	Tapentadol TRF (fed) 100 mg (Test) (Geometric mean) (n=12)	Tapentadol TRF (fasted) 100 mg (Reference) (Geometric mean) (n=12)	Ratio Test/ Reference , %	90% CI	%CV
C_{max}, ng/mL	63.45	41.06	154.52	136.79–174.53	16.3
AUC_{last}, ng.h/mL	559.96	498.23	112.39	105.26–120.01	8.8
AUC_{∞}, ng.h/mL	562.57	501.96	112.07	104.93–119.71	8.8

%CV=% Coefficient of Variation; TRF=tamper resistant formulation; CI=confidence interval, N=number of subjects included in the inferential statistical analysis

Additional clinical studies submitted in the Complete Response submission:

Study Number	Study Design	Treatment	Comment
HP5503/65	Single-center, sequential S- and M-dose administration, DB, R. To evaluate the PKs of S- and M-doses of tapentadol administered by i.v. infusion in healthy subjects	Single dose on Day 1 and multiple doses Q4h on Days 3 and 4 for a total of 7 doses. -Tapentadol i.v. 5 mg, 15 and 25 mg Day 1 and Days 3/4 separated by a 48-h washout i.v. infusion over 2 minutes	i.v. formulation – not reviewed
HP5503/69	Single-center, S-dose, OL, R, 2-period crossover. To assess BE of 2 tapentadol ER (PR) 25-mg tablets and a tapentadol ER (PR2small) 50-mg tablet in healthy subjects under fasted conditions.	Single dose per period -Tapentadol PR 25 mg x 2 -Tapentadol PR2small 50 mg Two 1-day periods with 7-14 days washout between Oral	PR formulation – not reviewed
HP5503/59	Single-center, S-dose, OL, R, 2-period crossover. To compare the BA of tapentadol 100-mg oral solution (OS) and tapentadol 100-mg IR tablet.	Single dose per period -Tapentadol IR 100 mg -Tapentadol OS 100 mg Two 1 day periods with 7-14 days washout between.	IR and oral solution formulations – not reviewed
HP5503/51 R331333-PAI-1052; US	Single-center, SD, OL, R, 2-period crossover. To evaluate the effect of food (standard Japanese meal) on the PKs of tapentadol TRF in healthy Japanese men.	Single dose per period -Tapentadol TRF 100 mg (fed) -Tapentadol TRF 100 mg (fasted) Two 1-day periods with 7-14 days washout between	Conducted in Japanese subjects (b) (4) – cursory review
HP5503/64 (GRT); R331333-PAI-1053	Single-center, S-dose, OL, R, 2-period crossover. Evaluate the relative BA of the tapentadol TRF tablet formulation to the tapentadol PR1 tablet formulation in Japanese healthy subjects under fasted conditions.	Single dose per period -Tapentadol TRF 100 mg -Tapentadol PR1 100 mg Two 1-day periods with 7-14 days washout between Oral	Comparison to PR1 formulation – not reviewed

2 QBR

2.1 General Attributes of the Drug and Drug Product

2.1.1 What are the highlights of the pharmaceutical development of tapentadol ER tablet formulation?

Several different formulations were developed: PR1 formulation was mostly used in Phase 1 and 2 clinical trials; PR2 formulation was mostly used in Phase 3 clinical trials; the tamper-resistant formulation (TRF) was subsequently developed to offer tamper-resistant properties with similar dissolution profile to PR2 formulation. The TRF tapentadol ER formulation is designated as commercial formulation.

Overall tablet formulation development

Phase 1 (P1) and 2 clinical trials were conducted with (b) (4) formulations of the tapentadol ER tablets, designated PR1. Phase 3 (P3) clinical trials, as well as additional P1 studies during that period, were conducted with the PR2 formulations. The PR2 tablets were similar in ingredients and dissolution to the PR1 tablets. The Applicant stated that the PR2 formulations were developed to accommodate the higher doses required for P3 clinical trials.

The tamper-resistant formulations (TRF) were subsequently developed to offer tamper-resistant properties with similar dissolution profile to the P3 PR2 formulations. The TRF tapentadol ER formulation is designated as commercial formulation. There are three TRF formulations, namely, pilot, registration and to-be-marketed (TBM) formulations. Registration stability batches of TRF tapentadol ER tablets were manufactured by J&JPRD (Beerse, Belgium). To-be-marketed stability batches of TRF tapentadol ER tablets were manufactured at the proposed commercial site, Janssen Ortho, L.L.C. (JOLLC) (Gurabo, Puerto Rico). (b) (4) ee original new drug application review dated 8/9/10 for further discussion on formulations.

2.1.2 What is tapentadol to-be-marketed formulation?

Tamper-resistant formulation is the to-be-marketed formulation.

Major excipients used in the TRF formulation

The excipients contained in tapentadol ER tablets are listed below. The excipients used in the core tablet are GRAS (generally regarded as safe) and are of compendial grade.

Excipients	Function	Reference to Standard
Polyethylene Oxide	(b) (4)	NF
Hypromellose (b) (4)		USP
Polyethylene Glycol (b) (4)		NF
Vitamin E (b) (4)		In-house
(b) (4)		In-house
		In-house

Compositions of the clinical, registration stability, commercial site stability and proposed commercial TRF tapentadol extended-release tablets are provided in the table below.

Composition of tapentadol TRF tablets: Pilot, Registration stability and to-be-marketed batches

Formulation	Pilot batches [a]			Registration stability batches and to-be-marketed batches [b]				
Formulation number	TF5, 6323SF	TF4, 6322SF	TF3, 6316SF	F029	F030	F031	F032	F033
Dose strength (tapentadol)	50 mg	100 mg	250 mg	50 mg	100 mg	150 mg	200 mg	250 mg
Tapentadol hydrochloride, mg	(b) (4)							
Polyethylene oxide, mg *(% w/w of core)*								
Hypromellose (b) (4) *(% w/w of core)*								
Polyethylene glycol (b) (4) *(% w/w of core)*								
Vitamin E, mg *(% w/w of core)*								
Tablet core weight								
Film coat (b) (4)								
Printing ink [c]								
Tablet size								
Tablet shape								
[a] (b) (4)								
[b]								
[c]								
[d]								

NA= not applicable

Composition core of the tapentadol TRF tablets: registration and TBM batches only

Component	Quality Reference	Function	Dose Strength (Free Base of Tapentadol)									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
Tapentadol HCl (R331333)	Non-compendial	(b) (4)										
Polyethylene Oxide	NF											
Hypromellose (b) (4)	USP											
Polyethylene Glycol (b) (4)	NF											
(b) (4)												
Vitamin E	USP											
Polyethylene Glycol (b) (4)	NF											
Total Core Tablet Weight												
[a] (b) (4)												
[b]												

-- = Not applicable

Composition coating of the tapentadol TRF tablets: registration and TBM batches only

Film Coat	Quality Reference	Function	Dose Strength									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
(b) (4)	Noncompendial											(b) (4)
	Noncompendial											
	Noncompendial											
	Noncompendial											
	Noncompendial											
	USP											
	Noncompendial											
	Noncompendial											
	NF											
Propylene Glycol[b]	USP											
[a] [b]		(b) (4)										

-- = Not applicable

2.1.3 What are the proposed dosage and route of administration?

Tapentadol HCl tablet is taken orally. As per the proposed package insert, the proposed tapentadol dosage and administration is as follows:

As with many centrally acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the previous experience with opioid analgesics and the ability to follow-up and provide oversight of treatment.

The NUCYNTA™ ER tablet formulation is designed to increase mechanical resistance to breakage and crushing. NUCYNTA™ ER tablets are to be swallowed whole with the aid of liquids, and must not be broken, chewed, dissolved, or crushed. Taking broken, chewed, dissolved, or crushed NUCYNTA™ ER Tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol.

The recommended NUCYNTA™ ER daily dose is 100 mg to 250 mg twice daily, taken approximately every 12 hours, with or without food.

Patients Currently Not Taking Opioid Analgesics
Patients currently not taking opioid analgesics should begin NUCYNTA™ ER therapy with 50 mg twice a day (approximately every 12 hours) and then be individually titrated to adjust to an optimal dose within the therapeutic range of 100 mg to 250 mg twice daily.

Patients Currently Taking Opioid Analgesics
When switching from opioids to NUCYNTA™ ER and choosing the initial dose, the nature of the previous medication, administration and the mean total daily dose should be taken into account.

Conversion from NUCYNTA™, the immediate-release formulation, to NUCYNTA™ ER
NUCYNTA™ can be converted to approximately equivalent total daily dose of NUCYNTA™ ER, and vice-versa, with equivalent efficacy and comparable tolerability. The total daily dose of

NUCYNTA™ ER should be divided into two equal administrations per day separated by approximately 12-hour intervals. As an example, a patient receiving 200 mg/day immediate-release formulation NUCYNTA™ may take 100 mg NUCYNTA™ ER twice a day (approximately every 12 hours). Although the total daily maintenance dose of immediate-release formulation NUCYNTA™ may be as high as 600 mg per day, total daily doses greater than 500 mg of NUCYNTA™ ER have not been studied and, therefore, are not recommended.

Individualization of Dose

NUCYNTA™ (the immediate release formulation) can be converted to approximately equivalent total daily dose of NUCYNTA™ ER, and vice-versa, with equivalent efficacy and comparable tolerability. Therefore, the dose recommendations in special population for NUCYNTA™ ER will be consistent with those in NUCYNTA™ label.

Pain relief and other opioid effects should be frequently assessed. In clinical practice, titration of the total daily dose of NUCYNTA™ ER should be based upon the amount of supplemental opioid utilization, severity of the patient's pain, and the patient's ability to tolerate NUCYNTA™ ER. Patients should be titrated to a dose providing a meaningful improvement of pain with acceptable tolerability.

Experience from clinical studies has shown that a titration regimen in increments of 50 mg NUCYNTA™ ER twice daily every 3 days was appropriate to achieve adequate pain control in most patients. Total daily doses greater than 500 mg of NUCYNTA™ ER have not been studied and, therefore, are not recommended [see Clinical Studies (14)].

If signs of excessive opioid-related adverse experiences are observed, the dose can be reduced depending on patient status and medical judgment. Adverse events can be treated symptomatically, as well. Once adverse events are under control, upward titration can continue to an acceptable level of pain control. During periods of changing analgesic requirement, including initial titration, frequent contact is recommended between physician and or health care provider and the patient.

Cessation of Therapy

Tapering NUCYNTA™ ER therapy was not required in the clinical studies; however, potential withdrawal symptoms may be reduced by tapering NUCYNTA™ ER [see Withdrawal].

Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment [see Clinical Pharmacology].

NUCYNTA™ ER has not been studied in patients with severe renal impairment. The use in this population is not recommended.

Hepatic Impairment

No dosage adjustment is recommended in patients with mild hepatic impairment [see Clinical Pharmacology].

NUCYNTA™ ER should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg NUCYNTA™ ER and not be administered more frequently than once every 24 hours. Further treatment should reflect maintenance of analgesia with acceptable tolerability [see Clinical Pharmacology].

NUCYNTA™ ER has not been studied in patients with severe hepatic impairment and use in this population is not recommended [see Warnings and Precautions].

Elderly Patients

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses.

There is no dosage and administration for pediatric patients and nursing mothers.

2.2 General Clinical Pharmacology – not applicable

2.3 Intrinsic Factors – not applicable

2.4 Extrinsic Factors – not applicable

2.5 General Biopharmaceutics

2.5.1 Are PR2 and To-be-marketed TRF formulations bioequivalent?

Summary: Tapentadol TRF and PR2 tablets are bioequivalent based on serum Cmax, AUClast, and AUCinf at the therapeutic doses of 100, 150, 200, and 250 mg when administered to healthy subjects in the fasted state.

Tapentadol TRF and PR2 tablets are bioequivalent for the 50-mg tapentadol titration dose based on the estimates of serum AUClast and AUCinf. Bioequivalence was not demonstrated based on serum Cmax. However, 50 mg dose will be strictly used for a titration purpose.

Based on cross-study comparisons, the systemic exposures of tapentadol are linear for the TRF and the PR2 tablets.

Bioequivalence study design

The bioequivalence studies compared the to-be-marketed tapentadol TRF tablets, produced at the commercial manufacturing site at Gurabo, Puerto Rico, US, to the current tapentadol PR2 tablets manufactured in Springhouse, PA, US used in pivotal Phase 3 efficacy studies in healthy subjects under fasted conditions.

All of the bioequivalence studies had the following study design: Study was an open-label, single-center, in-house, randomized, 2-way crossover study of a single dose of tapentadol to evaluate the bioequivalence, safety, and tolerability of the to-be-marketed tapentadol TRF tablet with the currently used tapentadol PR2 tablet in healthy men and women under fasted conditions. Subjects were included in the analyses if they did not vomit after first 6 hours post dosing and during at least 1 treatment period. Subjects fasted for at least 10 hours overnight prior to dosing. Study drug was administered with 240 mL of noncarbonated water. Subjects consumed food no earlier than 4 hours after study drug administration. Subjects received standardized meals given at the same time in each treatment period. Subjects had a standard diet. Water was allowed ad libitum, except for 2 hours before and after study drug administration. Study drug administration was separated by a washout period of at least 7 and no more than 14 days. Blood samples were collected at predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48 hours post dose.

For each treatment, descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, geometric mean (PK parameters only), median, minimum, and

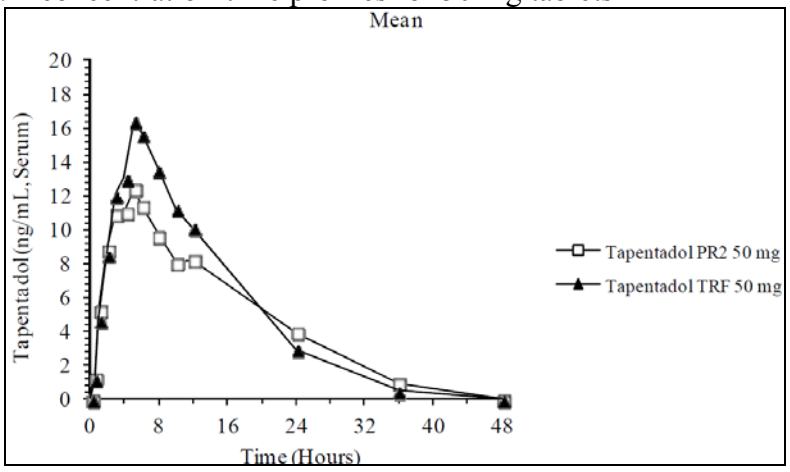
maximum were calculated for tapentadol serum concentrations at each sampling time and for all PK parameters of tapentadol. The primary parameters of interest for the statistical analysis were AUClast, AUC∞, and Cmax of tapentadol. The analysis was performed on log-transformed estimated PK parameters A mixed-effect model that included treatment, period, and treatment sequence as fixed effects, and subject as random effect was used to estimate the least squares means and intrasubject variance. Using these estimated least squares means and intrasubject variance, the point estimate and 90% confidence intervals (CI) for the difference in means on a log scale between Treatment A and Treatment B were constructed. The limits of the CI were retransformed using antilogarithms to obtain 90% CI for the ratios of the mean values for AUC and Cmax of the test to reference formulation. Tapentadol TRF and tapentadol PR2 doses were considered bioequivalent if the 90% CI for the ratio of the means (TRF/PR2) fell within 80% to 125%.

50 mg titration dose

Study HP5503/82 evaluated tapentadol 50 mg tablets. Sixty-four subjects (32 men and 32 women) were enrolled for the study. The batch numbers for test (TRF 50-mg tablet) and reference (PR2 50-mg tablet) products were 9EG9279-X and PD3137, respectively. Subjects were excluded from bioequivalence analyses if they did not complete both treatments and vomited anytime during the treatments.

The mean serum concentration-time profiles were somewhat dissimilar between two formulations.

The mean serum concentration-time profiles for 50 mg tablets



The tapentadol pharmacokinetic parameters and a summary of statistical results are presented below.

Mean (±SD) Serum Pharmacokinetic Parameters of Tapentadol
(Study HP5503/82: Pharmacokinetic Data Analysis Set)

Treatment	N	Tapentadol TRF 50 mg (Test)			N	Tapentadol PR2 50 mg (Reference)		
PK Parameters		Mean	±	SD		Mean	±	SD
C_{max}, ng/mL	62	16.9	±	5.36	62	12.8	±	3.44
[a]t_{max}, h	62	5		(2.00-11.98)	62	5		(2.00-12.00)
AUC_{last}, h.ng/mL	62	236	±	66.1	62	215	±	61.4
AUC_{∞}, h.ng/mL	62	242	±	64.8	61	224	±	60.7
$t_{1/2}$, h	62	5.9	±	1.7	61	7.7	±	2.0

[a] t_{max}: median (minimum - maximum)

Note: Four subjects (Subjects 105911, 105913, 105943, and 105951) discontinued from the study. Subject 105911 tested positive for alcohol prior to dosing in Period 2. Subjects 105913, 105943 and 105951 withdrew consent from the study after completion of Period 1.

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study HP5503/82: Pharmacokinetic Data Analysis Set)

PK Parameter	N	Tapentadol TRF 50 mg LSM	Tapentadol PR2 50 mg LSM	Ratio TRF/PR2	90% CI	%CV
C_{max}, ng/mL	60	16.04	12.41	129.26	123.46 - 135.34	15.1
AUC_{last}, ng·h/mL	60	224.72	204.22	110.04	105.66 - 114.60	13.4
AUC_{∞}, ng·h/mL	59	233.41	214.32	108.91	104.42 - 113.58	13.7

CI = confidence interval, %CV = % coefficient of variation, LSM = least squares mean
N = number of subjects included in the inferential statistical analysis
TRF = tamper-resistant formulation (to-be-marketed formulation)
PR2 = prolonged release formulation 2 (used in the Phase 3 studies)

Note: As noted previously, four subjects (Subjects 105911, 105913, 105943, and 105951) discontinued from the study. The Applicant stated that Subject 105909 was also excluded from AUC∞ statistical analysis due to an >20% extrapolation for PR2 formulation.

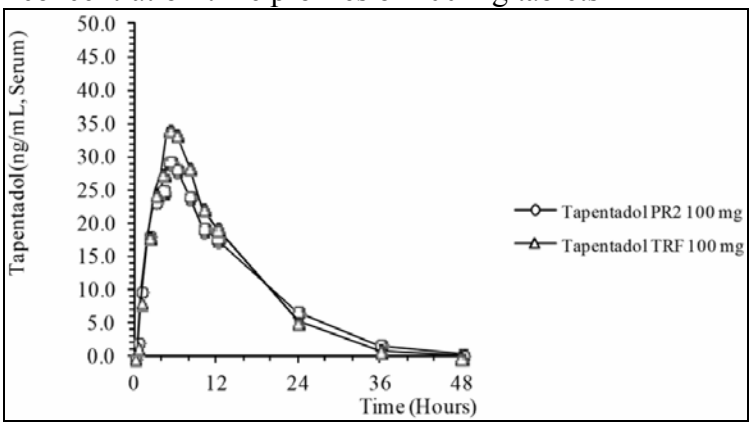
The corresponding 90% CI for AUC values were within the 80% to 125% range, but, not for the Cmax. Thus, the two formulations are not bioequivalent. However, 50 mg dose will be strictly used for a titration purpose. Therefore, the result is considered acceptable after discussion with the clinical team.

100 mg dose

Study HP5503/83 evaluated tapentadol 100 mg tablets. Sixty-four subjects (32 men and 32 women) were enrolled for the study. The batch numbers for test (TRF 100-mg tablet) and reference (PR2 100-mg tablet) products were 9EG9280-X and PD2717, respectively. Subjects were excluded from bioequivalence analyses if they did not complete both treatments and vomited anytime during the treatments.

The mean serum concentration-time profiles were similar between two formulations.

The mean serum concentration-time profiles of 100 mg tablets



The tapentadol pharmacokinetic parameters and a summary of statistical results are presented below.

Mean (±SD) Serum Pharmacokinetic Parameters of Tapentadol
(Study HP5503/83: Pharmacokinetic Data Analysis Set)

	Mean (±SD)	
PK Parameter	Treatment A Tapentadol TRF 100 mg N=63	Treatment B Tapentadol PR2 100 mg N=62
t_{max}[a], h	5.00 (3.00 - 11.98)	5.00 (1.98 – 8.02)
C_{max}, ng/ml	35.6 ± 13.1	30.2 ± 10.9
AUC_{last}, ng·h/ml	470 ± 159	460 ± 135
AUC_{∞}, ng·h/ml	474 ± 159	466 ± 134
$t_{1/2}$, h	5.1 ± 1.0	6.5 ± 2.1

[a] t_{max}: median (minimum-maximum)

Note: Two subjects (Subjects 106010 and 106062) discontinued from the study. Subject 106062 discontinued from the study after vomiting within 6 hours following treatment with tapentadol PR2 100 mg in Period 1. Therefore, samples from this subject were available for PK analysis following only this treatment and for up to 0.5 hours after dosing. Subject 106010 withdrew consent after receiving tapentadol TRF 100 mg in Period 1. Tapentadol serum concentrations for this subject were available for the TRF treatment only. These two subjects were excluded from the bioequivalence analyses.

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study HP5503/83: Pharmacokinetic Data Analysis Set)

PK Parameter	N	Tapentadol TRF 100 mg LSM	Tapentadol PR2 100 mg LSM	Ratio TRF/PR2	90% CI	%CV
C_{max}, ng/mL	62	33.55	28.48	117.78	112.35 – 123.47	15.8
AUC_{last}, ng.h/mL	62	447.60	440.09	101.71	97.71 – 105.87	13.4
AUC_{∞}, ng.h/mL	62	452.22	446.98	101.17	97.21 – 105.30	13.4

CI = confidence interval
%CV = % coefficient of variation
LSM = least squares mean
N = number of subjects included in the inferential statistical analysis
TRF = tamper-resistant formulation
PR2 = prolonged release formulation 2

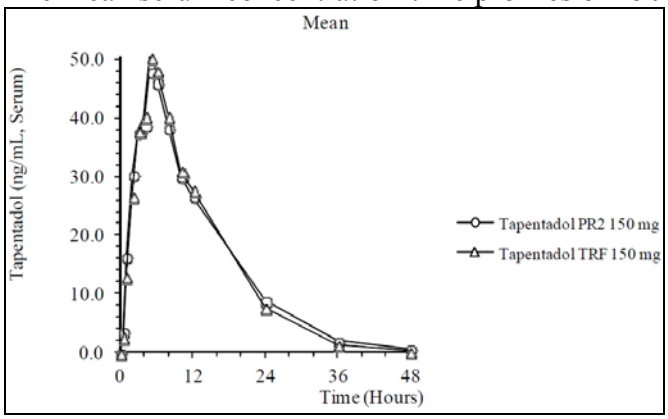
The corresponding 90% CI for Cmax and AUC were within the 80% to 125% range indicating that both formulations are bioequivalent.

150 mg dose

Study HP5503/80 evaluated tapentadol 150 mg tablets. Sixty-four subjects (32 men and 32 women) were enrolled for the study. The batch numbers for test (TRF 150-mg tablet) and reference (PR2 150-mg tablet) products were 9EG9281-X and PD3167, respectively. Subjects were excluded from bioequivalence analyses if they did not complete both treatments and vomited anytime during the treatments.

The mean serum concentration-time profiles were similar between two formulations.

The mean serum concentration-time profiles of 150 mg tablets



The tapentadol pharmacokinetic parameters and a summary of statistical results are presented below.

Mean (±SD) Serum Pharmacokinetic Parameters of Tapentadol
(Study HP5503/80: Pharmacokinetic Data Analysis Set)

	Mean (±SD)	
	Treatment A Tapentadol TRF 150 mg	Treatment B Tapentadol PR2 150 mg
PK Parameter		
C_{max}, ng/mL	52.2 ± 20.4	50.3 ± 18.4
t_{max}[a], h	5.00 (2.00 – 12.13)	5.00 (1.98 – 8.00)
AUC_{last}, ng·h/mL	685 ± 205	694 ± 186
AUC_{∞}, ng·h/mL	689 ± 206	702 ± 186
$t_{1/2}$, h	5.0 ± 1.1	6.0 ± 2.2

[a] t_{max}: median (minimum-maximum)

TRF=tamper-resistant formulation
PR2=prolonged-release formulation

Note: Two subjects (Subjects 105711 and 105766) discontinued from the study due to treatment-emergent adverse events of vomiting before the 6-hour postdose time point (a protocol-specific criterion for discontinuation from the study); Subject 105711 discontinued on the first day of Period 2 and Subject 105766 discontinued on the first day of Period 1. These two subjects were excluded from bioequivalence analyses.

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study HP5503/80: Pharmacokinetic Data Analysis Set)

		Tapentadol TRF 150 mg	Tapentadol PR2 150 mg	Ratio		
	N	(LSM)	(LSM)	TRF/PR2	90% CI	%CV[a]
PK Parameter						
C_{max}, ng/mL	60	48.67	47.01	103.53	98.27- 109.06	17.2
AUC_{last}, ng·h/mL	60	661.50	663.47	99.70	96.81- 102.68	9.7
AUC_{∞}, ng·h/mL	60	665.44	671.12	99.15	96.28 - 102.11	9.6

[a] % CV was derived from the mean square error of the ANOVA test.
CI=confidence interval
%CV=% coefficient of variation
LSM=least squares mean
N=number of subjects included in the inferential statistical analysis
TRF=tamper-resistant formulation
PR2=prolonged-release formulation

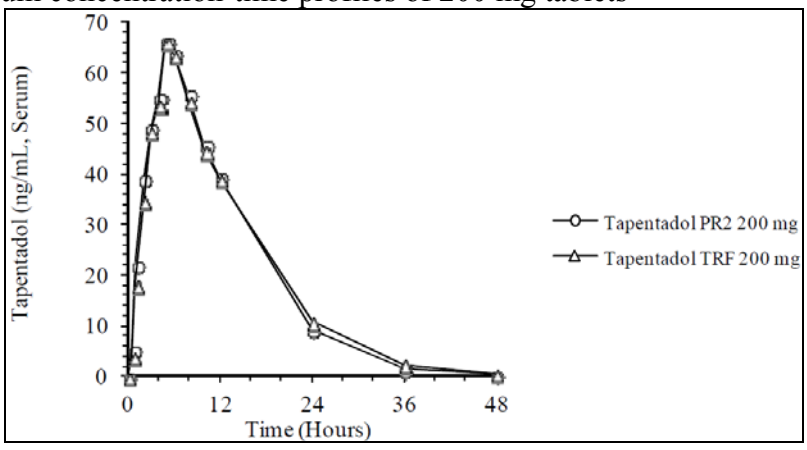
The corresponding 90% CI for Cmax and AUC were within the 80% to 125% range indicating that both formulations are bioequivalent.

200 mg dose

Study HP5503/81 evaluated tapentadol 200 mg tablets. Sixty-four subjects (32 men and 32 women) were enrolled for the study. The batch numbers for test (TRF 200-mg tablet) and reference (PR2 200-mg tablet) products were 9EG9282-X and PD2983, respectively. Subjects were excluded from bioequivalence analyses if they did not complete both treatments and vomited anytime during the treatments.

The mean serum concentration-time profiles were similar between two formulations.

The mean serum concentration-time profiles of 200 mg tablets



The tapentadol pharmacokinetic parameters and a summary of statistical results are presented below.

Mean (±SD) Serum Pharmacokinetic Parameters of Tapentadol
(Study HP5503/81: Pharmacokinetic Data Analysis Set)

	Mean (±SD)	
PK Parameter	Treatment A Tapentadol TRF 200 mg N=57	Treatment B Tapentadol PR2 200 mg N=58
t_{max}[a], h	5.00 (2.00 - 10.00)	5.00 (2.98 - 9.98)
C_{max}, ng/ml	69.0 ± 23.2	69.2 ± 22.9
AUC_{last}, ng·h/ml	942 ± 216	928 ± 220
AUC_{∞}, ng·h/ml	949 ± 216	933 ± 221
$t_{1/2}$, h	5.2 ± 1.5	5.0 ± 1.0

[a] t_{max}: median (minimum-maximum)

Note: Eighty-nine percent (57/64) of subjects completed the study. Serum concentrations of tapentadol for subjects who vomited within 6 hours after drug intake (4 following intake of the TRF 200-mg tablet [Subjects 105806, 105814, 105832, and 105863] and 3 following intake of the PR2 200-mg tablet [Subjects 105826, 105827, and 105864]) were excluded from descriptive statistics and PK parameter calculations for that treatment. Serum concentrations from Subjects 105825, 105831, 105853, and 105856 were included in descriptive statistics and PK parameter calculations for the corresponding treatments because vomiting occurred after 6 hours postdose. All subjects who vomited were excluded from bioequivalence analyses.

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study HP5503/81: Pharmacokinetic Data Analysis Set)

PK Parameter	N	Tapentadol TRF 200 mg (LSM)	Tapentadol PR2 200 mg (LSM)	Ratio TRF/PR2	90% CI	%CV[a]
C_{max}, ng/mL	53	65.80	64.43	102.13	96.35 - 108.25	18.0
AUC_{last}, ng.h/mL	53	923.25	889.93	103.74	100.60 - 106.99	9.5
AUC_{∞}, ng.h/mL	53	930.96	894.95	104.02	100.88 - 107.26	9.4

[a] % CV was derived from the mean square error of the ANOVA test.
CI = confidence interval
%CV = % coefficient of variation
LSM = least squares mean
N = number of subjects included in the inferential statistical analysis
TRF = tamper-resistant formulation
PR2 = prolonged release formulation 2

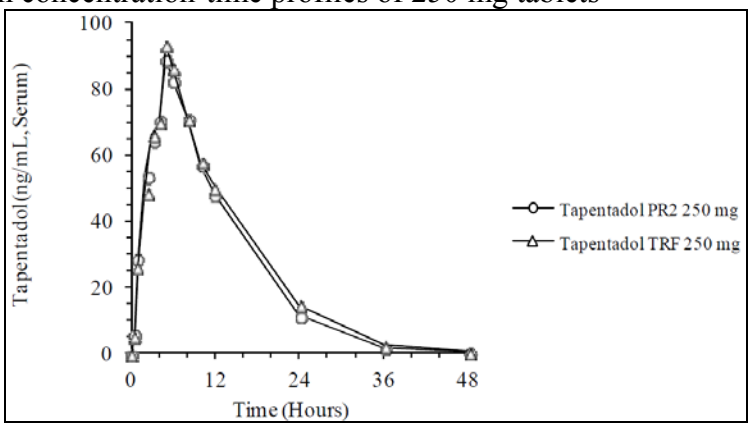
The corresponding 90% CI for Cmax and AUC were within the 80% to 125% range indicating that both formulations are bioequivalent.

250 mg dose

Study HP5503/84 evaluated tapentadol 250 mg tablets. Sixty-four subjects (32 men and 32 women) were enrolled and fifty subjects were included in the bioequivalence analyses. Eleven subjects were excluded due to vomiting (first 6 hours post dosing) during at least 1 treatment period, and one subject, from the PR2 formulation treatment group, was excluded since the PK parameters could not be accurately estimated. The batch numbers for test (TRF 250-mg tablet) and reference (PR2 250-mg tablet) products were 9EG9283-X and PD2732, respectively. Subjects were excluded from bioequivalence analyses if they did not complete both treatments and vomited anytime during the treatments.

The mean serum concentration-time profiles were similar between two formulations.

The mean serum concentration-time profiles of 250 mg tablets



The tapentadol pharmacokinetic parameters and a summary of statistical results are presented below.

PK Parameter	Treatment A Tapentadol TRF 250 mg N = 57	Treatment B Tapentadol PR2 250 mg N = 55[b]	Treatment B Tapentadol PR2 250 mg N = 54[d]
t_{max}[a], h	5.00 (1.98 - 11.98)	5.00 (1.98 – 8.00)	5.00 (1.98 – 8.00)
C_{max}, ng/ml	97.7 ± 39.5	92.2 ± 40.9	93.9 ± 39.3
AUC_{last}, ng·h/ml	1250 ± 417	1180 ± 400	1202 ± 369
AUC_{∞}, ng·h/ml	1257 ± 418	1207 ± 370[c]	1207 ± 370
$t_{1/2}$, h	4.9 ± 0.9	4.9 ± 0.9[c]	4.9 ± 0.9

[a] t_{max}: median (minimum-maximum)
[b] Descriptive statistics including Subject 106107
[c] N = 54 (excluding Subject 106107 due to $AUC_{\infty, ex}$ value greater than 20%)
[d] Descriptive statistics excluding Subject 106107 as a PK outlier

Note: Pharmacokinetic parameters were calculated for all subjects, except those subjects who vomited within 6 hours after dosing. The exceptions included 2 subjects (106101 and 106122) for the TRF 250 mg group and 5 subjects (106103, 106113, 106121, 106129, and 106171) for the PR2 250 mg group. Subjects 106014, 106028, 106030, 106062 were included in descriptive statistics because vomiting occurred after 6 h post dose. *Outlier:* Subject 106107 following PR2 250 mg in Period 1 had up to 232 times lower than the corresponding mean and median drug concentrations observed for that treatment sequence group; the Applicant reported that this subject had no relevant adverse events (e.g., vomiting) or concomitant medications; the site personnel confirmed that this subject did receive and swallow the tapentadol PR2 250-mg tablet. The Applicant stated that sample reanalysis of the 5- and 24-hour samples confirmed the low serum concentrations of tapentadol following this treatment and no explanation can be given. However, serum drug concentrations post TRF 250 mg was similar to the mean and median for the TRF 250-mg treatment group. The descriptive statistics of serum drug concentrations for the PR2 250 mg reference formulation were performed with and without Subject 106107. All subjects who vomited were excluded from bioequivalence analyses.

To assess whether there are any differences in pharmacokinetic parameters between how the Applicant assessed (e.g., exclude if vomited before 6 h and include if vomited after 6 h post dose) and simply excluding all subjects who vomited, all subjects who vomited were excluded. The results indicated that there were no significant differences between the results presented by the Applicant (above table) and reassessed values (see below).

Reassessed mean (±SD) Serum Pharmacokinetic Parameters of Tapentadol by excluding all subjects who vomited (Study HP5503/84: Pharmacokinetic Data Analysis Set)

Parameter	Treatment A TRF n=50		Treatment B PR2 n=50	
	Mean	SD	Mean	SD
Cmax (ng/mL)	94.15	38.38	90.87	33.98
AUClast (ng.h/mL)	1243.64	422.16	1189.98	372.76
AUC0-∞ (ng.h/mL)	1249.78	423.81	1194.36	373.91
t½ (h)	4.89	0.91	4.84	0.89

Summary Statistics on the Pharmacokinetic Parameters of Tapentadol
(Study HP5503/84: Pharmacokinetic Data Analysis Set)

PK Parameter	N	Tapentadol TRF 250 mg LSM	Tapentadol PR2 250 mg LSM	Ratio TRF/PR2	90% CI	%CV
C_{max}, ng/mL	50	87.10	84.67	102.87	96.39 - 109.79	19.6
AUC_{last}, ng·h/mL	50	1187.80	1140.92	104.11	100.46 - 107.89	10.7
AUC_{∞}, ng·h/mL	50	1193.79	1145.36	104.23	100.59 - 107.99	10.6

CI = confidence interval, %CV = % coefficient of variation. LSM = least squares mean
N = number of subjects included in the inferential statistical analysis, PK = pharmacokinetics
TRF = tamper-resistant formulation (to-be-marketed formulation)
PR2 = prolonged release formulation 2 (used in the Phase 3 studies)

Note: All subjects who vomited and Subject 106107 were excluded from bioequivalence analyses.

The corresponding 90% CI for Cmax and AUC were within the 80% to 125% range indicating that both formulations are bioequivalent.

2.5.2 Are there any comparability or interchangeability issues if smaller-dose unit is administered as multiple units to achieve a particular dose?

Summary: The cross-study dose linearity assessment indicated that tapentadol 50 mg Cmax and AUC∞ values are in line with higher doses and do not expect to provide greater exposure when a smaller-dose unit is administered as multiple units. The observed serum tapentadol concentrations following administration of a particular dose as combinations of 50-mg and 100-mg TRF tablets, e.g., 200 mg: two 100 mg tablets or two 50 mg and one 100 mg tablets, in a Phase 3 study PAI-3027/KF56 were within the 90 percent confidence interval established by the population pharmacokinetic model. However, the observed data do not provide a robust comparison, e.g., five units of 50 mg tablets compared to a single unit of 250 mg tablet, and can not be used as a strong supportive argument in the comparability discussion. In all, the results from the linearity assessment and the supportive information from the observed Phase 3 trial indicate that patients would not be at risk for over-exposure to tapentadol if multiple tablets are administered.

As there are several TRF ER tablet strengths available for this drug product, the interchangeability of the tablets of different strengths to achieve a particular total dose, e.g., two 100 mg TRF tablets instead of one 200 mg TRF tablet, was assessed from a safety perspective. The concern was that there may be increase in tapentadol exposure if multiple tablets are administered. In particular, the 50 mg strength was of interest due to the lack of bioequivalence between the 50 mg PR2 and TRF ER tablet formulations (50 mg TRF formulation had approximately 29% greater Cmax compared to PR2 formulation).

The Applicant addressed this issue by looking at the tapentadol exposure from 1) cross-study comparisons (cross-study linearity assessment from the single dose bioequivalence studies discussed above), and, 2) by looking at the observed tapentadol concentrations (pharmacokinetic samples were collected during the open-label titration phase) from a Phase 3 diabetic peripheral neuropathy (DPN) trial, PAI-3027/KF56, which the patients took combinations of 50 and 100 mg tablets in order to achieve a total dose of 150, 200 or 250 mg. Study KF56 allowed the following combinations of TRF tablet strengths:

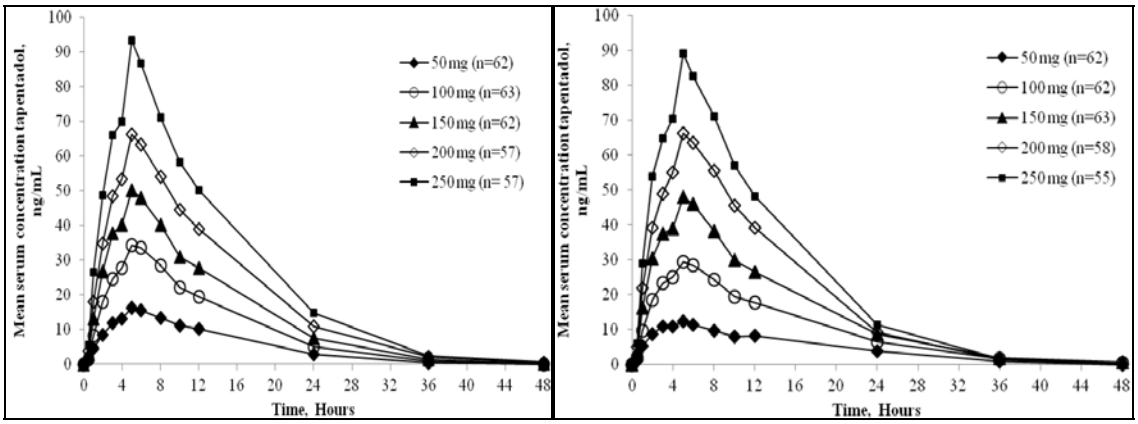
- 150 mg: 50 mg + 100 mg TRF tablets
- 200 mg: 50 mg + 50 mg + 100 mg TRF tablets OR 100 mg + 100 mg TRF tablets
- 250 mg: 50 mg + 100 mg + 100 mg TRF tablets

The information from Study KF56 was compared to the population pharmacokinetic analysis model developed using the data from Study PAI-3015/KF36, previously conducted with PR2 formulation also in DPN patients (subjects took tapentadol as single PR2 tablets twice daily). The population pharmacokinetic model based on the PR2 tablets was used to predict the expected steady-state tapentadol concentrations produced by twice daily administration of 150 mg, 200 mg, and 250 mg (1000 subjects per dose). The model constructed 90 % confidence intervals for each dose. The observed tapentadol concentrations in patients with DPN during the open-label, titration phase of Study PAI-3027/KF56 were overlaid on the prediction intervals.

Results from inter-study linearity assessment:

The mean serum tapentadol concentration-time profiles from both TRF and PR2 tablets are presented below from single dose bioequivalence studies (HP82 [50 mg], HP83 [100 mg], HP80 [150 mg], HP81 [200 mg], and HP84 [250 mg]). The general shape of the profiles was similar.

Mean Serum Concentration-Time Profiles of Tapentadol After Single Oral Administration of the **TRF (left panel) and PR2 (right panel)** Tablets in Healthy Subjects



The mean serum tapentadol parameters from both TRF and PR2 tablets are presented below.

Serum Tapentadol Pharmacokinetic Parameters After Single-Dose Administration of the **TRF** Tablet in Healthy Subjects

Parameter	50 mg (n=62)	100 mg (n=63)	150 mg (n=62)	200 mg (n=57)	250 mg (n=57)
t_{max}, h	5.00 (2.00–11.98)	5.00 (3.00–11.98)	5.00 (2.00–12.13)	5.00 (2.00–10.00)	5.00 (1.98–11.98)
C_{max}, ng/mL	16.9 ± 5.36	35.6 ± 13.1	52.2 ± 20.4	69.0 ± 23.2	97.7 ± 39.5
AUC_{last}, ng.h/mL	236 ± 66.1	470 ± 159	685 ± 205	942 ± 216	1250 ± 417
AUC_{∞}, ng.h/mL	242 ± 64.8	474 ± 159	689 ± 206	949 ± 216	1257 ± 418
$t_{1/2}$, h	5.9 ± 1.7	5.1 ± 1.0	5.0 ± 1.1	5.2 ± 1.5	4.9 ± 0.9

Results expressed as mean ± SD, except for t_{max}, where median (range) is provided
The TRF tablets were produced at the commercial manufacturing site at Gurabo, PR

(Studies (HP82 [50 mg], HP83 [100 mg], HP80 [150 mg], HP81 [200 mg], and HP84 [250 mg])

Serum Tapentadol Pharmacokinetic Parameters After Single-Dose Administration of the **PR2** Tablet in Healthy Subjects

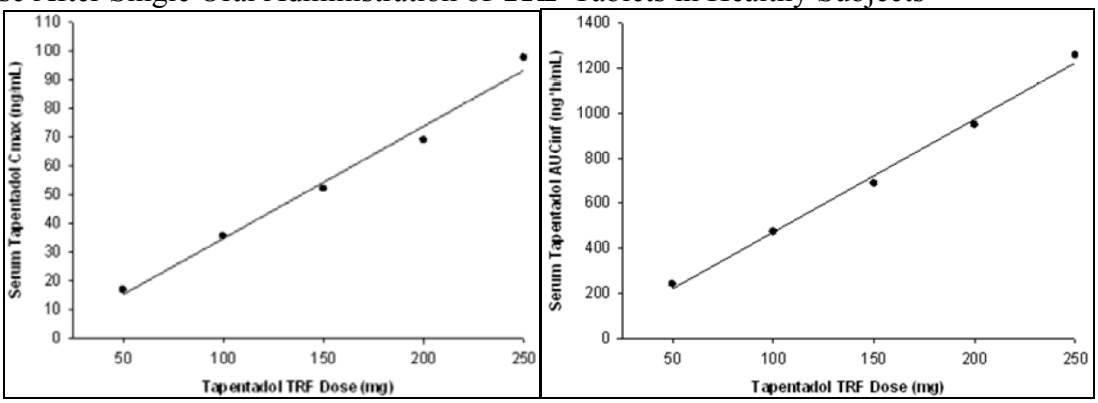
Parameter	50 mg [a] (n=62)	100 mg (n=62)	150 mg (n=63)	200 mg (n=58)	250 mg [c] (n=54)
t_{max}, h	5.00 (2.00–12.00)	5.00 (1.98–8.02)	5.00 (1.98–8.00)	5.00 (2.98–9.98)	5.00 (1.98–8.00)
C_{max}, ng/mL	12.8 ± 3.44	30.2 ± 10.9	50.3 ± 18.4	69.2 ± 22.9	93.9 ± 39.3
AUC_{last}, ng.h/mL	215 ± 61.4	460 ± 135	694 ± 186	928 ± 220	1202 ± 369
AUC_{∞}, ng.h/mL	224 ± 60.7 [b]	466 ± 134	702 ± 186	933 ± 221	1207 ± 370
$t_{1/2}$, h	7.7 ± 2.0 [b]	6.5 ± 2.1	6.0 ± 2.2	5.0 ± 1.0	4.9 ±0.9

[a] Analysis 2 from Study PAI-1059/HP82
[b] n=61
[c] Data Set B from Study PAI-1061/HP84
Results expressed as mean ± SD, except for t_{max}, where median (range) is provided
The PR2 tablets were produced at the Phase 3 clinical supply manufacturing site at Springhouse, PA

(Studies (HP82 [50 mg], HP83 [100 mg], HP80 [150 mg], HP81 [200 mg], and HP84 [250 mg])

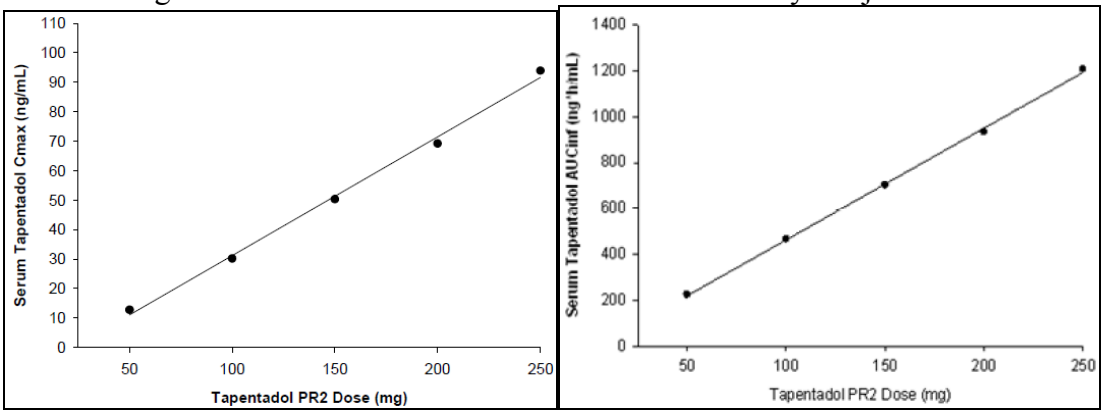
The mean serum Cmax and AUC values were plotted against the dose administered for TRF and PR2 formulations. The results of these cross-study comparisons indicate that the pharmacokinetics of tapentadol appears to be linear with respect to the ER doses administered.

Mean Serum **Cmax (left panel) and AUCinf (right panel)** Values of Tapentadol as a Function of Dose After Single Oral Administration of **TRF** Tablets in Healthy Subjects



(Studies (HP82 [50 mg], HP83 [100 mg], HP80 [150 mg], HP81 [200 mg], and HP84 [250 mg])

Mean Serum **Cmax (left panel) and AUCinf (right panel)** Values of Tapentadol as a Function of Dose After Single Oral Administration of **PR2** Tablets in Healthy Subjects



(Studies (HP82 [50 mg], HP83 [100 mg], HP80 [150 mg], HP81 [200 mg], and HP84 [250 mg])

The statistical evaluation (a linear regression model fitted to the log dose-normalized (dose-normalized (to 50 mg) pharmacokinetic parameter as the dependent variable and the log of dose as the predictor; the slope of the regression line and 90% confidence interval for the slope of the regression line were estimated from the model, and, dose-proportionality was concluded if the 90% confidence interval of the estimated slope contained zero) of dose proportionality of tapentadol pharmacokinetic parameters showed that the single dose pharmacokinetics of tapentadol given as TRF formulation tablets was dose proportional (the slope estimates were not statistically significant different from zero. All corresponding 90% confidence intervals contained zero).

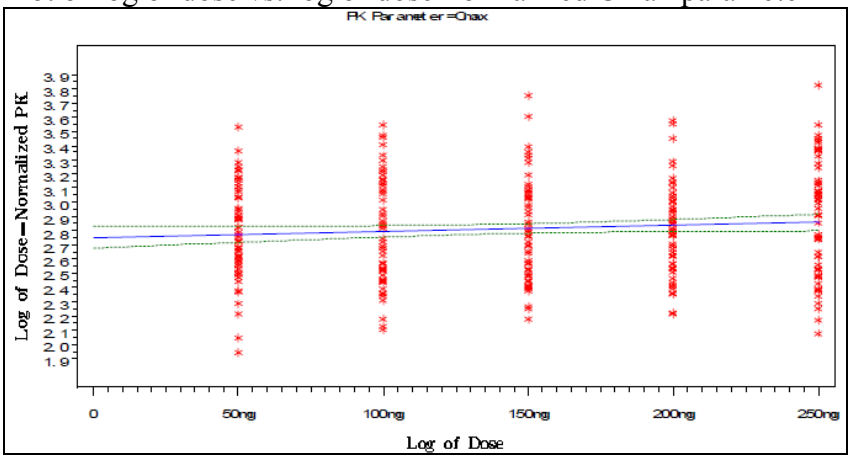
When Cmax and AUCinf values from TRF tablets were dose-normalized to 50 mg, the dose-normalized values were similar across the tablet strengths. More importantly, the dose-normalized mean values for Cmax were numerically higher for all higher strengths (100 mg to 250 mg) compared to that of 50 mg strength.

Descriptive Statistics of Tapentadol Log-Transformed, Dose-Normalized to 50 mg, Pharmacokinetic Parameters (TRF Tablets)

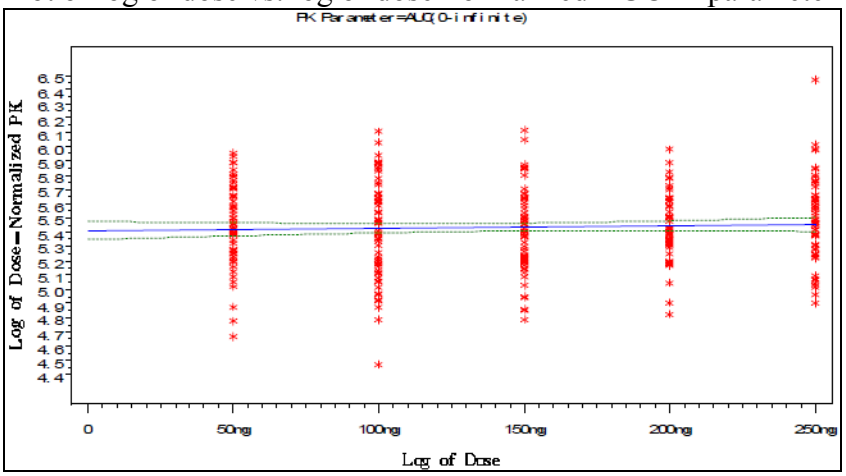
PK Parameter	Dose (mg)	N	Mean	SD	Minimum	Maximum
C_{max} (ng/mL)	50	60	16.85	5.375	6.97	34.20
	100	62	17.91	6.548	8.20	34.65
	150	60	17.37	6.892	8.80	42.67
	200	53	17.32	5.929	9.13	35.75
	250	51	19.03	7.731	7.98	45.80
AUCinf (ng h/mL)	50	34	258.87	63.779	106.47	386.40
	100	62	238.82	78.780	87.67	448.75
	150	60	231.25	68.312	128.57	454.17
	200	53	239.10	54.448	124.84	369.56
	250	50	249.96	84.770	134.70	645.03

x-fold Ratio: dose normalized to 50 mg					
		Cmax		AUCinf	
	x-fold	PR2	TRF	PR2	TRF
50	1	1	1	1	1
100	2	2.36	2.11	2.08	1.96
150	3	3.93	3.09	3.13	2.85
200	4	5.41	4.08	4.17	3.92
250	5	7.34	5.78	5.39	5.19

Plot of log of dose vs. log of dose-normalized Cmax parameter



Plot of log of dose vs. log of dose-normalized AUCinf parameter



PK PARAMETER = C_{max}

The estimated slope and 90% confidence intervals are given below. The 90% confidence interval contained 0. Thus, dose proportionality was concluded.

Statistics	Estimate	SE	DF	T value	P-value	α	Lower bound	Upper bound
Slope	0.037	0.037	284	1.00	0.32	5%	-0.036	0.109

PK PARAMETER = AUC_{∞}

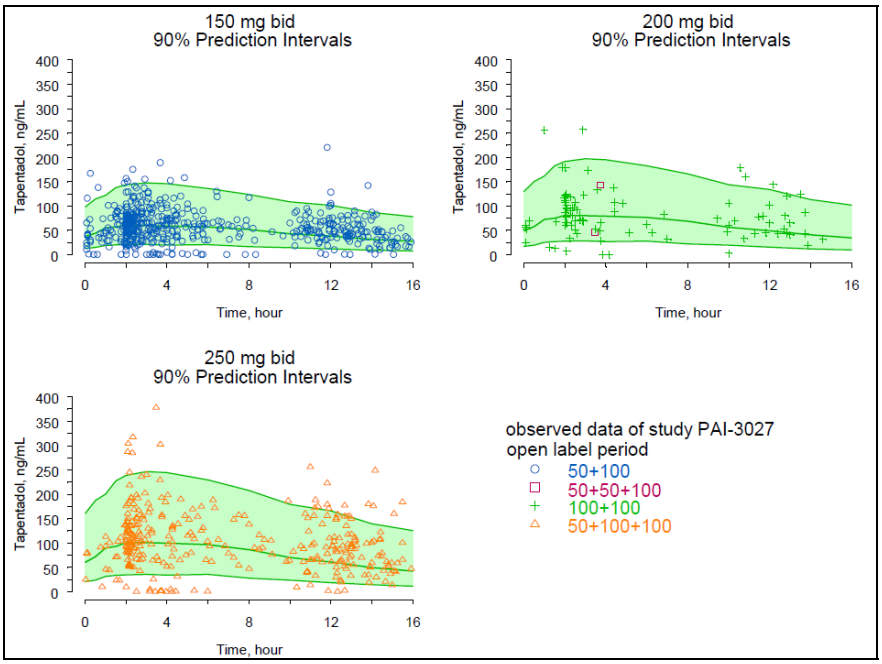
The estimated slope and 90% confidence intervals are given below. The 90% confidence interval contained 0. Thus, dose proportionality was concluded.

Statistics	Estimate	SE	DF	T value	P-value	α	Lower bound	Upper bound
Slope	-0.022	0.035	257	-0.62	0.54	5%	-0.091	0.047

Results from comparing the tapentadol exposure after administration of multiple tablet strengths

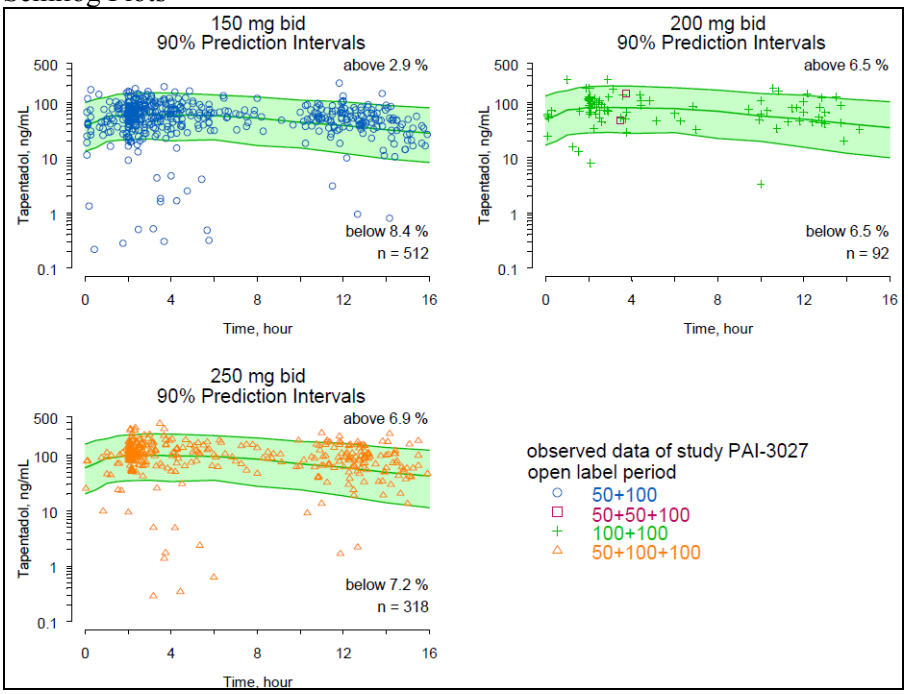
During Study KF56, no subject took only multiples of the 50-mg TRF tablet strength to reach a higher total dose (e.g., 150 mg, 200 mg, or 250 mg), which was of interest due to the lack of bioequivalence between the 50 mg PR2 and TRF ER tablet formulation. The only TRF tablets used during open-label titration phase of the study were the 50-mg and 100-mg strengths. Since there are no clear-cut comparisons to address the 50-mg TRF tablet usage, the findings from this study are considered not pivotal in providing in the interchangeability discussion. The conclusion can not be made from this assessment if patients are at risk for over-exposure to tapentadol if multiple 50-mg tablets are administered to achieve a particular dose. However, the results show that the majority of the observed tapentadol concentrations were within the predicted intervals when different 50-mg and 100-mg TRF tablet strengths are administered. Note it appears that there were two patients in the 50+50+100 mg treatment.

Serum Tapentadol Concentrations Produced by PR2 Tablets (90% Prediction Intervals) and TRF Tablets (Observed Data) Following Twice-Daily Administration to Subjects With DPN
Linear Plots



Note (1): "study PAI-3027" refers to study PAI-3027/KF56
Note (2): Simulations for PR2 were based on data from subjects who took tapentadol as single PR2 tablets; the TRF tablets were given as combinations of 50 mg and 100 mg tablets

Serum Tapentadol Concentrations Produced by PR2 Tablets (90% Prediction Intervals) and TRF Tablets (Observed Data) Following Twice-Daily Administration to Subjects With DPN
Semilog Plots



2.6 Analytical Section

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

Bioanalytical samples were analyzed [redacted] (b) (4) (Validation Report BA1539) by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) (Bioanalytical study numbers are BA1733, BA1734, BA1770, BA1771, and BA1772, for Studies PAI-1057/HP80 (150 mg), PAI-1058/HP81 (200 mg), PAI-1059/HP82 (50 mg), PAI-1060/HP83 (100 mg), and PAI-1061/HP84 (250 mg), respectively). The bioanalytical method had a validated range of 0.200 to 200 ng/mL for tapentadol and 10.0 to 10,000 ng/mL for tapentadol-O-glucuronide. The following tables show various parameters.

Validation parameters for serum/plasma bioanalytical methods for tapentadol and tapentadol-O-glucuronide

[redacted] (b) (4) serum method BA1539	Tapentadol	Tapentadol-O-glucuronide
	Validation original method	Validation original method
Validated concentration range	0.200 – 200 ng/mL	10.0 – 10000 ng/mL
Inter-run accuracy (%)	101.3 – 104.3	95.8 – 104.9
Total precision (% CV)	2.8 – 8.0	4.2 – 5.8
Intra-run accuracy (%)	98.0 – 108.2	94.5 – 105.2
Intra-run precision (% CV)	1.2 – 7.7	2.4 – 7.5
Intra-run accuracy (10x dilution) (%)	99.2	94.5
Intra-run precision (10x dilution) (%)	2.9	4.6
Selectivity (interference < 20% of lower limit of quantification)	5 of 6 sources of serum	6 of 6 sources of serum
Extraction recovery (%)	See BA1427 [a]	See BA1427 [a]
Extraction recovery internal standard (%)	See BA1427 [a]	See BA1427 [a]
Stability in serum	See BA525 [a]	See BA525 [a]
Processed sample stability	166 hours at RT	166 hours at RT
Stability in methanolic stock solution	See BA525 [a]	See BA525 [a]
Incurred sample reproducibility	Proven	-

[a] NDA 200533

CV= coefficient of variation; RT= room temperature

2.7 Office of Scientific Investigation inspection for the 250 mg bioequivalence study

An inspection for the 250 mg bioequivalence study was requested. The Division requested the inspection result be provided by July 28, 2011 and it is still pending as of today. Whether the bioequivalence study results are acceptable will depend on the inspection results.

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, in RED fonts, where appropriate.

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tapentadol is a centrally-acting synthetic analgesic. (b) (4) The exact mechanism of action is unknown, (b) (4) .

12.2 Pharmacodynamics

Tapentadol is (b) (4) 18 times less potent than morphine in binding to the human mu-opioid receptor and is 2-3 times less potent in producing analgesia in animal models. Tapentadol has been shown to inhibit norepinephrine reuptake in the brains of rats resulting in increased norepinephrine concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid antagonists (e.g., naloxone), whereas the norepinephrine reuptake inhibition is sensitive to norepinephrine modulators. Tapentadol exerts its analgesic effects without a pharmacologically active metabolite.

Effects on the cardiovascular system: There was no effect of therapeutic and supratherapeutic doses of tapentadol on the QT interval. In a randomized, double-blind, placebo- and positive-controlled crossover study, healthy subjects were administered five consecutive immediate-release formulation doses of tapentadol (b) (4) 100 mg every 6 hours, (b) (4) tapentadol 150 mg every 6 hours, placebo and a single oral dose of moxifloxacin. Similarly, the immediate-release formulation tapentadol (b) (4) had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

(b) (4)

12.3 Pharmacokinetics

Absorption

The m (b) (4) ean absolute bioavailability after single-dose administration (fasting) of (b) (4) NUCYNTA ER is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed between 3 and 6 hours after administration of NUCYNTA™ ER.

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 Individual study review

Not Applicable.

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	200533	Brand Name	Nucynta ER
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" if included at filing	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	2	2	
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-		3	3	
single dose:	X			
multiple dose:				
Dose proportionality -		1	1	
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -		6	6	
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 -		5	5	
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		1	1	
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?		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J LEE
07/29/2011

YUN XU
07/29/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200533	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAARP		
Sponsor:	J&J Pharmaceutical and GmbH	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Nucynta™	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Tapentadol Extended Release Tablet	**Date Assigned:**	March 1, 2011
Indication:	Management of moderate to severe pain	**Date of Review:**	July 08, 2011
Formulation	Extended Release Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Feb 28, 2011, May 16, 2011 Jul 18, 2011	Feb 28, 2011	March 1, 2011	Aug 2011
Type of Submission:	Responses to Complete Response dated Oct 1, 2010		
Type of Consult:	Dissolution specifications		

REVIEW SUMMARY:

Nucynta (Tapentadol) IR tablet received FDA approval on November 2008 for the relief of moderate to severe acute pain in patients 18 years of age or older under NDA 22-304.

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapentadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapentadol of the TRF (tamper resistant formulation) formulation are proposed for marketing.

In the original submission, the sponsor proposed the use of two IVIVC models and BA studies to bridge the pilot batches and the TRF registration batches (manufactured in Beerse, Belgium) to the to-be-marketed formulation (manufactured in Gurabo, Puerto Rico). However, during the review of the submission the biopharmaceutics team found the proposed IVIVC models unacceptable. The Agency's recommendations to the sponsor during a telecom dated April 21, 2010 were to reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model to (b) (4) In a submission dated June 6, 2010 the sponsor decided not to reconstruct the IVIVCs models; instead a proposal was included to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC.

The dissolution method to characterize the drug release of tapentalol TRF tablets used US Pharmacopoeia (USP) Apparatus 2 (paddle) (b) (4) at 100 rpm in 900 mL of simulated intestinal fluid without enzyme, i.e., 0.05 M phosphate buffer of pH 6.8 at 37°C. This method will also be used for the to-be-marketed batches. The proposed dissolution method was found acceptable in the first review cycle. The proposed dissolution specifications were found unacceptable at that time since these specifications were

based on the IVIVC models. The sponsor was advised to revise the dissolution specifications for all the strengths of the proposed product in the CR letter dated Oct 1, 2010.

Present Submission

The present submission consists of responses to the complete response letter dated Oct 1, 2010. The sponsor has conducted five BE studies linking all the proposed strengths. Is noted that a biowaiver request for the tapentadol ER intermediate strengths (100, 150, and 200 mg), that would include in vitro comparative dissolution profile data and f2 calculations is not needed as BE studies were also conducted with these intermediate strengths.

The following dissolution specifications have been agreed upon with the sponsor for all the strengths of Tapentalol ER tablets (refer to submission dated July 18, 2011):

- 30 minutes – (b) (4)
- 180 minutes – (b) (4)
- 360 minutes – (b) (4)
- 600 minutes – Not less than (b) (4)

These dissolution specifications are based on the mean dissolution profiles for data from registration stability batches, commercial site stability batches, and clinical (pivotal BE) and are deemed acceptable from Biopharmaceutics perspective.

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed NDA 200533 submitted on Feb 28, 2011, May 16, 2011, and July 18, 2011. We found this submission acceptable from the Biopharmaceutics perspective. The following dissolution method and specifications have been found acceptable:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance criteria
Tapentadol	ER Tablet	II (paddle) (b) (4)	100	pH 6.8 phosphate Buffer, Simulated intestinal fluid (without enzyme)	900, 37 °C ± 0.5 °C	30 minutes: (b) (4) 180 minutes: (b) (4) 360 minutes: (b) (4) 600 minutes: Not less than (b) (4)

There are no comments to be conveyed to the sponsor at this time.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200533, TBoui, ADorantes, CBertha, DChristodoulou

Introduction

Regulatory Background

Tapentadol IR tablet formulation received FDA approval on November 2008 for the relief of moderate to severe acute pain in patients 18 years of age or older under NDA 22-304.

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapentadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapentadol of the TRF (tamper resistant formulation) formulation are proposed to be marketed.

This submission includes data from 38 completed clinical studies (28 Phase 1 studies and 10 Phase 2/3 studies), including the report for two in vitro in vivo correlation (IVIVC) models. The development of tapentadol ER tablets can be divided into several stages as follows:

- Round ER tablets used in early Phase 1 and Phase 2 studies (PR1; 21.5 to 200 mg);
- Oblong shaped ER tablets used in Phase 1 and Phase 3 studies (PR2; 50, 100, 150, 200, 250 and 300 mg of tapentadol);
- Oblong shaped (50, 100, and 150 mg of tapentadol) or oblong with a depression in the middle running lengthwise on each side (200 and 250 mg of tapentadol) ER tablets used in Phase 1 studies and proposed to be marketed (TRF).

On April 21, 2010 the Agency held a teleconference with the sponsor to discuss several deficiencies related to their proposed IVIVC models for the higher (250 mg, 200 mg and 150 mg) and lower strengths (50 mg and 100 mg) of Tapentadol ER tablets. The models were proposed to waive the requirements of in vivo BE studies needed to link a change in manufacturing site. The Agency's recommendations were to reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model (b) (4).

On June 6, 2010, the sponsor proposed to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC. The sponsor stated that the BE studies being proposed comparing 150 and 200 mg TBM TRF to Phase 3 PR2 in fasted state will complete the bridging strategy for the tapentadol TRF formulation (i.e., will complete the demonstration of the bioequivalence of the Phase 3 PR2 tablets to the commercial site TRF tablets for all strengths). The sponsor proposed to submit the reports of these studies prior to the end of the 10-month review cycle in August.

Since the composition of the 50 mg tablet is not proportionally similar to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths, the

biopharmaceutics team recommended to conduct BE studies with the highest and lowest strengths instead (refer to Biopharmaceutics review in DARRTS dated June 14, 2010).

Dissolution Method

The proposed dissolution method to characterize the drug release of tapentadol TRF tablets used US Pharmacopoeia (USP) Apparatus 2 (paddles). This method will also be used for the to-be-marketed batches. The proposed dissolution method is summarized in the following table:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
Tapentadol	ER Tablet	II (paddle) (b) (4)	100	pH 6.8 phosphate Buffer, Simulated intestinal fluid (without enzyme)	900, 37 °C ± 0.5 °C

This method was found acceptable in the review of the original submission (refer to Biopharmaceutics review by Dr. Sandra Suarez entered in DARRTS on July 2010).

Proposed Dissolution Specifications

The following Biopharmaceutics comments were included as part of the CR letter dated Oct 1, 2010 and on April 11, 2011:

- *The proposed dissolution specifications for Tapentadol ER tables were established based on the IVIVC models which were found not acceptable by the Agency and therefore, they need to be revised. Recommendations in terms of the dissolution acceptance criteria will be finalized by the Agency upon submission and review of the following information:*
  - *Results of the proposed BE studies bridging the to-be marketed formulations with the clinical trial formulation.*
  - *Dissolution profile comparisons data.*
- *Submit the revised dissolution specifications for all the proposed strengths of Tapentadol ER Tablets.*
- *Submit dissolution profile data (raw data and mean values) from all the batches tested in the new proposed bioequivalence studies.*

Present Submission

The present submission consists of responses to the complete response letter dated Oct 1, 2010. The sponsor proposes the following dissolution specifications for all the strengths of Tapentalol ER tablets:

- 30 minutes – (b) (4)
- 180 minutes – (b) (4)
- 360 minutes – (b) (4)
- 600 minutes – Not less than (b) (4)

On May 13, 2011 the sponsor submitted the dissolution profile data (mean and individual values) for site registration stability batches (Janssen Ortho data), commercial site stability batches (Gurabo Puerto Rico), and clinical (pivotal BE) batches (Gurabo, Puerto Rico). Table 1 and Figure 1 summarize the data submitted by the sponsor.

Table 1. Mean dissolution data for Tapendalol ER tablets, 50, 100, 150, 200, and 250 mg for Registration Stability Batches, Commercial site Stability Batches and Pivotal BE study Batches (generated from sponsor's provided data).

50 MG STRENGHT									
Time (min)	**50MG_ 08G01**	**50MG_ 08G07**	**50MG_ 08G24**	**50MG_ 8MG7856**	**50MG_ 8MG7855**	**50MG_ 8MG7854**	**50MG_ 9EG9279**	**50MG_ 9EG9279R**	**MEAN**
30	(b) (4)								15.125
180									48.75
360									73.28
600									91.5
100 MG STRENGHT									
Time (min)	**100MG_ 08G23**	**100MG_ 08G25**	**100MG_ 08G29**	**100MG_ 8MG7857**	**100MG_ 9EG9280**	**100MG_ 9EG9280R**			**MEAN**
30	(b) (4)								16
180									50.83
360									75.4
600									92.83
150 MG STRENGHT									
Time (min)	**150MG_ 08G31**	**150MG_ 08H04**	**150MG_ 08H06**	**150MG_ 8MG7858**	**150MG_ 9EG9281**	**150MG_ 9EG9281R**			
30	(b) (4)								16.3
180									50.66
360									74.4
600									91.83
200 MG STRENGHT									
Time (min)	**200MG_ 08H20**	**200MG_ 08H22**	**200MG_ 08H26**	**200MG_ 8MG7859**	**200MG_ 9EG9282**	**200MG_ 9EG9282R**			**MEAN**
30	(b) (4)								17.33
180									49.83
360									72.2
600									90
250 MG STRENGHT									
Time (min)	**250MG_ 08G09**	**250MG_ 08G15**	**250MG_ 08G17**	**250MG_ 8MG7853**	**250MG_ 8MG7852**	**250MG_ 8MG7851**	**250MG_ 9EG9283**	**250MG_ 9EG9283R**	**MEAN**
30	(b) (4)								16.125
180									49.25
360									72
600									89.625
MEAN OF MEANS ALL STRENGHTS									
TIME (min)	**50 MG**	**100MG**	**150MG**	**200MG**	**250MG**	**MEAN**			
30	(b) (4)					16.18			

180	(b) (4)	49.87			
360		73.46			
600		91.16			

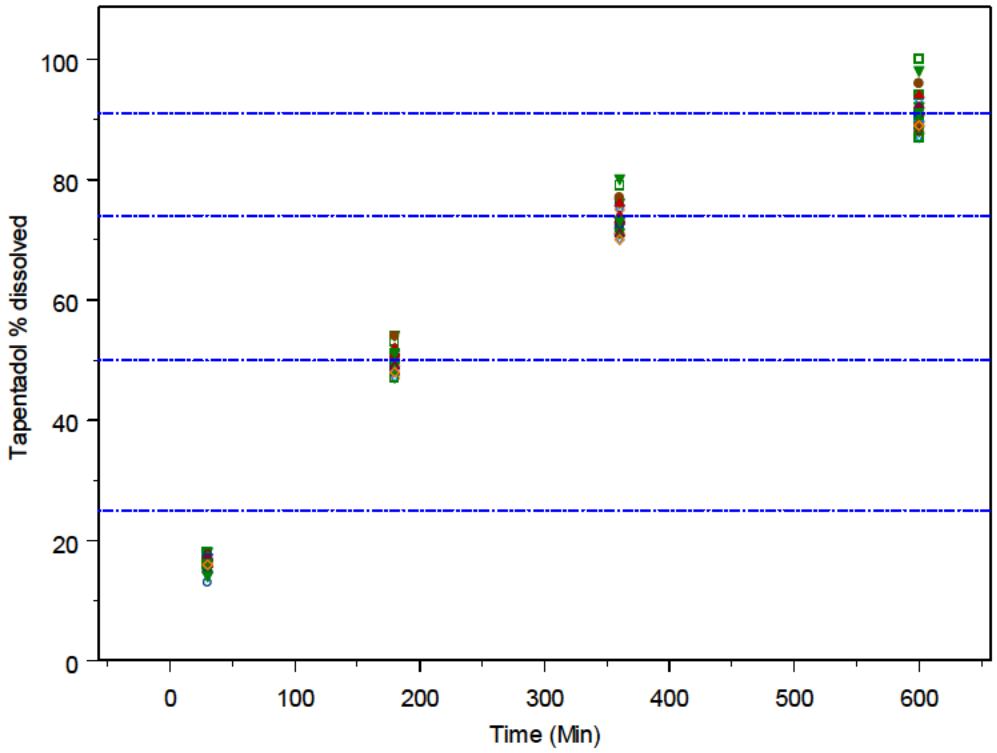

Figure 1. Mean dissolution profiles for Tapendalol ER tablets, 50, 100, 150, 200, and 250 mg for Registration Stability Batches, Commercial site Stability Batches and Pivotal BE study Batches (generated from sponsor's provided data).

Dissolution Specifications--Conclusion

The data presented in Table 1 and Figure 1 support the following dissolution specifications:

- 30 minutes – (b) (4)
- 180 minutes – (b) (4)
- 360 minutes – (b) (4)
- 600 minutes – Not less than (b) (4)

These specifications have been accepted by the sponsor (refer to submission dated July 18, 2011).

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/s/

SANDRA SUAREZ
07/19/2011

PATRICK J MARROUM
07/21/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200533 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAARP		
Sponsor:	J&J Pharmaceutical and GmbH	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Nucynta™	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Tapentadol Extended Release Tablet	**Date Assigned:**	Jul 28, 2010
Indication:	Management of moderate to severe pain	**Date of Review:**	Aug 15, 2010
Formulation	Extended Release Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Jul 23, 2010	Jul 23, 2010	July 29, 2010	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	**Addendum to original Biopharm review: IVIVC models**		

REVIEW SUMMARY:

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapentadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapentadol of the TRF (tamper resistant formulation) formulation are proposed for marketing.

Originally, two in vitro in vivo (IVIVC) models were used to bridge the pilot batches (manufactured in Aachen, Germany) and the TRF registration batches (manufactured in Beerse, Belgium) to the to-be-marketed formulation (manufactured in Gurabo, Puerto Rico). However, the models were found unacceptable. The Agency's findings with respect to the unacceptability of the IVIVC models were conveyed to the sponsor in a telecom April 21, 2010. The Agency recommended to reconstruct the models using individual plasma concentration values and to eliminate a mathematical term being used in the model (b) (4) In a submission dated June 6, 2010 the sponsor decided not to reconstruct the IVIVCs models; instead a proposal was included to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC. The sponsor proposed to submit the reports of these studies prior to the end of the 10-month review cycle in August (refer to Biopharmaceutics review dated June 14, 2010).

The present submission contains an attempt in the reconstruction of the IVIVC models. The IVIVC structural models originally proposed by the sponsor were reconstructed for tapentadol ER using the (b) (4) also used for the development of the two originally proposed IVIVC models (refer to Biopharmaceutics review entered in DARRTS on July 29, 2010). These new models used the individual tapentadol serum concentration-time data of the oral solution treatment arm to obtain the unit impulse response (UIR) instead of the mean values. In addition, individual tapentadol serum concentration-time data of the treatment with the slow, medium and fast formulation

were used to estimate individual IVIVC parameters for the low and high dose model. The structural model for the IVIVC was slightly modified to allow modeling on individual data as follows:

(b) (4)

The models were internally and externally validated by predicting the individual tapentadol serum concentration-time profiles. The individual UIR parameters and the final high and low dose IVIVC parameter values were used for these predictions. For each treatment arm in each Study, the predicted individual profiles were averaged and compared to the observed mean tapentadol serum concentration-time profiles.

The models failed the external validation indicating the lack of robustness. In addition, the new models still contain the mathematical term used (b) (4) During the telecom that took place on April 21, 2010, the biopharmaceutics team advised the sponsor to eliminate this term since it is not mechanistically founded. Therefore, the models are not acceptable. The waiver of the in vivo BE requirements is denied.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed the submission to NDA 200533 dated Jul 23, 2010. The reconstructed IVIVC models were found not acceptable. Therefore, waiver request of the in vivo BE requirements to support the bridging of the clinical study batches to the TBM TRF s denied. In addition, the sponsor's proposed dissolution specifications need to be revised (refer to biopharmaceutics review entered in DARRTS in July 2010). The following deficiencies have been conveyed to the sponsor regarding the acceptability of the reconstructed IVIVC models (refer to discipline letter entered in DARRTS on 8/11/10):

Deficiencies:

1. Your proposed IVIVC models do not support the bridging of the clinical study batches to the TBM TRF.
2. The re-constructed IVIVC models using individual plasma concentrations are not acceptable for the following reasons:
3. The models submitted on July 23, 2010, still include a mathematical term that has no mechanistic foundation and, therefore, are not acceptable.
    - The models using the individual subject concentrations failed the external validation, indicating a lack of robustness.
    - The proposed dissolution acceptance criteria for TBM TRF tapentadol ER tablets were based on the proposed IVIVC models. Because these models were not accepted, the dissolution acceptance criteria will need to be revised.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200533, TBoui, ADorantes, CBertha, Dchristodoulou

Background

On April 21, 2010 the Agency held a teleconference with the sponsor to discuss several deficiencies related to their proposed IVIVC models for the higher (250 mg, 200 mg and 150 mg) and lower strengths (50 mg and 100 mg) of Tapentadol ER tablets. The models were proposed to waive the requirements of in vivo BE studies needed to link a change in manufacturing site. The Agency's recommendations were to reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model (b) (4)

On June 6, 2010, the sponsor proposed to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC. The sponsor stated that the BE studies being proposed comparing 150 and 200 mg TBM TRF to Phase 3 PR2 in fasted state will complete the bridging strategy for the tapentadol TRF formulation (i.e., will complete the demonstration of the bioequivalence of the Phase 3 PR2 tablets to the commercial site TRF tablets for all strengths). The sponsor proposed to submit the reports of these studies prior to the end of the 10-month review cycle in August.

Since the composition of the 50 mg tablet is not proportionally similar to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths, the biopharmaceutics team recommended to conduct BE studies with the highest and lowest strengths instead (refer to biopharm review in DARRTS dated June 14, 2010).

The present submission contains an attempt on the reconstruction of the IVIVC models.

IVIVC Model Development Summary

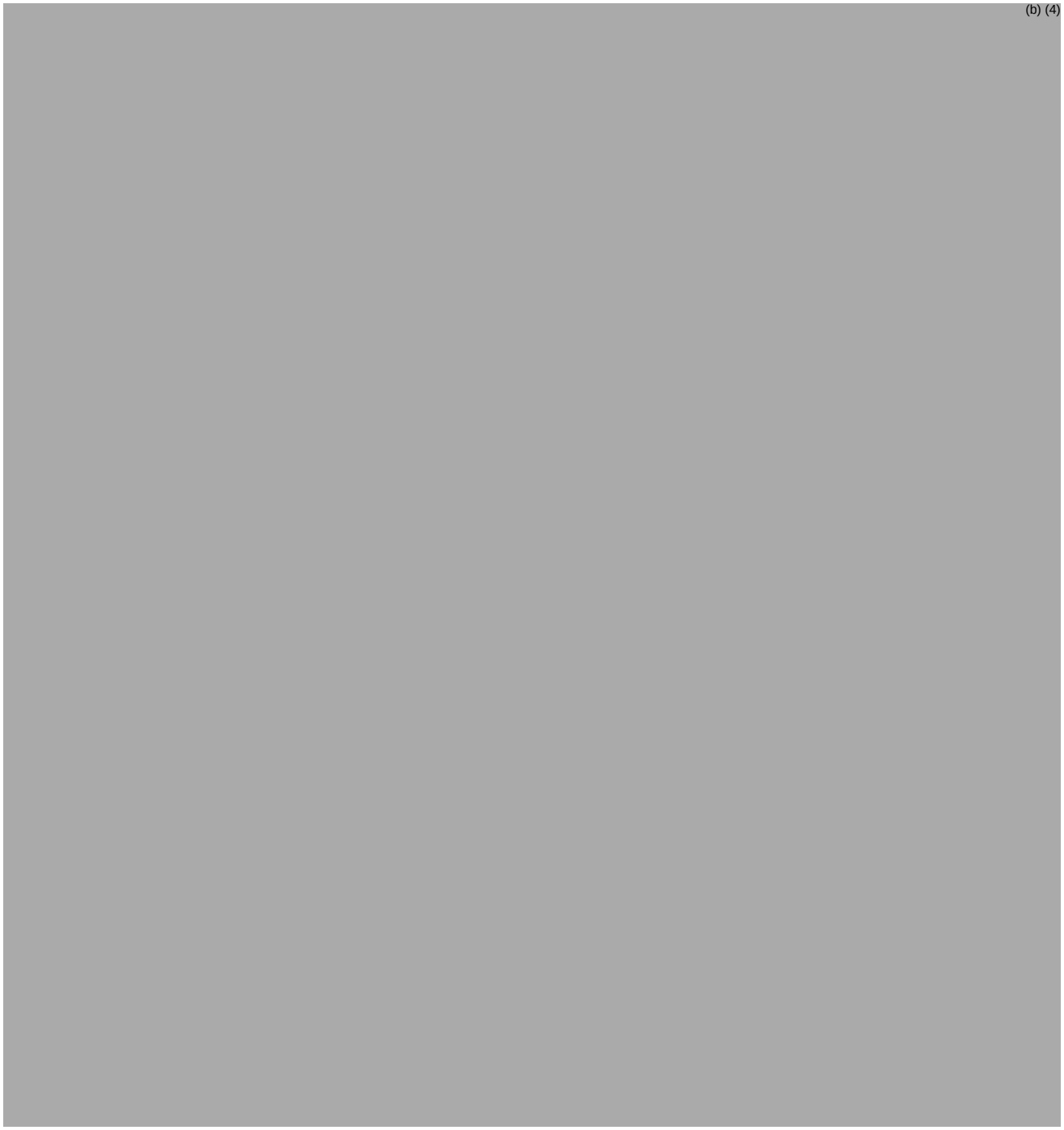
The IVIVC structural models originally proposed by the sponsor were reconstructed for tapentadol ER using the (b) (4) also used for the development of the two originally proposed IVIVC models. These new models used the individual tapentadol serum concentration-time data of the oral solution treatment arm to obtain the unit impulse response (UIR). In addition, Individual tapentadol serum concentration-time data of the treatment with the slow, medium and fast formulation were used to estimate individual IVIVC parameters for the low and high dose model.

The structural model for the IVIVC was slightly adapted to allow modeling on individual data:

(b) (4)

The models were internally and externally validated by predicting the individual tapentadol serum concentration-time profiles. The individual UIR parameters and the final high and low dose IVIVC parameter values were used for these predictions. For each treatment arm in each Study, the predicted individual profiles were averaged and compared to the observed mean tapentadol serum concentration-time profiles.

(b) (4)



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Reviewer's Conclusions Related to the IVIVC Models

Although the models met internal predictability these models are still not considered acceptable for the following reasons:

- *The models did not eliminate the mathematical term used to compensate for the fraction of tapentadol absorbed between 4 and 4.5 hrs after drug administration (start and stop time of lunch intake). As previously communicated to the sponsor, we consider that the inclusion of this non-mechanistically founded term is an artifact to explain the data used in the construction of the model.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICALS INC	TAPENTADOL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
08/20/2010

PATRICK J MARROUM
08/20/2010

CLINICAL PHARMACOLOGY REVIEW

NDA: 200-533	Submission Date: 11/30/09
Submission Type; Code:	Original; 505(b)(1); 1S
Brand/Code Name:	Nucynta™ ER
Generic Name:	Tapentadol HCl Extended Release tablet
Primary Reviewer:	David Lee, Ph.D.
Team Leader:	Suresh Doddapaneni, Ph.D.
OCP Division:	DCP 2
OND Division:	Division of Anesthesia and Analgesia Products
Sponsor:	J&J Pharmaceutical Research and Development, L.L.C., On behalf of Ortho-McNeil-Janssen Pharmaceuticals, Inc.
Relevant NDA(s)	22-304
Relevant IND(s):	61,345
Formulation; Strength(s):	Tablet; 50, 100, 150, 200 and 250 mg
Proposed Indication:	Management of moderate to severe chronic pain
Proposed Dosage Regimen:	• As with many centrally acting analgesic medications, the dosing regimen of NUCYNTA™ ER should be individualized according to the severity of pain being treated, the previous experience with similar drugs and the ability to follow-up and provide oversight of treatment. • The recommended NUCYNTA™ ER total daily dose is 100 mg to 250 mg twice daily approximately every 12 hours with or without food. *Patients currently not taking opioid analgesics should begin NUCYNTA™ ER therapy with 50 mg twice a day.* • Patients receiving NUCYNTA™ (immediate-release formulation) may be converted to NUCYNTA™ ER by administering the same total daily dose. Administer half the total daily dose of NUCYNTA™ ER approximately every 12 hours. *Daily doses greater than 500 mg of NUCYNTA™ ER have not been studied and, therefore, are not recommended.*

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1 Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology II (OCP/DCP-II) has reviewed the information submitted in the current application. The Applicant did not submit bioequivalence information bridging the PR2 Phase 3 clinical and tamper-resistant-formulation (TRF) to-be-marketed (TBM) tapentadol extended-release (ER) formulations. Instead, the Applicant utilized in vitro-in vivo correlation (IVIVC) data to bridge the two formulations. This information was reviewed by Dr. Sandra Suarez, the biopharmaceutics reviewer in Office of New Drug Quality Assessment (ONDQA). During the assessment of the IVIVC information, the biopharmaceutics reviewer identified several deficiencies related to the proposed IVIVC models and the findings were conveyed to the Applicant on April 21, 2010, during a teleconference. The Applicant was asked to 'reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model (b) (4) In response, the Applicant submitted an amendment to pending application on May 13, 2010, proposing to perform new fasted bioequivalence trials between the PR2 Phase 3 clinical and TRF TBM on the 150 mg and 200 mg strengths and proposing to submit the information prior to the end of the 10-month review cycle (See Biopharmaceutics Review dated June 14, 2010).

From clinical pharmacology perspective, since the proposed IVIVC modeling data is not sufficient to adequately bridge the PR2 and TRF TBM formulations, from a clinical pharmacology section of the NDA is not acceptable. In order to provide adequate information, the Applicant needs to submit bioequivalence information from two doses, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations along with in vitro dissolution data in support of the biowaiver request for the intermediate strengths.

With respect to Labeling, there are minor changes recommended for the Clinical Pharmacology section of the label. The recommended changes to the package insert are made by striking out the existing texts and adding new texts, in RED fonts, where appropriate (see section 3: Detailed Labeling Recommendations).

12.3 Pharmacokinetics
Absorption

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), and, having entered into a licensing agreement with Grünenthal GmbH, Aachen Germany (GRT), submitted on 11/30/09, the New Drug Application 200-533, tapentadol hydrochloride (HCl) extended release (ER) Tablets for the relief of moderate to severe chronic pain with 50, 100, 150, 200 and 250 mg doses to be taken every 12 h with or without food in patients at least 18 years of age. Patients currently not taking opioid analgesics should begin NUCYNTA™ ER therapy with 50 mg twice a day. Patients receiving NUCYNTA™ immediate-release (IR) formulation may be converted to NUCYNTA™ ER by administering the same total

daily dose. Patients are instructed to administer half the total daily dose of NUCYNTA™ ER approximately every 12 hours. In this submission, the Applicant submitted data from 28 Phase 1 trials and 10 Phase 2/3 trials. With respect to clinical pharmacology, 16 trials were reviewed. Throughout the submission the following notations were also used for tapentadol HCl: CG5503, R331333, and BN200.

It should be noted that tapentadol IR tablet has been approved for the relief of moderate to severe acute pain in patients 18 years of age or older (NDA 22-304, approved 20 November 2008).

Tapentadol is a centrally active antinociceptive drug and 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 as measured appropriately in serum and urine. *Since the metabolites (inactive) are excreted in the urine, glucuronide metabolites were measured in hepatic and renal studies.*

Phase 3 studies

There were four 'pivotal' Phase 3 trials. Three Phase 3 trials used a controlled dose adjustment regimen that included a 3-week titration period followed by a 12-week maintenance period where subjects could adjust their dose within pre-defined criteria in subjects with moderate to severe chronic low back pain (LBP) or moderate to severe chronic pain due to osteoarthritis (OA) of the knee. One Phase 3 trial used a fixed dose regimen during the maintenance period in subjects with painful diabetic peripheral neuropathy (DPN). This trial included an open-label 3-week titration followed by a randomized, double-blind withdrawal 12-week maintenance. At the end of the titration period, a responder criterion was used to select only subjects who had demonstrated pain relief from the treatment to continue into the withdrawal, fixed dose maintenance treatment period. To provide long-term tapentadol ER safety information as well as data on maintenance of pain relief, 1-year, open-label safety study in the management of mild to severe chronic pain in patients with OA or LBP was performed.

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

Thorough QT study

The Applicant submitted a QT study (HP5503/10) conducted in March, 2003. This study used 100 mg and 200 mg ER B.I.D. dosing. The total daily dose from this ER study was less than that of the total daily dose used in the TQT study (HP5503/25) with the IR product previously submitted and reviewed in NDA 22-304; therapeutic, 100 mg, and supratherapeutic doses, 150 mg, were administered every 6 hours on Day 1 and on Day 2 to achieve tapentadol steady-state (total of 5 doses each). Since total ER daily dose used in HP5503/10 was less than total IR daily dose used in HP5503/25, and the study did not

show any significant effect, QT-IRT was not consulted. The Labeling for this ER NDA will continue to reflect that no significant QT prolongation effect of tapentadol was detected. Previously submitted information (Nucynta IR NDA 22304) showed that no significant QT prolongation effect of tapentadol was detected.

Inter- and intra-subject variability

The data from the multiple-dose trial indicated the inter-subject variability was low (CV between 17.2% and 26.3%) after single- and multiple-dose.

Pediatric

Pediatric data has not been submitted seeking approval of pediatric indications at this stage. Instead, the Applicant requested a (b) (4) deferral of the requirement to conduct pain studies in the pediatric population. (b) (4)

Gender, Race, Elderly

No new information was submitted. The Applicant proposes to keep the dosing guideline as per the Nucynta™ IR tablets. This approach is acceptable since the tapentadol exposure is similar between IR and ER formulations.

Hepatic, Renal

No new information was submitted. The Applicant proposes to keep the renal dosing guideline as per the Nucynta™ IR tablets. This approach is acceptable since the tapentadol exposure is similar between IR and ER formulations.

Drug-Drug interaction

No new drug interaction information was submitted.

Bioequivalence

There are no bioequivalence trials conducted to bridge the Phase 3 clinical formulation, PR2 (b) (4)), to TRF TBM tapentadol ER formulation. In Phase 3 trials, PR2 ((b) (4) ER formulation was predominantly used. The Applicant utilized IVIVC modeling to link the two formulations. The IVIVC modeling information was reviewed by Dr. Sandra Suarez of the Biopharmaceutics Team in the Office of New Drug Quality Assessment (see review dated 7/29/10). The IVIVC modeling data was not sufficient to adequately bridge the PR2 and TRF TBM formulations.. As such, in order to provide adequate bridge, the Applicant needs to submit acceptable IVIVC data or bioequivalence information from two doses, at least, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations. The Applicant will

provide adequate in vitro dissolution data in support of the biowaiver for the intermediate doses.

Tapentadol 200 mg PR1 ('updated' formulation) and PR2 (b) (4) formulations were bioequivalent.

Tapentadol 50 and 100 mg PR2 (Phase 3 formulation) and 'pilot' TRF formulations were bioequivalent in fasted state.

Tapentadol 250 mg PR2 (Phase 3 formulation) and 'pilot' TRF formulations were bioequivalent in fed state.

Tapentadol 50, 100, and 250 mg PR2 (Phase 3 formulation) and 'Registration' TRF formulations were bioequivalent in fasted state.

Absolute Bioavailability

The absolute oral bioavailability of tapentadol RE tablet (PR1 formulation) was 32.0%. The relative oral bioavailability of 86 mg tapentadol PR2 Phase 3 formulation compared to 86 mg tapentadol IR tablet was similar.

Protein Binding

No new information was submitted. However, tapentadol protein binding is approximately 20%, mainly to albumin, and protein binding is independent of drug and protein concentration (from Nucynta™ IR tablet review).

Mass balance, Metabolism, Induction, and Inhibition Potential

No new information was submitted. 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 small percent (mean: 3%) was excreted as unchanged CG5503 base, 69% was excreted as conjugates. Approximately 27% was 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 CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 in vitro. Tapentadol is not an inducer of CYP450 1A2, 2C9 and 3A4 in vitro (from Nucynta™ IR tablet review).

Single-dose linearity

AUC or Cmax values increased linearly with increase in doses from 50 - 250 mg.

Multiple-dose

The estimated mean T1/2 for tapentadol 5.2 hours, which was similar to single dose. The data showed that there is minimal accumulation (accumulation ratio of 1.64 and 1.82 for Cmax and AUC, respectively) after multiple-dose of tapentadol ER tablets.

Food effect

Cmax and AUC increased by The AUC and Cmax increased by 17% and 6%, respectively, when TRF TBM tapentadol ER tablets were administered after a high-fat, high-calorie breakfast. The tmax was prolonged by about 1 hours with a median tmax of 6.00 hours (range: 2.98-12.0 hours) in the fed state and 5 hours (range: 2.00-12.0 hours) in the fasted state.

In Phase 3 studies, tapentadol ER tablets were administered without restriction to food. Study treatment was swallowed whole and not chewed, divided, dissolved, or crushed.

Effects of mastication

The mean tapentadol C_{max} following the intake of masticated (chewed) TRF tablets was lower compared to C_{max} after IR administration.

Effects of alcohol on ER formulation

There no alcohol interaction (240 mL 40% alcohol) was detected with 100 and 250 mg tapentadol ER TRF (Registration) formulation.

Population Pharmacokinetics and exposure-response information

The Applicant submitted population pharmacokinetic modeling. The modeling results did not enhance the overall understanding of tapentadol exposure administered as ER tablets.

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.

2 QBR

2.1 General Attributes of the Drug and Drug Product

2.1.1 What are known properties of drug substance, tapentadol?

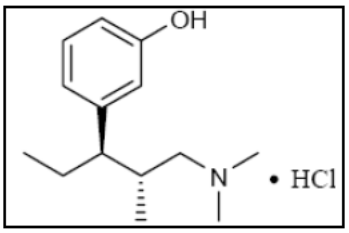
The following information is from Nucynta IR NDA 22-304. Tapentadol HCl is freely soluble in water, 0.1 N HCl and simulated intestinal fluid (34 g/100 mL and 35 g/100 mL, respectively). Its solubility decreases at higher pH. The hydrochloride salt was used because of its superior aqueous solubility in comparison with the free base. It is noted that the weight conversion factor of tapentadol HCl to the free-base equivalent is 0.8585. During the development program, doses of tapentadol were expressed in both salt and free base equivalents. Tapentadol is designated as a BCS Class 1 compound (N22-304 review).

Tapentadol HCl is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. Its molecular formula is $C_{14}H_{23}NO.HCl$. 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 (1*R*, 2*R*). The pKa1 and pKa2 are 9.34 (phenolic OH) and 10.45 (HN(CH3)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 because of its superior aqueous solubility in comparison with the free base. Tapentadol is designated as a BCS Class 1 compound (NDA 22304 review).

The drug substance weights used in early development were based on the hydrochloride salt of tapentadol. In order to express as free base, the conversion factor from salt to free base is 0.8585. For example, 116 mg tapentadol hydrochloride is equivalent to 100 mg tapentadol. Equivalent dose strengths of tapentadol expressed as the hydrochloride salt and free base are shown in the table below.

Tapentadol Hydrochloride Salt (mg)	Tapentadol Free Base (mg)
25	21.5
40	34
50	43
58	50
87	75
100	86
116	100
174	150
200	172
233	200
291	250
348	300

Chemical Structure of tapentadol HCl



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

Several different formulations were developed: PR1 formulation was mostly used in Phase 1 and 2 clinical trials; PR2 formulation was mostly used in Phase 3 clinical trials; the tamper-resistant formulation (TRF) was subsequently developed to offer tamper-resistant properties with similar dissolution profile to PR2 formulation. The TRF tapentadol ER formulation is designated as commercial formulation.

Overall tablet formulation development

Phase 1 (P1) and 2 clinical trials were conducted with (b) (4) formulations of the tapentadol ER tablets, designated PR1. Phase 3 (P3) clinical trials, as well as additional P1 studies during that period, were conducted with the PR2 formulations. The PR2 tablets were similar in ingredients and dissolution to the PR1 tablets. The Applicant stated that the PR2 formulations were developed to accommodate the higher doses required for P3 clinical trials.

The tamper-resistant formulations (TRF) were subsequently developed to offer tamper-resistant properties with similar dissolution profile to the P3 PR2 formulations. The TRF tapentadol ER formulation is designated as commercial formulation. There are three TRF formulations, namely, pilot, registration and to-be-marketed (TBM) formulations. Registration stability batches of TRF tapentadol ER tablets were manufactured by J&JPRD (Beerse, Belgium). To-be-marketed stability batches of TRF tapentadol ER tablets were manufactured at the proposed commercial site, Janssen Ortho, L.L.C. (JOLLC) (Gurabo, Puerto Rico). (b) (4) See next section for further discussion on tamper-resistant formulation.

The IR and ER tablets have different plasma profiles as the formulations will have different drug release characteristics due to formulation differences. The differences of tapentadol rate of absorption, Cmax and Tmax, between IR and ER formulations are expected, but, not the extent of absorption, AUC, distribution, metabolism and excretion.

Relative BA trial revealed that Cmax (and Tmax) values between IR and ER (PR1 early formulation) were different, but not the AUC or T1/2. The absolute BA trial revealed

that ER (PR1 early formulation) tablet has similar absolute BA (~32% under fasted condition) as IR tablets.

Summary of tapentadol ER formulations developed during clinical development are presented below in chronological order.

'Initial' and 'updated' PR1 formulations

(b) (4)

(b) (4) PR2 formulations

(b) (4)

(b) (4)

'Pilot', 'Registration/stability' and 'to-be-marketed' tamper-resistant formulations

The Applicant stated that the tamper-resistant formulation was co-developed with PR2 formulation. The main objective of the TRF, the Applicant believes, is that TRF tablet is more difficult to tamper with, thereby reducing the potential for both unintentional misuse and intentional abuse. (b) (4)

In all, a summary of the formulation development history is provided in the following table (listed in chronological order).

Tapentadol Extended-Release Tablet Formulations Used During Clinical Development

Formulation	Site of Manufacture	Dose Strengths (as free-base) (mg)	Tablet Core Weight (mg)	Rationale	Clinical Phase
Initial PR1	GRT	21.5, 42.9, 85.9, 171.8	[redacted] (b) (4)		1 and 2
Updated PR1	GRT J&JPRD	25, 50, 100, 150, 200			1 and 2
Initial PR2 [redacted] (b) (4)	GRT J&JPRD	200, 300			1
Final PR2 [redacted] (b) (4)	GRT J&JPRD	50, 100, 150, 200, 250			1 and 3
Pilot TRF	GRT	50, 100, 250			1
Registration Stability TRF	J&JPRD	50, 100, 150, 200, 250			1
Commercial Site Stability, Proposed Commercial TRF	JOLLC	50, 100, 150, 200, 250			1

TRF: tamper-resistant formulation

2.1.3 What is tapentadol to-be-marketed formulation?

Tamper-resistant formulation is the to-be-marketed formulation.

Major excipients used in the TRF formulation

The excipients contained in tapentadol ER tablets are listed below. The excipients used in the core tablet are GRAS (generally regarded as safe) and are of compendial grade.

Excipients	Function	Reference to Standard
Polyethylene Oxide	[redacted] (b) (4)	NF
Hypromellose [redacted] (b) (4)		USP
Polyethylene Glycol [redacted] (b) (4)		NF
Vitamin E [redacted] (b) (4)		In-house
[redacted] (b) (4)		In-house
		In-house

Compositions of the clinical, registration stability, commercial site stability and proposed commercial TRF tapentadol extended-release tablets are provided in the table below.

Composition of tapentadol TRF tablets: Pilot, Registration stability and to-be-marketed batches

Formulation	Pilot batches [a]			Registration stability batches and to-be-marketed batches [b]				
Formulation number	TF5, 6323SF	TF4, 6322SF	TF3, 6316SF	F029	F030	F031	F032	F033
Dose strength (tapentadol)	50 mg	100 mg	250 mg	50 mg	100 mg	150 mg	200 mg	250 mg
Tapentadol hydrochloride, mg								(b) (4)
Polyethylene oxide, mg *(% w/w of core)*								
Hypromellose (b) (4) *(% w/w of core)*								
Polyethylene glycol (b) (4) *(% w/w of core)*								
Vitamin E, mg *(% w/w or core)*								
Tablet core weight								
Film coat (b) (4)								
Printing ink [c]								
Tablet size								
Tablet shape								
[a]								(b) (4)
[b]								
[c]								
[d]								

NA= not applicable

Composition core of the tapentadol TRF tablets: registration and TBM batches only

Component	Quality Reference	Function	Dose Strength (Free Base of Tapentadol)									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
Tapentadol HCl (R331333)	Non-compendial											(b) (4)
Polyethylene Oxide	NF											
Hypromellose (b) (4)	USP											
Polyethylene Glycol (b) (4)	NF											
(b) (4)												
Vitamin E	USP											
Polyethylene Glycol (b) (4)	NF											
Total Core Tablet Weight												
[a]												(b) (4)
[b]												

-- = Not applicable

Composition coating of the tapentadol TRF tablets: registration and TBM batches only

Film Coat	Quality Reference	Function	Dose Strength									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
(b) (4)	Noncompendial											(b) (4)
	Noncompendial											
	Noncompendial											
	Noncompendial											
	Noncompendial											
	USP											
	Noncompendial											
	Noncompendial											
	NF											
Propylene Glycol[b]	USP											

a (b) (4)

b

-- = Not applicable

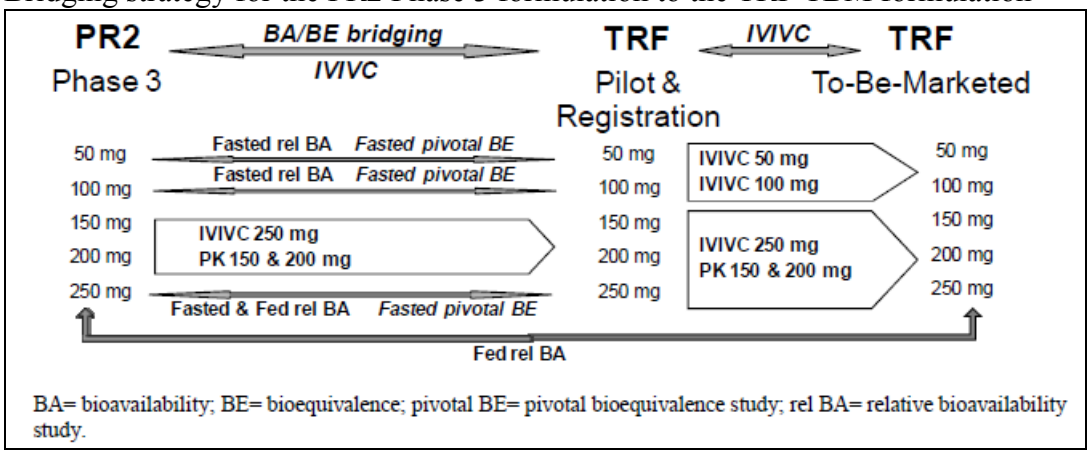
2.1.4 Are the to-be-marketed, tamper-resistant ER, and clinical trial, PR2, formulations bridged?

There are no bioequivalence trials conducted to bridge the Phase 3 clinical formulation, PR2 to TBM TRF tapentadol ER formulation. In Phase 3 trials, PR2 ER formulation was predominantly used. The Applicant utilized IVIVC modeling to link the two formulations. The IVIVC modeling information was reviewed by Dr. Sandra Suarez in the Office of New Drug Quality Assessment (ONDQA). She concluded that the IVIVC modeling data was not sufficient to adequately bridge the PR2 and TRF TBM formulations.. In order to provide adequate information, the Applicant needs to submit bioequivalence information from two doses, at least, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations. The Applicant will have to provide in vitro dissolution data in support of the biowaiver of the intermediate doses.

There were no bioequivalence trials conducted to bridge the clinical formulation, PR2, to TBM TRF tapentadol ER formulation. In Phase 3 trials, PR2 ER formulation was predominantly used and administered regardless of food intake. The Applicant stated that PR2 and TRF formulations were developed concurrently; the PR2 formulation was developed at J&JPRD and the TRF was developed at GRT. The tablets were carefully formulated to match the release profile between PR2 and TRF. The Applicant stated that the key ingredient in the formulations is (b) (4)

The Applicant attempted to utilize in-vitro-in-vivo-correlation method to bridge PR2 and TRF TBM formulations. The general approach was depicted in the diagram below provided by the Applicant:

Bridging strategy for the PR2 Phase 3 formulation to the TRF TBM formulation



BA= bioavailability; BE= bioequivalence; pivotal BE= pivotal bioequivalence study; rel BA= relative bioavailability study.

As seen in the figure above, two bridging strategies are applied: (1) bioequivalence bridging of the PR2 Phase 3 formulation to the pilot, registration and TBM batches of the TRF formulation and (2) use of IVIVC to bridge between the pilot and registration batches of the TRF formulation (TRF development site; Beerse, Belgium), and the TBM TRF formulation (TRF commercial site; Gurabo, Puerto Rico), as well as to bridge between the PR2 Phase 3 formulation and the TRF formulation. It is noted that this 2-part strategy was discussed and agreed upon during a Type C Meeting (9/5/08) and the pre-NDA meeting (1/23/09). For in vivo bridging results between PR2 and Pilot/Registration TRF formulations, as well as bridging PR1 to PR2 ER formulations, see Section 2.5, General Biopharmaceutics.

The IVIVC modeling assessment was conducted by the Dr. Sandra Suarez in ONDQA and concluded that the IVIVC modeling data was not sufficient to adequately bridge the PR2 and TRF TBM formulations.. In order to provide adequate information, the Applicant needs to submit bioequivalence information from two doses, 50 and 250 mg strengths, comparing PR2 and TRF TBM formulations. The Applicant has to provide adequate in vitro dissolution data in support of the biowaiver of the intermediate doses.

2.1.5 What is the proposed mechanism of action?

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

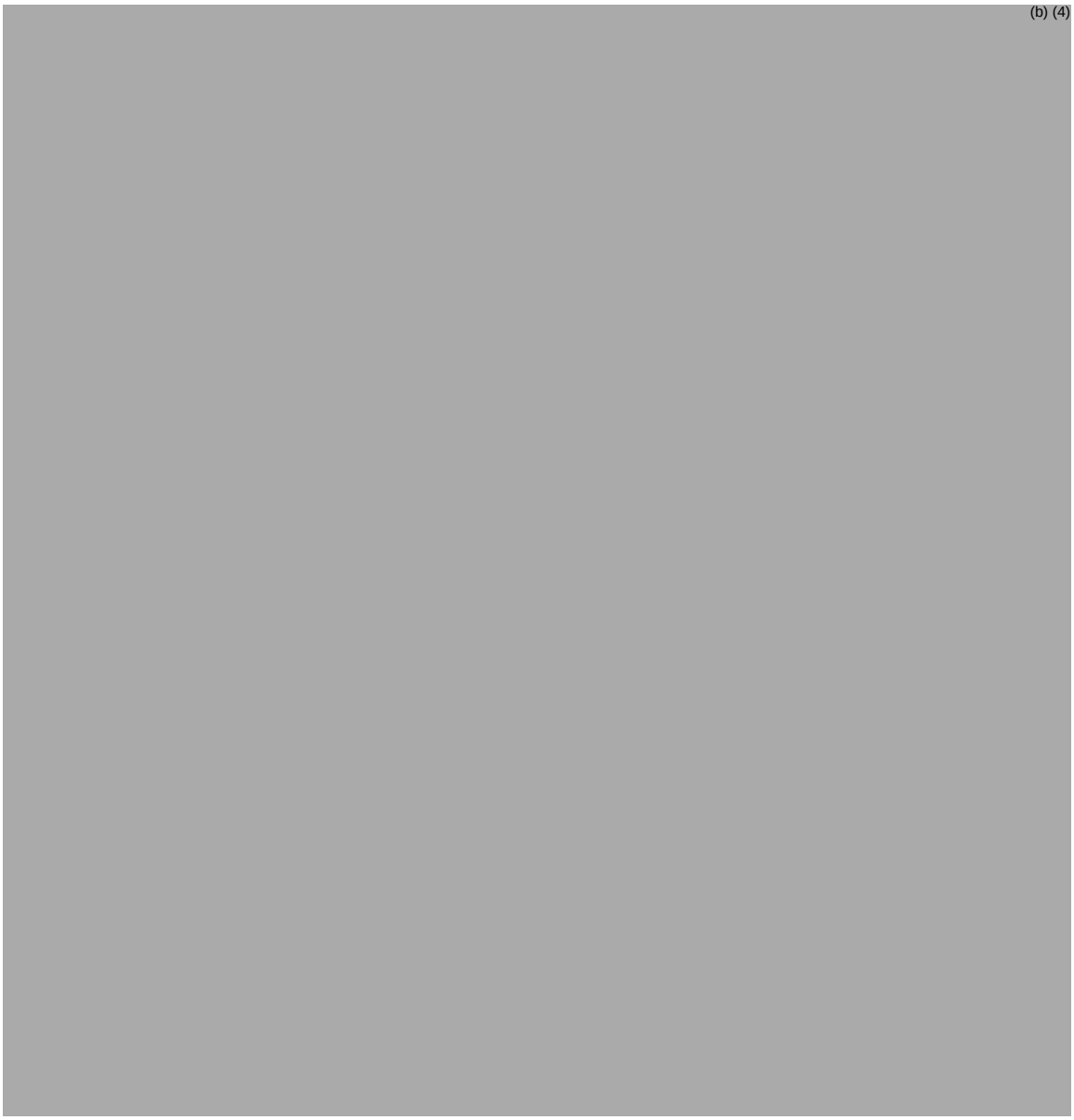
Tapentadol is a centrally active antinociceptive drug developed for the relief of moderate to severe acute pain. The proposed mechanism of action for tapentadol is that it is both a μ-opioid receptor (MOR) agonist and an inhibitor of norepinephrine (NE) re-uptake. Both mechanisms are likely to contribute 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.

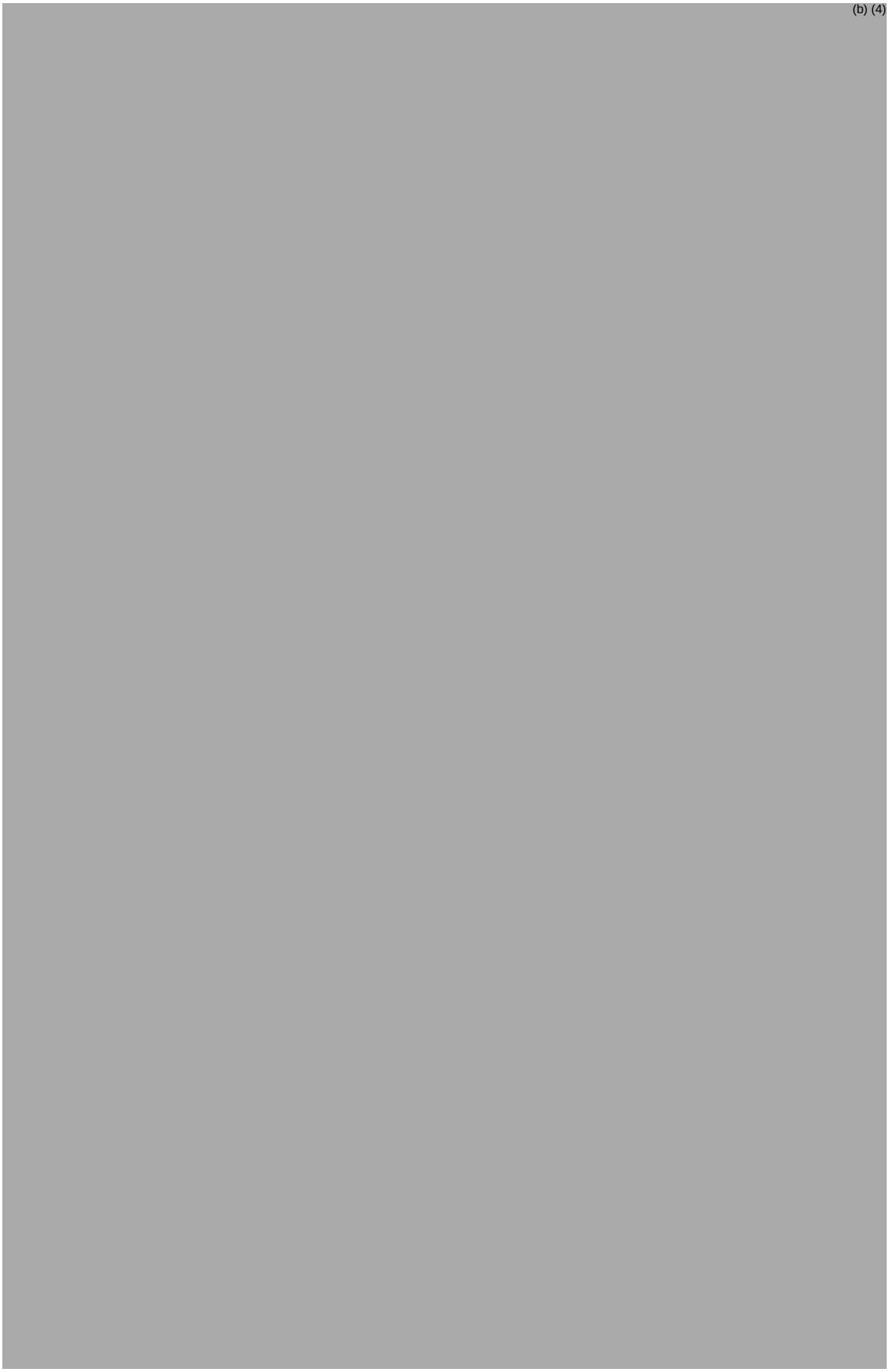
2.1.6 What are the proposed dosage and route of administration?

Tapentadol HCl tablet is taken orally. As per the proposed package insert, the proposed tapentadol dosage and administration is as follows:

2 DOSAGE AND ADMINISTRATION



(b) (4)



2.1 Renal Impairment

2.2 Hepatic Impairment

2.3 Elderly Patients

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses.

There is no dosage and administration for pediatric patients and nursing mothers. The following information is from Section 8 Use in Specific Populations

8.3 Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/ toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. NUCYNTA™ ER should not be used during breast-feeding.

8.4 Pediatric Use

The safety and effectiveness of tapentadol in pediatric patients <18 years of age have not been established and, therefore, use of tapentadol in this population is not recommended.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal clinical trials and efficacy measurements?

There were four 'pivotal' Phase 3 trials. Three Phase 3 trials used a controlled dose adjustment regimen that included a 3-week titration period followed by a 12-week maintenance period where subjects could adjust their dose within pre-defined criteria in subjects with moderate to severe chronic low back pain (LBP) or moderate to severe chronic pain due to osteoarthritis (OA) of the knee. One Phase 3 trial used a fixed dose regimen during the maintenance period in subjects with painful diabetic peripheral neuropathy (DPN). This trial included an open-label 3-week titration followed by a randomized, double-blind withdrawal 12-week maintenance. At the end of the titration period, a responder criterion was used to select only subjects who had demonstrated pain relief from the treatment to continue into the withdrawal, fixed dose maintenance treatment period. To provide long-term tapentadol ER safety information as well as data on maintenance of pain relief, 1-year, open-label safety study in the management of mild to severe chronic pain in patients with OA or LBP was performed.

There were four 'pivotal' Phase 3 trials. Three Phase 3 trials, in subjects with moderate to severe chronic low back pain (LBP) (PAI-3011/KF23) or moderate to severe chronic pain due to osteoarthritis (OA) of the knee (PAI-3008/KF11 and PAI-3009/KF12), used a controlled dose adjustment regimen that included a 3-week titration period followed by a 12-week maintenance period where subjects could adjust their dose within pre-defined criteria. These trials used randomized, double-blind, placebo- and active- controlled (oxycodone CR) design.

One Phase 3 trial, in subjects with painful diabetic peripheral neuropathy (DPN) (Study PAI-3015/KF36), used a fixed dose regimen during the maintenance period. This trial included an open-label 3-week titration followed by a randomized, double-blind withdrawal 12-week maintenance. At the end of the titration period, a responder criterion was used to select only subjects who had demonstrated pain relief from the treatment to continue into the withdrawal, fixed dose maintenance treatment period. This trial used randomized double-blind, placebo-controlled withdrawal design.

To provide long-term tapentadol ER safety information as well as data on maintenance of pain relief, a randomized, active-controlled, 1-year, open-label safety study (PAI-3007/KF24) in the management of mild to severe chronic pain in patients with OA or LBP was performed. An additional, study was performed in subjects with LBP to establish the dose equivalence and a direct conversion ratio between the IR and the ER tapentadol formulations (PAI-3019/KF39).

Note: The Agency accepted the study design of titration-to-optimal dose with a statistical comparison of all subjects treated with the study drug as one active group against the placebo group. At the meeting, it was also requested that the last observation carried forward (LOCF) imputation method should not be the only imputation method for missing pain assessments after subject discontinuation. Other imputation methods were recommended, such as baseline observation carried forward (BOCF) or worst observation carried forward (WOCF) including baseline. Also recommended was an analysis method, such as responder analysis, that treats all subjects who discontinued treatment as non-responders. A sensitivity analysis including additional imputation methods was included in all Phase 3 studies. In addition, the Agency requested that the primary endpoint in the pivotal Phase 3 studies be defined as the change from baseline of the average daily pain intensity on an 11-point numerical rating scale (NRS) over the last week of the Maintenance Period at Week 12. For non-US regulatory authorities, the primary endpoint was defined as the change from baseline of the average pain intensity over the 12-week Maintenance Period of the daily pain intensity (NRS). The primary endpoint for one authority was considered a secondary endpoint for the other.

Primary efficacy variables

The primary endpoint in the pivotal Phase 3 studies was defined as the change from baseline of the average daily pain intensity on an 11-point numerical rating scale (NRS) over the last week of the Maintenance Period at Week 12.

Secondary efficacy variables

There were various secondary efficacy endpoints included in the Phase 3 trials:

Patient Global Impression of Change (PGIC): The 7-point PGIC was chosen as a complementary assessment of efficacy.

- Brief Pain Inventory (BPI): The BPI is a patient-reported outcome that provides information on the intensity of pain (the sensory dimension) as well as the degree to which pain interferes with function (the reactive dimension).
- Western Ontario McMaster Questionnaire (WOMAC): The WOMAC is a patient-reported efficacy outcome specific to subjects with OA.
- Short Form-36 Health Survey (SF-36): The SF-36 is a widely used subject-based health status survey, and measures health status and outcomes from the subject's point of view.
- EuroQol-5 Dimension (EQ-5D): The EQ-5D health questionnaire which provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of health care and in population health surveys to assess health outcome from a wide variety of interventions.
- Sleep Questionnaire: A 4-item self-assessment sleep questionnaire evaluated sleep latency (Item 1), number of awakenings (Item 2), time slept (Item 3), and sleep quality (Item 4) experienced by the subject during the preceding night.

The following table contains the design of the clinical trials:

	Pain Condition	Design	Treatment dosing and duration	Active Control
Phase 2 Studies				
KF09	OA	DB/PC	4 weeks fixed dose	Oxycodone CR
KF10	LBP	DB/PC	4 weeks fixed dose	Tramadol PR
PAI-2001/KF19	OA	DB/PC	2 weeks forced dose titration 2 weeks fixed dose maintenance	Oxycodone CR
PAI-2002/KF20	LBP	DB/PC	2 weeks forced dose titration 2 weeks fixed dose maintenance	Tramadol PR
Phase 3 Studies				
PAI-3011/KF23	LBP	DB/PC	3 weeks flexible dose titration 12 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3015/KF36[a]	DPN	RW/DB/PC	3 weeks open-label flexible dose titration 12 weeks fixed dose maintenance	None
PAI-3008/KF11	OA	DB/PC	3 weeks flexible dose titration 12 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3009/KF12	OA	DB/PC	3 weeks flexible dose titration 12 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3007/KF24[b]	LBP, OA	OL	1 week titration 51 weeks controlled dose adjustment maintenance	Oxycodone CR
PAI-3019/KF39[c]	LBP	DB/CO (IR/ER)	3 weeks flexible dose titration (tapentadol IR) 2 weeks fixed dose maintenance per period	None

[a] Enrichment procedures (ie, responder criteria after the Titration Period) to continue long-term treatment on a fixed dose only in subjects who benefited from the treatment.
[b] Study designed primarily as long-term safety study with secondary efficacy evaluations.
[c] Tapentadol IR/ER 2-way crossover direct conversion study.
OA = osteoarthritis, LBP = low back pain, DPN = diabetic peripheral neuropathy, DB = double-blind, PC = placebo controlled, RW = randomized withdrawal, OL = open-label, CO = crossover, IR = immediate release; ER = extended release; CR = controlled release; SR = sustained release

The following study design was used for most of the Phase 3 trials.

Dosage and administration

Subjects were randomized in 1:1:1 ratio and received BID tapentadol ER 50 mg, oxycodone CR 10 mg, or placebo for the first 3 days (6 consecutive doses). They were then titrated upwards to receive BID tapentadol ER 100 mg, oxycodone CR 20 mg, or placebo for the following 4 days. These were the lowest study drug doses allowed for the remainder of the study. The study drug was taken orally BID in the morning and in the evening, with or without food. There were no special needs relating to administration.

At Visit T2 after 1 week of titration, subjects could have their study drug titrated upwards. Subjects further increased the dose of their study drug by specified amounts after 3 days (increments of tapentadol ER 50 mg BID, oxycodone CR 10 mg BID, or placebo). The maximum doses for tapentadol ER and oxycodone CR were to be 250 mg BID and 50 mg BID, respectively. Downward titration (but not below the minimum dose) was also permitted anytime using the same decrements. At Visit T3 after 2 weeks of titration, subjects could have their study drug titrated upwards or downwards depending on the degree of pain experienced and reported adverse events. Subjects were instructed that they could further increase their study drug by 50 mg BID after 3 days and decrease their study drug at any time. To enter the maintenance period, subjects could not use

acetaminophen and had to be on a stable dose of the study drug for the last 3 days of the titration period.

At Visit M1, the subject entered the controlled dose-adjustment, 12-week maintenance period. Study drug doses were assessed at the scheduled Visits M1 to M7. If needed, subjects could request an adjustment of their dose based on their individual analgesia requirements and/or tolerability experience. After evaluation by the Investigator, the dose was adjusted up or down to the next available dose of study drug to achieve the optimal therapeutic benefit. Subjects were instructed to maintain a steady study drug dose level over the course of the controlled adjustment as adjustments were to be kept at a minimum during the maintenance period. The total duration of study drug administration was 15 weeks.

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

There were no dynamic biomarkers measured in the trials for tapentadol ER tablets. For tapentadol IR tablets, pupillometry (the relationship between decreases 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) 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 IR tablet.

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.

2.2.4 Exposure-response

2.2.4.1 What are the dose ranges, dosing interval, controlled dose adjustment and fixed dosing, and rescue medication used for efficacy?

Dose range

The Applicant presented the following rationale for the selection of the dose ranges in the Phase 3 studies. The dose range studied in the Phase 3 studies was 100 mg to 250 mg BID, with a starting dose of 50 mg BID for the Titration Periods.

Phase 2 trials (Study PAI-2001/KF19 OA of the knee; Study PAI-2002/KF20 LBP) indicated that the lowest dose in the Maintenance Period was 100 mg BID; the 100 mg BID treatment arm showed a numerically greater decrease in pain intensity than placebo, although the difference was not statistically significant. Interestingly, the mean pain scores for tapentadol ER 25-50-100 mg were in the same range as with oxycodone CR 20

mg BID (-42.9 tapentadol ER versus -41.8) or tramadol PR 200 mg BID (-20.3 tapentadol ER versus -21.2). Results from Study PAI-2001/KF19 showed that, after 2 weeks of treatment, the subjects who were taking tapentadol ER 150 mg had statistically significantly greater pain improvement compared to the placebo group (p=0.002). In the same trial, Study PAI-2001/KF19, doses of tapentadol ER 200 mg BID for 2 weeks were superior to placebo. The incidence of treatment-emergent adverse events was similar in the tapentadol ER 100-150-200 mg BID group and the oxycodone CR 10-10-20 mg BID group. Tapentadol group had notably lower incidences of constipation and somnolence.

Tapentadol 250 mg dose was not explored in Phase 2. Rather, 250 mg BID was simply included in the Phase 3 studies. It is noted that the dose was increased 25% compared to the highest dose studied in Phase 2. Again, oxycodone CR BID was used was used as the active control, but, in the 20 mg to 50 mg range, for studies in LBP and OA. It should be noted that oxycodone is the commonly used opioid, and 20 to 50 mg is the commonly used range in clinical practice.

It appears that the rationale for dose selection as presented by the Applicant is acceptable, as indicated by the results presented in the previous section.

Dosing interval

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

The Applicant stated that the use of long-acting opioids or prolonged-release formulations may reduce the risk of intermittent withdrawal symptoms associated with pain peaks compared with the use of short-acting preparations. Therefore, a twice-daily (morning and evening) dosing scheme was explored in the Phase 2 and Phase 3 trials. Tapentadol has a relatively short half-life, approximately 4 to 5 hours. It would benefit the patient if a formulation was developed to maintain therapeutic serum concentrations with minimal fluctuations and stable pain relief throughout the day. The pharmacokinetic data from the Phase 1 trials supplemented the BID dosing regimen. This BID dosing was explored in subjects with moderate to severe chronic pain in the tapentadol ER Phase 3 placebo-controlled efficacy studies (15 week dosing; the first 3 weeks allowing titration to an optimal dose in terms of efficacy and tolerability, followed by a 12-week maintenance period).

It appears that the rationale for dosing interval as presented by the Applicant is acceptable, as indicated by the results presented in the previous section.

Controlled dose adjustment and fixed dosing

The design of the Phase 3 studies in subjects with LBP (PAI-3011/KF23) and OA (PAI-3008/KF11 and PAI-3009/KF12) included an initial flexible 3 week titration period to reach the optimal dose followed by controlled dose adjustment during a 12 week maintenance period. The reasons for the use of flexible titration and controlled dose

adjustment are typical characteristic of opioid trials, as an individual's response to opioid therapy varies, requiring individual dose adjustments to achieve optimal efficacy and to minimize adverse effects (gastrointestinal- or central nervous system-related symptoms). Additionally, the flexible titration to optimal dose and controlled dose adjustment during the maintenance period would reduce the number of subjects discontinuing due to adverse events or lack of efficacy.

It is noted that a fixed dosing scheme during the 12-week maintenance period was used in the PAI-3015/KF36 DPN study so that efficacy and safety per dose category could be assessed without influence of dose adjustment. In this study, patients were titrated to their optimal individual dose (ranging from 100 to 250 mg BID) with tapentadol ER over a 3-week period. After the titration period, patients were maintained on a fixed dose of tapentadol ER or placebo.

Rescue medication

As far as rescue medication is concern, acetaminophen/paracetamol 1 to 4 g per day was allowed. Rescue medication is a major confounding factor for efficacy results in chronic pain studies due to the fact that higher frequency/amount or rescue medications are used in ineffective drug or placebo treatment groups. In the Phase 3 studies of LBP (PAI-3011/KF23) and OA (PAI-3008/KF11 and PAI-3009/KF12), acetaminophen/paracetamol was allowed up to 1 g per day during the titration period, but was not allowed during the last 3 days of the titration period or at all during the maintenance period with the exception of up to 1 g per day for no more than 3 consecutive days for reasons other than the study-related pain.

In the DPN study (PAI-3015/KF36), supplemental acetaminophen/paracetamol (up to 2 g per day) was allowed during the titration open-label period, except for the last 4 days of titration when eligibility for randomization to subsequent tapentadol ER or placebo treatment during the maintenance period was determined. Due to the randomized withdrawal design of the study, supplemental analgesia with tapentadol ER 25 mg was allowed twice daily for the first 4 days of the maintenance period and once daily for the rest of the maintenance period. The use of tapentadol ER supplemental analgesia were to aid in alleviating potential withdrawal symptoms, preventing rebound or relapse of pain due to withdrawal of opioid treatment in subjects receiving placebo, maximizing subject retention, and maintaining the study blind.

During the 1-year safety study, PAI-3007/KF24, acetaminophen/paracetamol up to 1 g daily was allowed as additional analgesic medication for a maximum of 7 consecutive days and no more than 14 days out of 30 days. In PAI-3019/KF39 (comparing tapentadol IR and tapentadol ER) in chronic LBP, acetaminophen/paracetamol up to 2 g per day was allowed at any time.

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

There is no dose-response or concentration-response information in the application due to the fact that the trial design allowed initial dose titration and flexible dosing in maintenance phase. Patients were allowed to titrate upward or downward in both phases, which the dose-response analysis made difficult since there is no 'fixed' dose category, per se. However, tapentadol efficacy by dose range or dose category was assessed based on the pooled efficacy data (comprising of PAI-3011/KF23 [LBP], PAI-3008/KF11 [OA of the knee], and PAI-3009/KF12 [OA of the knee] trials). The analysis of average pain intensity score by dose category, dose range, and dose changes supports the conclusion that tapentadol ER doses ranging from 100 mg to 250 mg given twice daily were efficacious.

Primary endpoint

The following table contains the Applicant's analyses on the primary endpoint.

Summary of Primary Endpoint: Change From Baseline to Week 12 of Maintenance (LOCF, Intent-to-Treat Analysis Set)

Study	Statistic	Placebo	Tapentadol ER	Oxycodone CR
PAI-3011/ KF23 (LBP)	N	316	312	323
	Mean (SD)	-2.1 (2.33)	-2.9 (2.66)	-2.9 (2.52)
	Median (Range)	-1.7 (-10 to 3)	-2.7 (-10 to 2)	-2.8 (-10 to 4)
	LS Mean Change	-2.1	-2.9	-2.9
	LS Mean Difference versus placebo (SE)		-0.8 (0.19)	-0.9 (0.19)
	95% CI (versus placebo)		(-1.22,-0.47)	(-1.24,-0.49)
	P-value (versus placebo) [a]		<0.001	<0.001
PAI-3015/ KF36 (DPN)	N	192	193	
	Mean (SD)	1.3 (2.41)	-0.1 (1.69)	
	Median (Range)	1.0 (-7 to 9)	-0.1 (-7 to 5)	
	LS Mean Change	1.4	0.0	
	LS Mean Difference versus placebo (SE)		-1.3 (0.20)	
	95% CI (versus placebo)		(-1.70, -0.92)	
	P-value (versus placebo) [b]		<0.001	
PAI-3008/ KF11 (OA)	N	336	344	342
	Mean (SD)	-2.2 (2.54)	-3.0 (2.39)	-2.6 (2.38)
	Median (Range)	-1.9 (-10 to 5)	-2.8 (-10 to 3)	-2.3 (-10 to 3)
	LS Mean Change	-2.3	-2.9	-2.6
	LS Mean Difference versus placebo (SE)		-0.7 (0.18)	-0.3 (0.18)
	95% CI (versus placebo)		(-1.04, -0.33)	(-0.68, 0.02)
	P-value (versus placebo) [a]		<0.001	0.069
PAI-3009/ KF12 (OA)	N	336	319	331
	Mean (SD)	-2.5 (2.30)	-2.7 (2.40)	-2.3 (2.36)
	Median (Range)	-2.2 (-9 to 3)	-2.7 (-9 to 3)	-2.0 (-9 to 5)
	LS Mean Change	-2.4	-2.6	-2.2
	LS Mean Difference versus placebo (SE)		-0.3 (0.18)	0.2 (0.18)
	95% CI (versus placebo)		(-0.61, 0.09)	(-0.16, 0.54)
	P-value (versus placebo) [a]		0.152	0.279

[a] Test for no difference between treatments from ANCOVA model with factor(s) treatment, pooled center and baseline pain intensity as covariate (type 3 SS) unadjusted p-value.

[b] Test for no difference between treatments from ANCOVA model with factor(s) treatment, country, subject's tapentadol ER dose category at the end of open-label Titration Period, and subject's prior opioid use status, (type 3 SS) unadjusted p-value.

Baseline is before start of Double-Blind Titration in PAI-3011/KF23, PAI-3008/KF11, and PAI-3009/KF12, and Baseline in PAI-3015/KF36 is before start of Double-Blind Maintenance.

ANCOVA = analysis of covariance; CI = confidence interval; CR = controlled release; DPN = diabetic peripheral neuropathy; ER = extended release; LBP = low back pain; OA = osteoarthritis; LS = least square; N = number of subjects; SD = standard deviation; SE = standard error

The Applicant stated that tapentadol ER consistently demonstrated numerically greater and statistically significant pain relief compared with placebo in 2 studies of similar design and duration: 1 study of LBP (PAI-3011/KF23) and 1 study in pain due to OA (PAI-3008/KF11). The effect size was at least -0.7 on an 11-point NRS (least square mean difference to placebo) for the primary endpoint. Similar results were observed for oxycodone CR treatment in both trials.

For patients with painful DPN Study PAI-3015/KF36, the Applicant stated that the, using a responder criterion before randomization, the difference in analgesic effect between tapentadol ER and placebo (a least square mean difference to placebo of -1.3) at the end of the Maintenance Period was statistically significant.

The Applicant stated that statistically significant improvements in pain intensity were not demonstrated in the second OA trial (PAI-3009/KF12), neither for tapentadol ER nor for oxycodone CR. As both treatments did not differentiate from placebo, assay sensitivity was not demonstrated in this study. However, a numerically greater decrease from baseline in average pain intensity with tapentadol ER than with placebo. The magnitude of the change in this trial was smaller than the other OA trial (PAI-3008/KF11). The Applicant stated that they did not notice any noteworthy differences between the populations of the 2 OA studies with regard to baseline pain intensity or demographic characteristics. However, Study PAI-3008/KF11 enrolled subjects primarily from the US and Canada, whereas Study PAI-3009/KF12 (OA) enrolled subjects from 12 countries throughout Europe. In Study PAI-3009/KF12 (OA), there was large variability in discontinuation rates and effect sizes across countries.

Secondary endpoints

Responder Rates - Average Pain Intensity Score at Week 12 of the Maintenance Period

Based on the distributions of the responder rates (as defined by the magnitude of response) at Week 12 of the double-blind Maintenance Period, Studies PAI-3011/KF23 (LBP) (50% vs. 40%) and PAI-3015/KF36 (DPN) (63.8% vs. 61.5%) showed a statistically significantly greater percentage of subjects in the tapentadol ER group than in the placebo group. There were no statistically significant differences in overall distributions of responders in the PAI-3008/KF11 and PAI-3009/KF12 OA studies for tapentadol ER and placebo.

Patient Global Impression of Change

At the end of the treatment period, 55.5% to 64.4% of tapentadol ER-treated subjects in all trials reported “very much improved” or “much improved” in the overall status, compared with only 32.7% to 43.2% of placebo-treated subjects. These findings were consistent and statistically significant across studies.

Brief Pain Inventory

The BPI was evaluated in Studies PAI-3011/KF23 (LBP) and PAI-3015/KF36 (DPN). In both studies, there were improvements observed in BPI Item 1 (pain other than everyday

kinds of pain) and Item 8 (percent pain relief) for subjects in the tapentadol ER treatment group. Subjects in the tapentadol ER group compared with the placebo group reported statistically significant improvements in pain interference score (Items 9A to 9G), pain subscale scores (Items 3 to 6), and the total score (Items 9A to 9G, Items 3 to 6).

Western Ontario McMaster Questionnaire
The WOMAC was evaluated in the two OA studies (PAI-3008/KF11 and PAI-3009/KF12). The change from baseline in WOMAC global score at Week 12 of the Maintenance Period was greater for tapentadol ER (-1.2) relative to placebo (-0.9) in Study PAI-3008/KF11. Additionally, pain, stiffness, and physical function mean changes from baseline to Week 12 of the Maintenance Period were greater in the tapentadol ER treatment group than in the placebo group.

Short Form 36 Health Survey Scores
Tapentadol ER treatment had statistically significant better scores than placebo for physical function, role-physical, bodily pain, and physical component of the SF-36 health survey in Studies (PAI-3011/KF23 [LBP] and PAI-3008/KF11 [OA]). Tapentadol ER treatment was statistically significantly better than placebo for the role-physical, bodily pain, and social function components in painful DPN study (PAI-3015/KF36).

EuroQuol-5 Dimension
Tapentadol ER treatment had statistically significantly greater improvements on the EQ-5D health status index at the end of the study compared with those receiving placebo in Studies (PAI-3011/KF23 [LBP], PAI-3015/KF36 [DPN], and PAI-3008/KF11 [OA])

Sleep Questionnaire
No clinically meaningful differences were observed between the tapentadol ER and placebo groups in terms of changes in sleep latency, number of awakenings, or the reported sleep duration in all trials.

See Clinical review by Dr. Eric Brodsky for final assessment of the efficacy findings of the phase III trials.

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

The Applicant pooled the safety data from the completed Phase 2/3 clinical trials and compared pooled tapentadol ER, pooled oxycodone ER and placebo groups. In the 9 Phase 2/3 studies in the pooled analysis, the overall percentage of subjects with at least 1 treatment-emergent-adverse-events (TEAE) was greater in the "all" tapentadol ER group (71.7%) than in the placebo (54.5%), placebo-post tapentadol ER (51.8%), and "all" tramadol PR (65.5%) groups but was less than for subjects in the "all" oxycodone CR group (86.3%). The most commonly reported TEAEs (reported in at least 10% of subjects) in the “all” tapentadol ER group were nausea, dizziness, constipation, headache, and somnolence. Of the most commonly reported TEAEs, nausea, dizziness,

constipation, and somnolence were reported in a higher percentage of subjects in the "all" tapentadol ER group than for subjects in the placebo group.

Nausea, vomiting, constipation, dizziness, somnolence, and pruritus were reported less frequently for subjects in the "all" tapentadol ER group than for subjects in the "all" oxycodone CR group. This indicates that the adverse event profile for tapentadol ER is similar to those of centrally acting analgesics, while at the same time a lower incidence of a number of adverse events typically associated with a mu-opioid receptor-agonism was observed (ie, gastrointestinal events such as nausea, vomiting, constipation, as well as pruritus). The majority of subjects had TEAEs that were mild to moderate in intensity.

Incidence of TEAEs by System Organ Class and Preferred Term in at Least 10% of Subjects in Any Pooled Treatment Group (All Studies)

System Organ Class Preferred Term	Placebo (N=1498) n (%)	Pla (Post Tap ER) (N=193) n (%)	All Tap ER (N=3613) n (%)	All Oxy CR (N=1472) n (%)	All Tra PR (N=249) n (%)
Total no. subjects with TEAEs	817 (54.5)	100 (51.8)	2589 (71.7)	1271 (86.3)	163 (65.5)
Gastrointestinal disorders	370 (24.7)	27 (14.0)	1464 (40.5)	952 (64.7)	93 (37.3)
Nausea	128 (8.5)	12 (6.2)	704 (19.5)	531 (36.1)	55 (22.1)
Constipation	85 (5.7)	2 (1.0)	493 (13.6)	464 (31.5)	29 (11.6)
Vomiting	44 (2.9)	2 (1.0)	269 (7.4)	292 (19.8)	34 (13.7)
Nervous system disorders	288 (19.2)	27 (14.0)	1308 (36.2)	662 (45.0)	65 (26.1)
Dizziness	77 (5.1)	3 (1.6)	495 (13.7)	291 (19.8)	25 (10.0)
Headache	170 (11.3)	10 (5.2)	427 (11.8)	174 (11.8)	23 (9.2)
Somnolence	44 (2.9)	0	408 (11.3)	240 (16.3)	20 (8.0)
Skin and subcutaneous tissue disorders	80 (5.3)	15 (7.8)	481 (13.3)	332 (22.6)	40 (16.1)
Pruritus	20 (1.3)	0	176 (4.9)	183 (12.4)	10 (4.0)
Hyperhidrosis	16 (1.1)	6 (3.1)	160 (4.4)	75 (5.1)	27 (10.8)

Adverse events were coded using MedDRA Version 11.0. Preferred term = Dictionary derived term
Tap=Tapentadol, Oxy=Oxycodone, Tra=Tramadol. Tapentadol ER = Tapentadol PR.
Pla (Post Tap ER) indicates data relating to subjects in PAI-3015/KF36 who received placebo after dosing with tapentadol ER.
Note: Percentages calculated using the number of subjects in each treatment group as a denominator.

2.2.4.4 Does tapentadol prolong the QT interval?

Previously submitted information (Nucynta IR NDA 22304) showed that no significant QT prolongation effect of tapentadol was detected. In this ER NDA, the Applicant submitted a QT study (HP5503/10) conducted in March, 2003. This study used 100 mg and 200 mg ER B.I.D. dosing. The total daily dose from this ER study was less than that of the total daily dose used in IR study, HP5503/25; therapeutic, 100 mg, and supratherapeutic doses, 150 mg, were administered every 6 hours on Day 1 and on Day 2 to achieve tapentadol steady-state (total of 5 doses each). Since total ER daily dose used in HP5503/10 was less than total IR daily dose used in HP5503/25, QT-IRT was not consulted. The Labeling for this ER NDA will continue to reflect that no significant QT prolongation effect of tapentadol was detected.

Study HP5503/10 was a double-blind, double-dummy, randomized, placebo- and 400 mg moxifloxacin positive-controlled, 4-way crossover study in healthy subjects (20 men and 19 women) aged 45 to 65 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. Each subject received 100 mg or 200 mg ER BID for 2 days. A single oral dose of 800 mg moxifloxacin was given. Twelve-lead ECGs were taken immediately before and up to 24 hours after the last dose of study drug (steady-state) in the morning of Day 3. Blood samples for the determination of tapentadol and moxifloxacin were collected from predose up to 48 hours after the last dose. The table below contains the Applicant's descriptive statistics for the differences to baseline for the mean of Day 3 +3 to +7 hours for baseline corrected QTc (ms) analysis. The Applicant concluded that tapentadol did not exhibit any QTc prolongation effects.

Mean changes of 100 and 200 mg tapentadol ER tablet

Treatment	Arith. Mean	SD	Minimum	Median	Maximum
100 mg	-6.629	6.986	-21.98	-5.889	10.18
200 mg	-7.781	7.102	-19.97	-7.692	11.85
placebo	-4.714	5.621	-21.49	-4.883	8.73
moxifloxacin	11.526	9.027	-3.57	12.298	36.80

The results of the statistical analysis are given in the following table.

Estimated Mean (DF[1]) (90% CI)			
100 mg CG5503	200 mg CG5503	100 mg-200 mg	Moxifloxacin
PR - Placebo	PR - Placebo	CG5503 PR	- Placebo
-0.617 (93)	-2.269 (93)	1.652 (93)	15.543 (93)
(-3.181, 1.946)	(-7.151, 2.613)	(-3.235, 6.538)	(13.059, 18.027)

* QTc corrected by QT + a(1-RR**0.5) from regression on all baseline measurements on day 0 using equation QT = b + aRR**0.5.

[1] DF = degrees of freedom as calculated from the ANOVA procedure

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

The absolute oral bioavailability of tapentadol from the PR1 tablets was 32% in the fasted state. The Cmax and AUC of tapentadol PR1 86-mg tablets with a high-fat breakfast increased 61% and 19%, respectively, compared with the fasted state. The ER properties of the tapentadol PR1 formulation had no impact on the extent of exposure of tapentadol compared with the IR formulation. The rate of exposure clearly changed, expressed by a decrease in Cmax of approximately 60% and a higher median value for tmax of 5 hours compared with 1 to 1.5 hours for the IR formulation. The exposure of tapentadol increased dose proportionally after single oral administration of tapentadol PR2 tablets of 50, 100, 200 and 250 mg as assessed by AUC. Cmax increased with dose, but did not fulfill the criteria for dose proportionality. Graphical exploration of the data, however, suggested approximate linearity between Cmax and dose in the dose range of 50 to 250 mg.

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 CYP450 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 in vitro. Tapentadol is not an inducer of CYP450 1A2, 2C9 and 3A4 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.

Absolute bioavailability with PR1 'early' formulation:

Study HP08 was a single-center, open-label, single-dose, randomized, 4-period, 4-way crossover study in healthy white men to determine the absolute bioavailability of tapentadol PR1 86-mg and 21.5-mg tablets. Subjects received tapentadol as 1) a 15-min i.v. infusion of 34 mg (69 mg/50 mL, batch ALAI02), 2) a PR1 86-mg tablet (batch AMEG27) after an overnight fast and after a high-fat, high calorie breakfast; and, 3) a PR1 21.5-mg tablet (batch AMKD07) after an overnight fast. Serial blood samples were collected from predose up to 24 hours (i.v. and oral 21.5 mg) or 32 hours (oral 86 mg) postdose, respectively, for the analysis of tapentadol.

Mean PK parameter estimates of tapentadol and the statistical comparison are presented in the following table. The absolute bioavailability of the PR1 tablets was 32% in the fasted state. AUCinf and Cmax from the tapentadol PR1 86-mg tablets under fed conditions were 119% and 161%, respectively, compared with fasted administration.

Tapentadol PK Parameters and Statistical Comparison After Single-Dose Administration as i.v. Infusion (34 mg Tapentadol), PR1 Tablets (86 mg Tapentadol) Fed and Fasted, and PR1 Tablets (21.5 mg Tapentadol) Fasted (HP08)

N=18	**34 mg i.v.**	**86 mg p.o. fasted**	**86 mg p.o. fed**	**21.5 mg p.o. fasted**
Cmax, ng/mL	172 ± 78.5	**22.0 ± 6.30**	37.2 ± 10.4	4.61 ± 1.14
AUClast, ng.h/mL	361 ± 51.9	**290 ±71.3**	355 ± 91.9	57.4 ± 12.5
AUCinf, ng.h/mL	364 ± 52.2	**298 ± 74.4**	359 ± 93.9	75.0 ± 20.4
tlag, h	0.00 (0.00-0.00)	**0.00 (0.00-0.50)**	0.00 (0.00-1.00)	0.00 (0.00-0.75)
tmax, h	0.22 (0.13-0.42)	**5.00 (1.00-7.00)**	5.00 (2.00-8.00)	5.00 (1.50-6.00)
t1/2, h	3.43 ±0.46	**4.19 ± 1.55**	3.89 ± 0.96	10.1 ± 4.66
CL (CL/F), L/h	96.2 ± 13.6	**305 ± 73.1**	254 ± 61.8	307 ± 82.2
CL (CL/F), mL/min[a]	1603 ± 227	**5083 ± 1218**	4233 ± 1030	5117 ± 1370
F, % (95% CI)[b]	-	**31.7 (28.0-35.9)**	37.7 (33.3-42.7)	31.6 (27.9-35.8)

[a] Post-hoc evaluation.
[b] After dose-normalization (based on log-transformed data for treatment comparisons).
Data expressed as mean ± SD, except for t_{max} and t_{lag} where median (range) is provided.

Ratio:

	34 mg i.v.	86 mg PO fasted	86 mg PO fed	21.5 PO fasted
Cmax	-	-	160.8 (132.8-194.7)	-
AUC0-inf	-	-	119.0 (107.3-132.1)	-

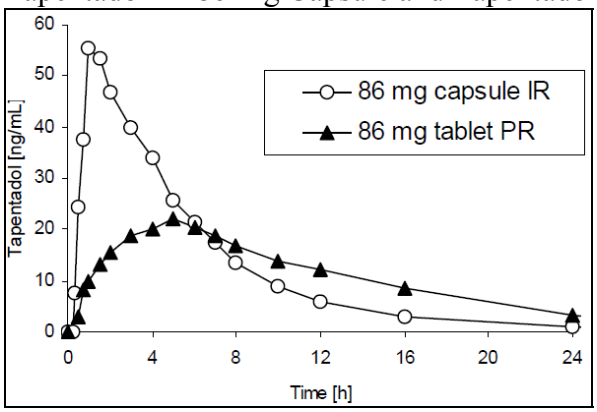
Relative bioavailability with PR1 'early' formulation:

Study HP08 was a single-center, open-label, single-dose, randomized, 4-period, 4-way crossover study in healthy white men to determine the relative bioavailability of tapentadol early PR1 tablets of 86 mg (batch AEEG19) and 172 mg (batch AAGAU03) and tapentadol IR capsules of 21.5 mg (batch AEAM06) and 86 mg (batch AEFD04). Serial blood samples were collected from predose up to 24 hours (21.5 mg only) or 32 hours postdose for the analysis of tapentadol.

Mean PK parameter estimates of tapentadol and the statistical comparison are presented below. The treatment ratios of AUCinf for the tapentadol PR1 86-mg and 172-mg tablets versus the tapentadol IR 86-mg capsules were 95.8% and 105.3%, respectively. The 90% CIs were contained within the accepted 80.00% to 125.00% bioequivalence range. The treatment ratios of Cmax were drastically different; approximately 60%. Tmax values were also drastically different, 5 hours for the PR1 formulation compared with a median of 1 to 1.5 hours for the IR formulation. Half life values were similar for all treatments.

If the regulatory standard of 80.00% to 125.00% bioequivalence range is applied, dose proportionality was met for the tapentadol PR1 86-mg and 172-mg tablets regarding AUCinf. A minor deviation from dose proportionality was observed for Cmax (upper limit of 90% CI was 126.7%).

Mean Serum Concentration-Time Profiles of Tapentadol After Administration of Tapentadol IR 86-mg Capsule and Tapentadol PR1 86-mg Tablets (HP07)



Tapentadol PK Parameters and Statistical Comparison After Single-Dose Administration of Tapentadol PR1 86-mg and 172-mg Tablets; and Tapentadol IR 21.5-mg and 86-mg Capsules (HP07)

n=16	21.5 mg IR	86 mg IR	86 mg PR1	172 mg PR1
C_{max}, ng/mL	14.0 ± 3.83	64.2 ± 18.7	22.5 ± 4.60	51.2 ± 12.6
AUC_{last}, ng.h/mL	66.3 ± 13.8	316 ± 56.0	295 ± 50.1	658 ± 139
AUC_{inf}, ng.h/mL	69.1 ± 14.0	318 ± 55.9	299 ± 50.7	668 ± 143
t_{lag}, h	0.00 (0.00-0.33)	0.00 (0.00-0.50)	0.00 (0.00-0.00)	0.00 (0.00-0.50)
t_{max}, h	1.00 (0.75-2.00)	1.50 (0.75-4.00)	5.00 (2.00-7.00)	5.00 (3.00-6.07)
$t_{1/2}$, h	4.07 ± 0.85	4.74 ± 1.12	4.03 ± 0.75	4.04 ± 0.91
HVD, h	3.48 ± 1.20	3.60 ± 1.11	12.5 ± 2.74	12.0 ± 2.30
MRT, h	5.81 ± 0.70	5.96 ± 0.91	10.6 ± 1.39	10.3 ± 1.07
Point Estimates, % (90% CI)	86 mg PR1/ 86 mg IR	172 mg PR1/ 86 mg IR	172 mg PR1/ 86 mg PR1	
C_{max} [a]	36.4 (32.4-40.9)	41.1 (36.6-46.1)	112.9 (100.5-126.7)	
AUC_{inf} [a]	95.8 (87.8-104.4)	105.3 (96.6-114.9)	110.0 (100.9-120.0)	

[a] After dose-normalization to 86 mg, based on log-transformed data.
Data expressed as mean ± SD, except for t_{max} and t_{lag} where median (range) is provided.
HVD= half value duration.

Relative BA and dose linearity with PR2 (Phase 3 – [redacted] (b) (4) formulation):

Study HP27 was an open-label, single-dose, 5-period, sequential, ascending-dose, single-center study to evaluate the dose proportionality of tapentadol following increasing single doses of tapentadol PR2 tablets ([redacted] (b) (4) Phase 3 formulation) of 50 mg (batch PD2124), 100 mg (batch PD2127), 200 mg (batch PD2136), and 250 mg (batch PD2139) in healthy men and women. Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol and tapentadol-O-glucuronide.

Results: Mean PK parameter estimates of tapentadol are presented in the table below. One subject vomited within 6 hours after dose administration, and, was excluded from the analysis. The table showed that 50 mg AUCinf values from IR and PR2 ([redacted] (b) (4) Phase 3 formulation) were comparable, 198 ng.h/mL vs. 185 ng.h/mL. However, as expected Cmax values between the two formulations were drastically different.

Tapentadol PK Parameters After Single-Dose Administration of Tapentadol IR 50-mg Tablets and Tapentadol PR2 50-, 100-, 200-, and 250-mg Tablets (PAI-1021/HP27)

	IR	PR2			
	50 mg (n=36)	50 mg (n=36)	100 mg (n=36)	200 mg (n=36)	250 mg (n=35)
C_{max}, ng/mL	54.6 ± 19.9	10.1 ± 2.59	25.5 ± 6.38	62.5 ± 17.9	89.3 ± 28.1
AUC_{last}, ng.h/mL	195 ± 51.9	176 ± 42.8	377 ± 90.0	819 ± 191	1087 ± 249
AUC_{inf}, ng.h/mL	198 ± 52.9	185 ± 43.4	387 ± 89.1	825 ± 191	1096 ± 250
t_{max}, h	1.00 (0.50-3.00)	5.00 (0.50-12.00)	5.00 (1.00-12.00)	5.00 (1.00-9.00)	5.00 (1.00-6.00)
t_{lag}, h	0.00 (0.00-0.00)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
$t_{1/2}$, h	4.3 ± 0.6	7.6 ± 2.9	6.4 ± 1.6	5.2 ± 0.9	5.4 ± 1.0
Frel, %	100	95.3	99.4	106	113
Dose-normalized to 200 mg					
C_{max}, ng/mL		40.4 ± 10.4	51.0 ± 12.8	62.5 ± 17.9	71.5 ± 22.5
AUC_{last}, ng.h/mL		705 ± 171	754 ± 180	819 ± 191	869 ± 199
AUC_{inf}, ng.h/mL		741 ± 174	774 ± 178	825 ± 191	877 ± 200

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

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

The following information is from the tapentadol IR tablet NDA. As stated above, the extent of tapentadol absorption, and, thus, distribution, metabolism and excretion of tapentadol from ER tablets are not expected to be different from that of IR tablets.

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.

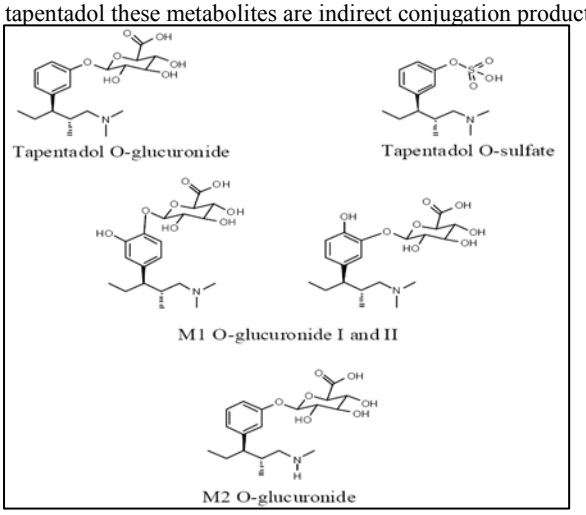
Metabolism:

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-sulphate 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 CY2D6 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 being 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 390μM or higher, which is approximately 400-fold the maximum clinical serum concentration of around 1μM. Therefore, limitation of this metabolic elimination route by direct drug-drug interactions during treatment is considered to be unlikely.

2.2.5.2 **What are the single dose and multiple dose PK parameters?**

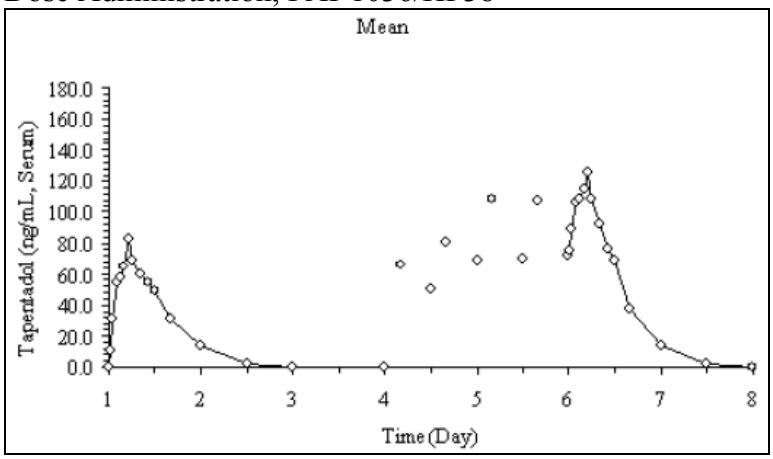
Tapentadol ER has minimal accumulation after multiple dose of tapentadol ER tablets. The data from the multiple-dose trial indicated the inter-subject variability was low (CV between 17.2% and 26.3%) after single- and multiple-dose.

TRF 'registration/stability' formulation

Study 38 was an open-label, single-center, single- and multiple-dose study using tapentadol ER (registration TRF) 250 mg tablets in healthy subjects. Subjects sequentially received a single oral dose of tapentadol 250 mg ER administered to each subject on Day 1 of the study after a standardized breakfast and multiple doses of tapentadol 250 mg ER each administered every 12 hours on Days 4, 5 and 6 (total of 5 doses). PK blood sampling for the analysis of tapentadol and its metabolite tapentadol-O-glucuronide was performed at specified times during the 48-hour period after the single-dose administration, before each morning drug administration of the multiple-dose period and during the 48-hour period after the final dose in the multiple-dose period.

The following figure shows that trough serum tapentadol concentrations increased with consecutive doses until steady state was achieved approximately at Day 5 (i.e., 24 hours after first multiple dose administration started).

Mean Serum Concentration-Time Profiles for Tapentadol After Single- and Multiple-Dose Administration, PAI-1036/HP38



The following table contains PK parameters after single-and multiple-dose of tapentadol ER formulation.

Single- and Multiple-Dose PK Parameters of Tapentadol and Tapentadol-O-Glucuronide, PAI-1036/HP38

		Tapentadol		Tapentadol-O-glucuronide	
Parameters	n	Mean ± SD	%CV	Mean ± SD	%CV
Single Dose 250 mg					
C_{max}, ng/mL	15	88.0 ± 27.8	31.6	3669 ± 963	26.3
t_{max}, h	15	5.00 (2.00 - 12.00)	-	5.00 (2.02 – 12.00)	-
AUC_{0-12h}, ng.h/mL	15	651 ± 202	31.1	26527 ± 5623	21.2
AUC_{inf}, ng.h/mL	15	1070 ± 303	28.3	42835 ± 9239	21.6
$t_{1/2}$, h	15	4.4 ± 0.8	17.9	4.1 ± 0.9	20.7
250 mg b.i.d., 5 doses					
$C_{max,ss}$, ng/mL	17	132 ± 35.1	26.7	5714 ± 985	17.2
$t_{max,ss}$, h	17	5.00 (2.00 – 10.02)	-	5.00 (4.00 – 10.02)	-
AUC_{τ}, ng.h/mL	16	1144 ± 339	29.7	48246 ± 9061	18.8
$t_{1/2}$, h	16	5.2 ± 1.0	18.8	4.9 ± 0.9	18.8
$C_{avg,ss}$, ng/mL	16	95.2 ± 28.1	29.5	4014 ± 755	18.8
FI, %	16	65.3 ± 27.1	41.4	67.5 ± 26.7	39.6
Acc.Ratio (C_{max})	17	1.60 ± 0.605	37.7	1.64 ± 0.338	20.6
Acc.Ratio (AUC)	14	1.86 ± 0.552	29.7	1.82 ± 0.328	18.0

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

The estimated mean T1/2 for tapentadol was similar after single- and multiple-dose (4.4 hours vs. 5.2 hours, respectively). The data showed that there is minimal accumulation after multiple-dose of tapentadol ER tablets. The data from the multiple-dose trial indicated the inter-subject variability was low (CV between 17.2% and 26.3%) after single- and multiple-dose.

2.2.5.3 **Does the ER formulation show linear pharmacokinetic behavior?**

Tapentadol ER showed dose linearity from 50 to 150 mg from PR2 (b) (4) *formulation, which is the clinical Phase 3 formulation. Tapentadol ER showed dose*

linearity from 86 and 172 mg from PR1 'early' formulation; it is noted that this trial had 2 doses.

Several studies were conducted to assess dose linearity.

Linearity with PR1 'early' formulation:

Study HP08 was a single-center, open-label, single-dose, randomized, 4-period, 4-way crossover study in healthy white men to determine the relative bioavailability of tapentadol early PR1 tablets of 86 mg (batch AEEG19) and 172 mg (batch AAGAU03) and tapentadol IR capsules of 21.5 mg (batch AEAM06) and 86 mg (batch AEFD04). Serial blood samples were collected from predose up to 24 hours (21.5 mg only) or 32 hours postdose for the analysis of tapentadol.

Mean PK parameter estimates of tapentadol and the statistical comparison are presented below. The AUCinf value approximately doubled (~2.23-fold) for 172 mg PR2 tablet compared to 86 mg PR2 formulation.

Tapentadol PK Parameters and Statistical Comparison After Single-Dose Administration of Tapentadol PR1 86-mg and 172-mg Tablets; and Tapentadol IR 21.5-mg and 86-mg Capsules (HP07)

n=16	21.5 mg IR	86 mg IR	86 mg PR1	172 mg PR1
C_{max}, ng/mL	14.0 ± 3.83	64.2 ± 18.7	22.5 ± 4.60	51.2 ± 12.6
AUC_{last}, ng.h/mL	66.3 ± 13.8	316 ± 56.0	295 ± 50.1	658 ± 139
AUC_{inf}, ng.h/mL	69.1 ± 14.0	318 ± 55.9	299 ± 50.7	668 ± 143
t_{lag}, h	0.00 (0.00-0.33)	0.00 (0.00-0.50)	0.00 (0.00-0.00)	0.00 (0.00-0.50)
t_{max}, h	1.00 (0.75-2.00)	1.50 (0.75-4.00)	5.00 (2.00-7.00)	5.00 (3.00-6.07)
$t_{1/2}$, h	4.07 ± 0.85	4.74 ± 1.12	4.03 ± 0.75	4.04 ± 0.91
HVD, h	3.48 ± 1.20	3.60 ± 1.11	12.5 ± 2.74	12.0 ± 2.30
MRT, h	5.81 ± 0.70	5.96 ± 0.91	10.6 ± 1.39	10.3 ± 1.07
Point Estimates, % (90% CI)	86 mg PR1/ 86 mg IR	172 mg PR1/ 86 mg IR	172 mg PR1/ 86 mg PR1	
C_{max} [a]	36.4 (32.4-40.9)	41.1 (36.6-46.1)	112.9 (100.5-126.7)	
AUC_{inf} [a]	95.8 (87.8-104.4)	105.3 (96.6-114.9)	110.0 (100.9-120.0)	

[a] After dose-normalization to 86 mg, based on log-transformed data.
Data expressed as mean ± SD, except for t_{max} and t_{lag} where median (range) is provided.
HVD= half value duration.

Linearity with PR2 ((b) (4) formulation; Phase 3 formulation):

Study HP27 was an open-label, single-dose, 5-period, sequential, ascending-dose, single-center study to evaluate the dose proportionality of tapentadol following increasing single doses of tapentadol PR2 tablets (Phase 3 formulation) of 50 mg (batch PD2124), 100 mg (batch PD2127), 200 mg (batch PD2136), and 250 mg (batch PD2139) in healthy men and women. Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol and tapentadol-O-glucuronide.

It should be noted that the treatment period with administration of tapentadol IR 50-mg tablet was included for an exploratory IVIVC.

Mean PK parameter estimates of tapentadol are presented in table below. One subject vomited within 6 hours after dose administration. This subject was excluded from the analysis. A moderate intersubject variability (coefficient of variation between 16.4% and 38.2%) was observed among PR2 formulations.

The statistical analysis of dose-normalized parameters showed that the 90% CIs of the AUClast and AUCinf for any pair of doses was always within the 80.00% to 125.00% bioequivalence limit. Graphical exploration of the data, however, suggested approximate linearity between Cmax and the dose in the dose range of 50 to 250 mg.

Tapentadol PK Parameters After Single-Dose Administration of Tapentadol IR 50-mg Tablets and Tapentadol PR2 50-, 100-, 200-, and 250-mg Tablets (PAI-1021/HP27)

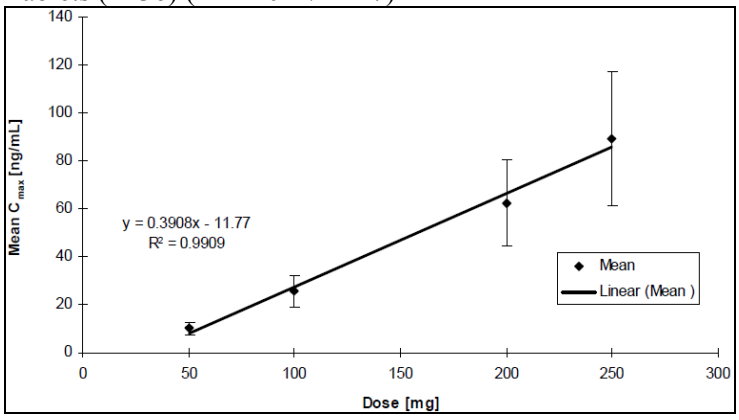
	IR	PR2			
	50 mg (n=36)	50 mg (n=36)	100 mg (n=36)	200 mg (n=36)	250 mg (n=35)
C_{max}, ng/mL	54.6 ± 19.9	10.1 ± 2.59	25.5 ± 6.38	62.5 ± 17.9	89.3 ± 28.1
AUC_{last}, ng.h/mL	195 ± 51.9	176 ± 42.8	377 ± 90.0	819 ± 191	1087 ± 249
AUC_{inf}, ng.h/mL	198 ± 52.9	185 ± 43.4	387 ± 89.1	825 ± 191	1096 ± 250
t_{max}, h	1.00 (0.50-3.00)	5.00 (0.50-12.00)	5.00 (1.00-12.00)	5.00 (1.00-9.00)	5.00 (1.00-6.00)
t_{lag}, h	0.00 (0.00-0.00)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)	0.00 (0.00-0.50)
$t_{1/2}$, h	4.3 ± 0.6	7.6 ± 2.9	6.4 ± 1.6	5.2 ± 0.9	5.4 ± 1.0
Frel, %	100	95.3	99.4	106	113
Dose-normalized to 200 mg					
C_{max}, ng/mL		40.4 ± 10.4	51.0 ± 12.8	62.5 ± 17.9	71.5 ± 22.5
AUC_{last}, ng.h/mL		705 ± 171	754 ± 180	819 ± 191	869 ± 199
AUC_{inf}, ng.h/mL		741 ± 174	774 ± 178	825 ± 191	877 ± 200

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

Pair-Wise Comparisons of PK Parameters After Single-Dose Administration of Tapentadol 50-, 100-, 200- and 250-mg PR2 Tablets Following Dose Normalization (PAI-1021/HP27)

PR2 tablets		90% CI of the ratio (test/reference)		
Test dose	Reference dose	C_{max}	AUC_{last}	AUC_{∞}
100 mg	50 mg	118.09 – 132.90	103.08 – 110.78	100.28 – 108.05
200 mg	50 mg	145.03 – 163.22	112.19 – 120.57	107.05 – 115.35
250 mg	50 mg	164.38 – 185.00	118.96 – 127.84	113.67 – 122.49
200 mg	100 mg	115.77 – 130.29	104.99 – 112.83	102.85 – 110.82
250 mg	100 mg	131.22 – 147.67	111.33 – 119.64	109.21 – 117.67
250 mg	200 mg	106.84 – 120.24	102.29 – 109.92	102.29 – 110.22

Mean Cmax After Single-Dose Administration of Tapentadol PR2 50-, 100-, 200- and 250-mg Tablets (n=36) (PAI-1021/HP27)



The solid line is the regression line, the means are indicated by dots and the SD by error bars. R2= coefficient of correlation.

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?

The data from the multiple-dose trial indicated the inter-subject variability was low (CV between 17.2% and 26.3%) after single- and multiple-dose.

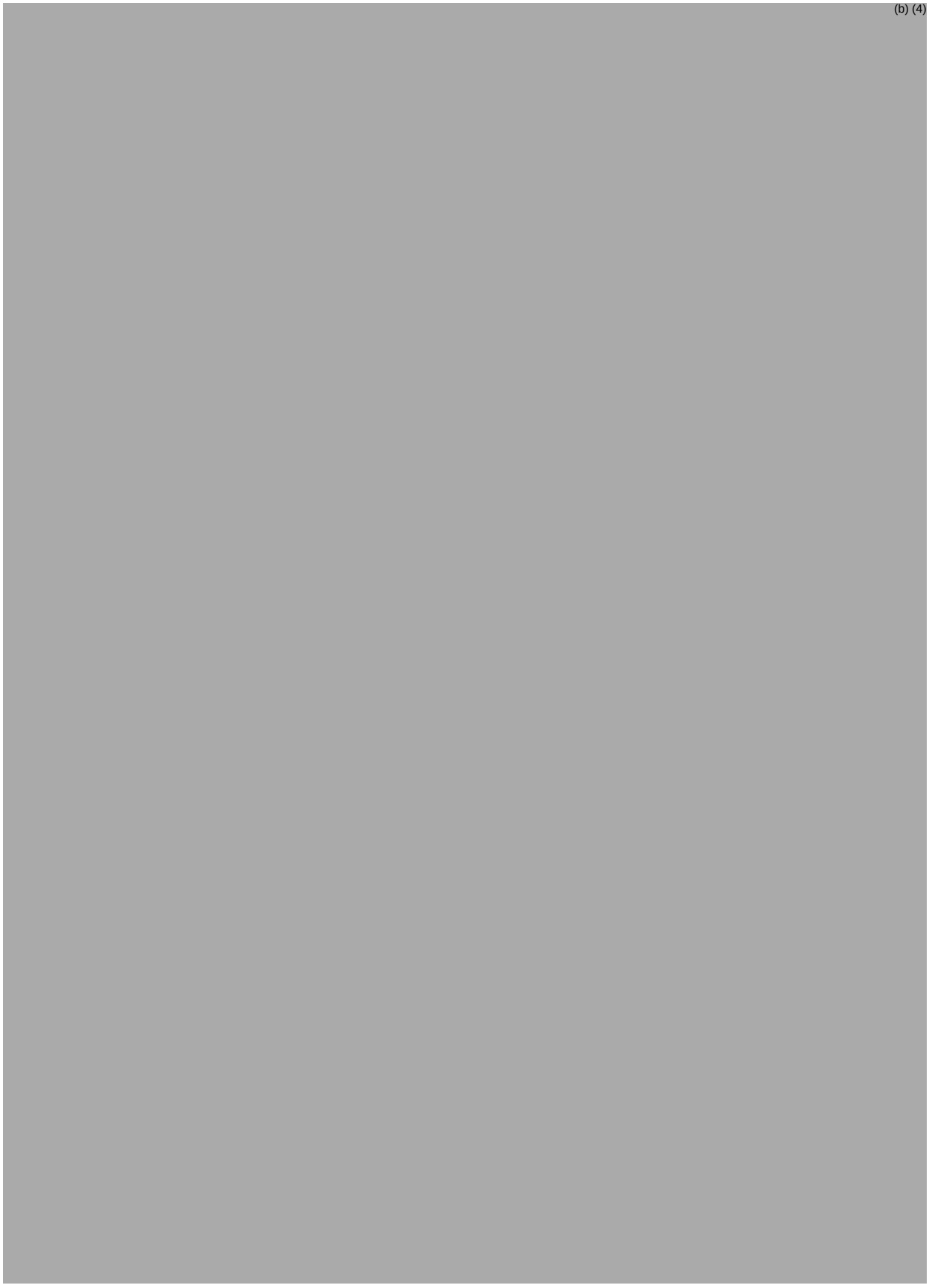
2.3 Intrinsic Factors

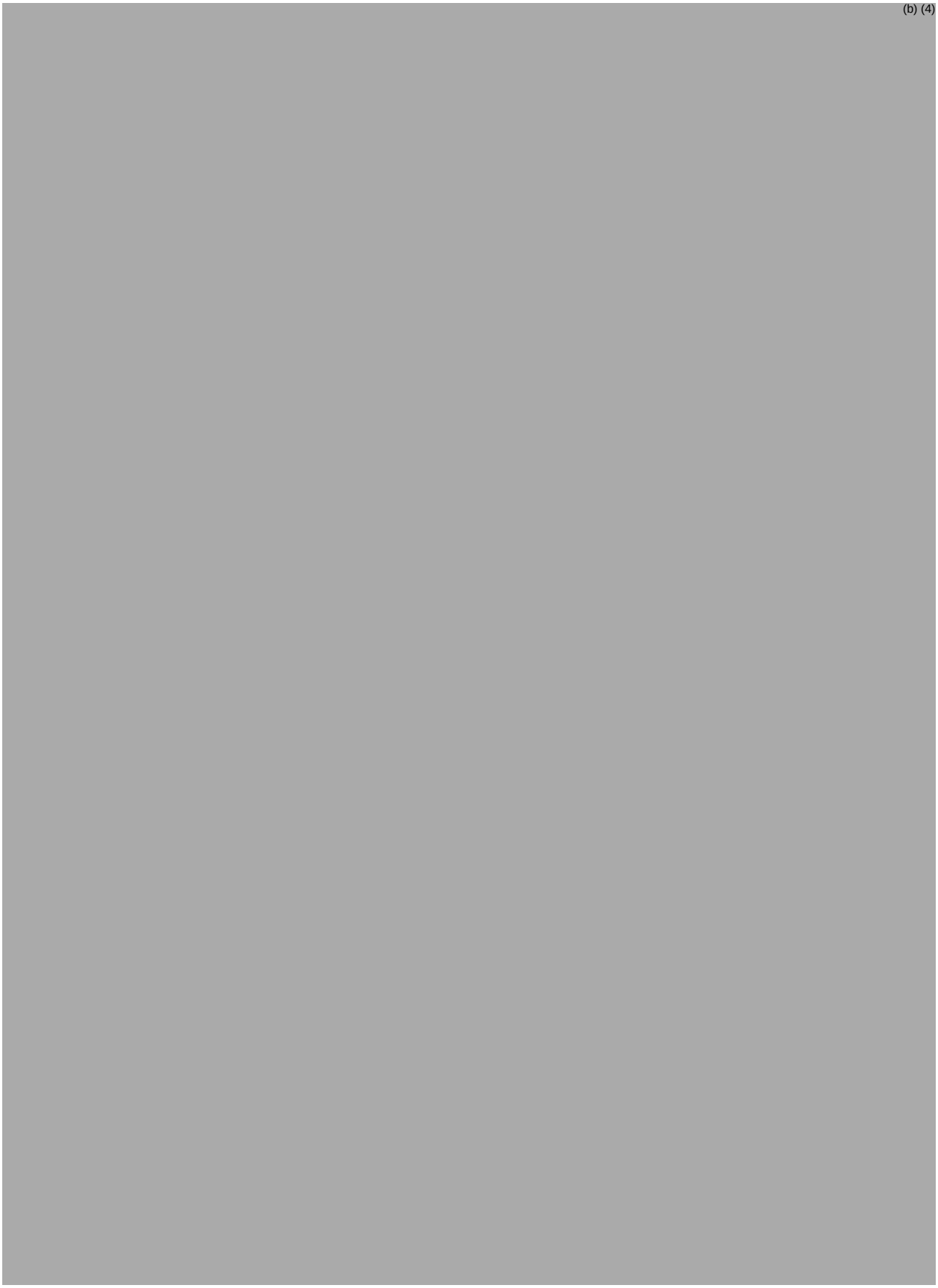
2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

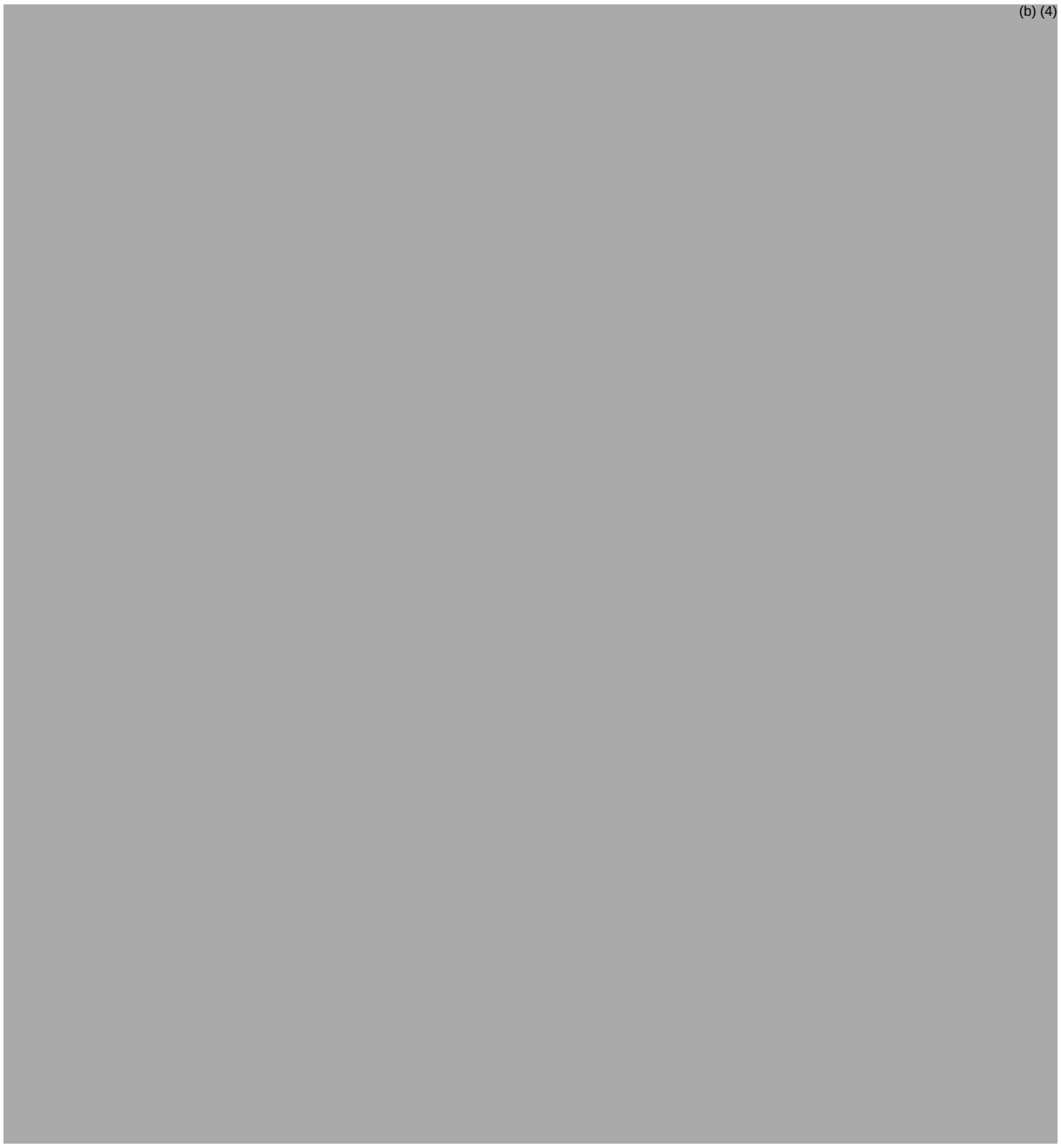
2.3.1.1 What is the status of pediatric studies and/or any pediatric plan for study?

Pediatric data has not been submitted seeking approval of pediatric indications at this stage. Instead, the Applicant requested a (b) (4) *deferral of the requirement to conduct pain studies in the pediatric population.* (b) (4)

(b) (4)


(b) (4)


(b) (4)



2.3.1.2 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.

2.3.1.3 Race

No separate studies were conducted to evaluate the effects of race on the PK of tapentadol. However, pharmacokinetic data obtained in Japanese subjects in study PAI-1026/HP47 showed similar tapentadol exposure in Japanese subjects as compared to non-Japanese subjects.

Study HP47 was a single-center, randomized, double-blind, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, PK and PD of tapentadol ER (PR1 'updated' formulation) at doses of 25, 50, 100 and 200 mg in 12 healthy Japanese men.

Single-Dose PK Parameters of Tapentadol in Japanese Healthy Men, PAI-1026/HP47

	Tapentadol Dose			
Parameter	25 mg (n=9)	50 mg (n=8)	100 mg (n=8)	200 mg (n=7)
C_{max}, ng/mL	7.84 ± 1.94	17.4 ± 2.16	46.9 ± 9.70	76.9 ± 30.1
AUC_{inf}, ng.h/mL	106 ± 30.3	220 ± 41.1	490 ± 69.0	870 ± 210
t_{max}, h	5.00 (1.50 - 9.00)	3.50 (2.00 - 6.00)	3.00 (1.50 - 6.00)	3.00 (3.00 - 9.00)
$t_{1/2}$, h	7.5 ± 2.9	5.2 ± 1.1	4.5 ± 0.8	4.1 ± 0.3
CL/F, mL/min	4500 ± 2309	3925 ± 849	3479 ± 631	4051 ± 1067
Vd_z/F, L	2590 ± 711	1752 ± 444	1371 ± 354	1470 ± 476
Dose-normalized to 25 mg				
C_{max}, ng/mL	7.84 ± 1.94	8.71 ± 1.08	11.7 ± 2.42	9.61 ± 3.77
AUC_{inf}, ng.h/mL	106 ± 30.3	110 ± 20.5	122 ± 17.3	109 ± 26.2

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

Maximum serum concentrations were obtained within 3 to 5 hours after dosing. The average half-life of tapentadol ranged from 4 to 7.5 hours across doses. The C_{max} and AUC values appear to increase with an increase in tapentadol dose in this study.

2.3.1.4 Elderly

No new information was submitted to characterize tapentadol ER formulation.

The characteristics for tapentadol exposures from IR formulation were similar in elderly and healthy subjects, suggesting that age has no impact on the PK of tapentadol. No dosage adjustment scheme was proposed, since tapentadol will be titrated to effect. 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.

2.3.1.5 Renal impairment

No new information was submitted to characterize tapentadol ER formulation.

The characteristics for tapentadol exposures from IR formulation were 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.

With respect to tapentadol-O-glucuronide, the O-glucuroinide 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. (b) (4)

Currently, the tapentadol IR tablet, Nucynta™ tablet, package insert proposes the following:

> No dosage adjustment is recommended in patients with mild or moderate renal impairment *[see Clinical Pharmacology (12.3)]*.
> NUCYNTA™ has not been studied in patients with severe renal impairment. The use in this population is not recommended.

2.3.1.6 Hepatic impairment

No new information was submitted to characterize tapentadol ER formulation.

The characteristics for tapentadol exposures from IR formulation indicated that 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 with IR formulation. 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.

Currently, the tapentadol IR tablet, Nucynta™ tablet, package insert proposes the following:

> No dosage adjustment is recommended in patients with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.
> NUCYNTA™ should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg with the interval

between doses no less than every 8 hours (maximum of three doses in 24 hours). Further treatment should reflect maintenance of analgesia with acceptable tolerability, to be achieved by either shortening or lengthening the dosing interval *[see Clinical Pharmacology (12.3)]*.

NUCYNTA™ has not been studied in patients with severe hepatic impairment and use in this population is not recommended *[see Warnings and Precautions (5.10)]*.

2.4 Extrinsic Factors

2.4.1 Drug-Drug Interactions

No new information was submitted to characterize tapentadol ER formulation.

2.4.2 Effects of Alcohol on Tapentadol

No significant dose dumping was detected with tapentadol ER TRF (Registration) formulation.

Study HP44 (single-center, randomized, open-label, 2-part (Part 1 and Part 2), single-dose, 2-way crossover, Phase 1 study after a fasting period of at least 10 hours; washout period of at least 7 days within Part 1 or Part 2; subjects participated in Part 1 are not the same as in Part 2) explored the effect of concomitant intake of alcohol (240 mL Absolut Vodka®, containing 40% alcohol administered in a single aliquot over approximately 12 minutes) with 100 and 250 mg TRF ER tablets.

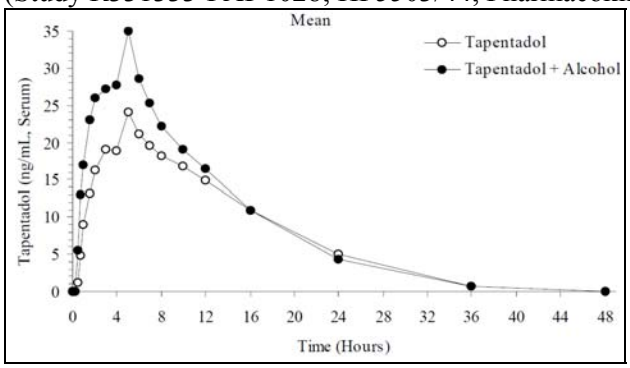
No changes were observed for T_{max} or T1/2 of tapentadol. However, based upon the least squares mean ratios, alcohol intake increased mean C_{max}, $AUC_{last,}$ and AUC_{∞} by of 48%, 17%, and 17%, respectively, was observed for tapentadol TRF 100 mg. For TRF ER 250 mg, alcohol intake increased mean C_{max}, $AUC_{last,}$ and AUC_{∞} by 28%, 16%, and 16%, respectively,

The increase in mean tapentadol C_{max} was most apparent in the 100-mg dose group, with individual C_{max} value increases in the range of 0.99-fold up to 4.38-fold following concomitant administration of 40% alcohol. However, it should be noted that in cases where the C_{max} increased about 4 times relative to control, the C_{max} values in the control treatment group were relatively low when compared to the mean C_{max} value of the control treatment.

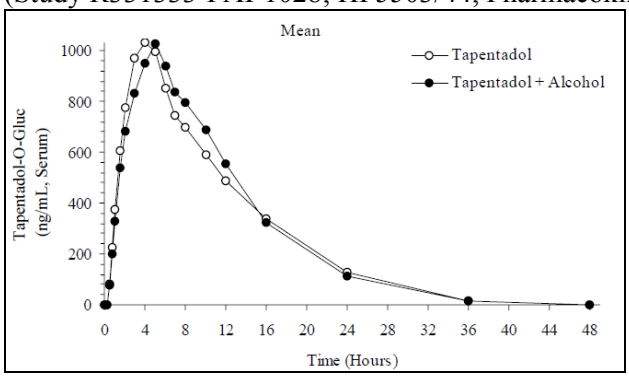
Note: With respect to safety, the dose strength of 100-mg was selected for Part 1 of the study as this dose was thought to be safe for subjects in case the formulation would not retain its extended-release properties with concurrent alcohol ingestion. Based on interim PK and safety results and a medical safety review* of Part 1 of the study and based on defined criteria**, the decision was to be made to further escalate the dose to 250 mg (FDA request to test highest clinically used dose in humans) in Part 2 of the study.

Formulation Batch/Lot Numbers Expiration Date
Tapentadol TRF 100-mg tablet 08G23/F030 July 2009
Tapentadol TRF 250-mg tablet 08G09/F033 July 2009

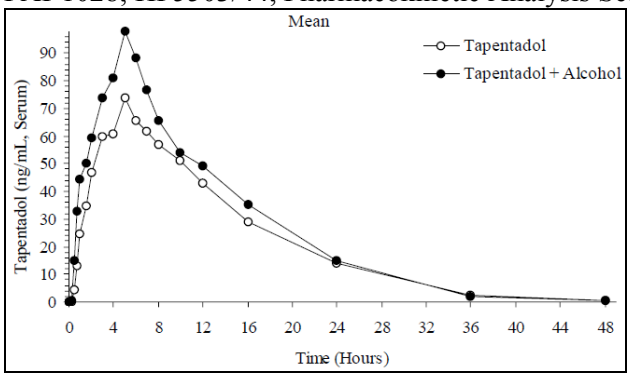
Mean Serum Concentration-Time Profiles of Tapentadol **100-mg** Dose Group (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)



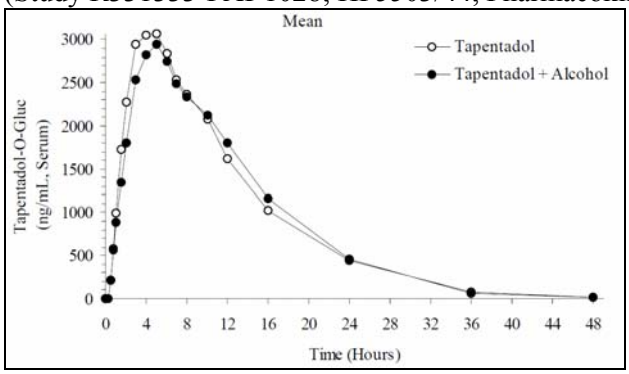
Mean Serum Concentration-Time Profiles of Tapentadol-O-Glucuronide **100-mg** Dose Group (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)



Mean Serum Concentration-Time Profiles of Tapentadol **250-mg** Dose Group (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)



Mean Serum Concentration-Time Profiles of Tapentadol-O-Glucuronide **250-mg** Dose Group (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)



Serum Pharmacokinetic Parameters (Mean ± SD) of Tapentadol (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)

Parameter	Tapentadol TRF 100 mg N=19	Tapentadol TRF 100 mg + Alcohol N=20
C_{max}, ng/ml	24.8 ± 8.64	38.0 ± 15.4
t_{max}[a], h	5.00 (1.00 to 10.00)	5.00 (1.00 to 12.00)
AUC_{last}, ng·h/ml	353 ± 98.0	420 ± 141
AUC_{∞}, ng·h/ml	357 ± 97.4	425 ± 144
$t_{1/2}$, h	5.0 ± 0.7	4.9 ± 1.3

[a] t_{max}: median (minimum to maximum); TRF: tamper resistant formulation

Summary of Analysis on the Pharmacokinetic Parameters of Tapentadol (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)

	N[a]	Treatment B: Tapentadol TRF 100 mg + Alcohol (Test) (LSM)	Treatment A: Tapentadol TRF 100 mg (Reference) (LSM)	Ratio Test/Reference	90% CI	%CV[b]
C_{max}, ng/mL	19	35.05	23.65	148.25	127.53 to 172.34	29.4
AUC_{last}, ng.h/mL	19	398.51	339.36	117.43	104.17 to 132.37	26.2
AUC_{∞}, ng.h/mL	19	403.09	343.48	117.36	104.09 to 132.31	26.3

[a] One subject (100101) dropped out in Part I, Period 2 (Day –1) of the study.
[b] %CV was derived from the MSE of the ANOVA test.
LSM: Least Squares Means; MSE: Mean Squared Error (estimated on log scale);
CI: confidence interval; %CV: % Coefficient of Variation; ANOVA: analysis of variance;
TRF: tamper resistant formulation.

Serum Pharmacokinetic Parameters (Mean ± SD) of Tapentadol (Study R331333-PAI-1028; HP5503/44: Pharmacokinetic Analysis Set)

Parameter	Tapentadol TRF 250 mg N=20	Tapentadol TRF 250 mg + Alcohol N=20
C_{max}, ng/mL	77.4 ± 19.6	104 ± 44.4
t_{max}[a], h	5.00 (3.00 to 12.00)	5.00 (0.75 to 5.00)
AUC_{last}, ng·h/mL	1046 ± 204	1253 ± 424
AUC_{∞}, ng·h/mL	1051 ± 206	1256 ± 423
$t_{1/2}$, h	5.0 ± 1.2	4.8 ± 0.7

[a] t_{max}: median (minimum to maximum); TRF: tamper resistant formulation

Summary of Analysis on the Pharmacokinetic Parameters of Tapentadol (Study R331333-PAI-1028; HP5503/44, Pharmacokinetic Analysis Set)

	N	Treatment B: Tapentadol TRF 250 mg + Alcohol (Test) (LSM)	Treatment A: Tapentadol TRF 250 mg (Reference) (LSM)	Ratio Test/Reference	90% CI	%CV[a]
C_{max}, ng/mL	20	96.31	75.12	128.20	115.87 –141.84	24.1%
AUC_{last}, ng.h/mL	20	1190.66	1026.33	116.01	105.31 – 127.80	23.6%
AUC_{∞}, ng.h/mL	20	1194.45	1031.23	115.83	105.17 – 127.57	23.6%

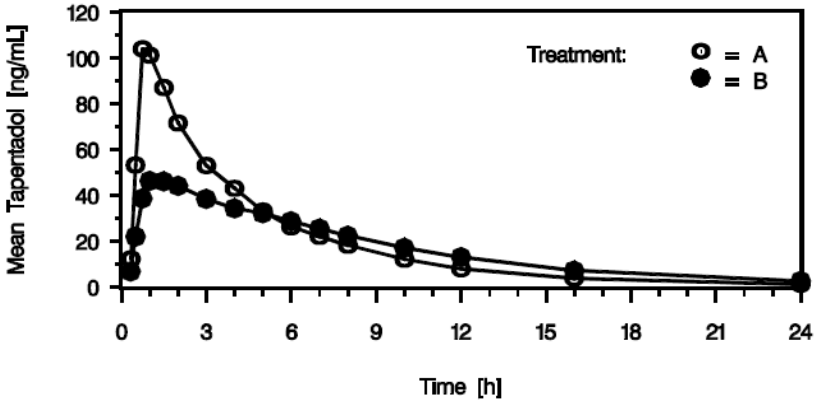
[a] %CV was derived from the MSE of the ANOVA test.
LSM: Least Squares Means; MSE: Mean Squared Error (estimated on log scale);
CI: confidence interval; %CV: % Coefficient of Variation; ANOVA: analysis of variance; TRF: tamper resistant formulation

2.4.3 Effects of mastication on Tapentadol

The mean tapentadol C_{max} following the intake of masticated (chewed) TRF tablets was lower compared to C_{max} after IR administration.

Study HP62 was a single-center, open-label, single-dose, randomized, 2-way crossover study to evaluate the safety, tolerability and pharmacokinetics following mastication (chewing) for 3 min and subsequent swallowing of a tapentadol ER ('registration' TRF) tablet compared to tapentadol IR tablet, swallowed intact. A total of 24 healthy men, aged 21 to 53 years, received at least 1 dose of tapentadol and 23 subjects completed both treatment arms. A single dose of 100 mg tapentadol ER (TRF) and 100 mg tapentadol IR tablet were administered to subjects in a randomized fashion under fasted conditions. Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol.

Mean Serum Concentration-Time Profiles of Tapentadol ER (TRF) 100 mg, Masticated Before Swallowing and Tapentadol IR 100 mg Swallowed Intact, PAI-1047/HP62



A = One 100 mg tapentadol IR tablet swallowed whole; B = One 100 mg tapentadol ER (TRF) tablet swallowed completely after mastication
Blood sampling was carried out up to 48 h. Due to the number of values below LLOQ after 24 h, means were only calculated up to 24 h.

Tapentadol PK Parameters After Single-Dose Administration of Tapentadol ER (TRF) 100 mg Masticated or Tapentadol IR 100 mg Swallowed Intact, PAI-1047/HP62

	Tapentadol IR 100 mg swallowed whole (n=23)	Tapentadol ER (TRF) 100 mg swallowed completely after mastication (n=23)
C_{max}, ng/mL	129 ± 59.9	55.8 ± 30.7
AUC_{last}, ng.h/mL	457 ± 130	417 ± 116
AUC_{inf}, ng.h/mL	462 ± 132	424 ± 114
t_{max}, h	1.00 (0.50-2.00)	1.50 (0.75-8.00)
$t_{1/2}$, h	4.78 ± 0.96	4.99 ± 0.91

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

Summary of Statistical Analyses of Pharmacokinetic Parameters of Tapentadol (n=23), PAI-1047/HP62

Parameter	Ratio TRF/IR (%)	90% CI	CV (%)
AUC_{last}	91.08	86.67 - 95.71	9.78
AUC_{inf}	91.65	87.28 - 96.23	9.63
C_{max}	43.09	35.36 - 52.50	40.44

The data indicated that Cmax value from chewed TRF ER formulation was drastically lower than that of the IR tablet, whereas, AUC values from both formulations were similar.

2.5 General Biopharmaceutics

2.5.1 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?

Tapentadol was designated as BCS Class I drug (Nucynta IR N22304). The Applicant conducted IVIVC modeling using all dose ranges strengths of TRF tapentadol ER tablets to link the Phase 3 trial TR2 'final' formulation to that of the TRF TBM formulation. The results of IVIVC was reviewed by the Biopharmaceutics team in ONDQA.

2.5.2 What is the relationship between the various formulations developed in the overall product development stages, namely, 'early' and 'updated' PR1 formulations, (b) (4) PR2 formulations, and, 'pilot', 'Registration/stability' and 'to-be-marketed' TRF formulations, in terms of comparative exposure?

As stated above in section 2.1.2, there are several formulations developed throughout the product development. These formulations were used in various trials providing unique pieces of information for the tapentadol ER tablet. In order to utilize useful information, e.g., in order to relative BA information of ER tablet compared to IR tablets, the following comparison was made. Initially, the within formulation comparison was made primarily using the in vitro dissolution data:

1. 'Initial' vs. 'Updated' PR1
    a. Initial PR1 - absolute bioavailability (BA) to tapentadol intravenous infusion (Study HP08)
    b. 'Initial' PR1 – relative BA to IR capsule (Study HP07)

2. [redacted] PR2; it is noted that [redacted] formulation was mostly used for P3 trials
    a. [redacted] PR2 – food effect (Study HP28) and dose linearity (Study HP27)

3. 'Pilot' vs. 'Registration/stability' vs. 'TRF' TBM
    a. 'Registration' TRF - relative BA 150 and 200 mg fasted vs. 75 mg tapentadol oral solution (Study HP57)
    b. 'Registration' TRF – 100 and 250 mg alcohol interaction study (Study HP44)
    c. 'Registration' TRF – Single and multiple dose fed study 250 mg (Study HP38)
    d. 'Registration' TRF vs. IR tablet – SD 100 mg TRF chewed/swallowed vs. 100 mg IR swallowed (Study HP62)

Further comparison was made with in vitro/in vivo information, if available, e.g.:

1. Compare 'updated' PR1 vs. [redacted] PR2 – relative BA; note that if PR1 initial and updated is same and PR2 [redacted] is same, we can use this linkage (Study HP18)

2. Compare [redacted] PR2 vs. 'pilot' TRF
    a. relative BA 50 mg (Study HP41)
    b. relative BA 100 mg (Study HP36)
    c. relative BA 250 mg (Study HP35)

3. Compare [redacted] PR2 vs. 'registration' TRF
    a. relative BA 50 mg (Study HP42)
    b. relative BA 100 mg (Study HP61)
    c. relative BA 250 mg (Study HP31)

4. Compare [redacted] PR2 vs. 'TBM' TRF – relative BA 250 mg PR2 fed, TRF fed and fasted (Study HP67)

PR1 'Initial' vs. 'updated' formulations comparison

The following table compares PR1 formulations. [redacted]

There were no in vivo trials conducted to compare the two PR1 formulations. However, the dissolution profiles of the PR1 tablets indicated that the release characteristics from 'early' and 'updated' PR1 formulations look similar. Although there are no in vivo trials,

it is not likely that 'early' and 'updated' PR1 formulations differ in tapentadol exposure in vivo.

PR1 Formulations Manufactured by GRT and Used for Phase 1 and 2 Clinical Studies

(b) (4)

[redacted]

PR2 (b) (4) formulation comparison

The following table contains PR2 tablet formulations. (b) (4)

[redacted]

(b) (4)

[redacted]

(b) (4)

As stated previously, the (b) (4) PR2 formulation was used in P3 trials.

There were no in vivo trials conducted to compare the two PR2 formulations. However, the dissolution profiles indicated that the release characteristics from (b) (4) PR2 formulations look similar.

PR2 (b) (4) formulations

(b) (4)

TRF 'Pilot', 'Registration/Stability' and TBM formulation comparison

The Applicant stated that the tamper-resistant formulation was co-developed with PR2 formulation. The main objective of the TRF, the Applicant believes, is that TRF tablet is more difficult to tamper with, thereby reducing the potential for both unintentional misuse and intentional abuse. (b) (4)

(b) (4)

The Pilot ER tablets were manufactured by Grünenthal GmbH, Aachen Germany (GRT). Registration/Stability ER tablets were manufactured by J&JPRD (Beerse, Belgium). To-be-marketed ER tablets were manufactured at the proposed commercial site, Janssen Ortho, L.L.C. (JOLLC) (Gurabo, Puerto Rico).

Pilot vs. Registration/stability TBM formulations

(b) (4)

Formulation	Pilot batches [a]			Registration stability batches and to-be-marketed batches [b]				
Formulation number	TF5, 6323SF	TF4, 6322SF	TF3, 6316SF	F029	F030	F031	F032	F033
Dose strength (tapentadol)	50 mg	100 mg	250 mg	50 mg	100 mg	150 mg	200 mg	250 mg
Tapentadol hydrochloride, mg								(b) (4)
Polyethylene oxide, mg								
(% w/w of core)								
Hypromellose (b) (4)								
(% w/w of core)								
Polyethylene glycol (b) (4)								
(% w/w of core)								
Vitamin E, mg								
(% w/w or core)								
Tablet core weight								
Film coat (b) (4)								
Printing ink [c]								
Tablet size								
Tablet shape								
[a]								(b) (4)
[b]								
[c]								
[d]								

NA= not applicable

Registration/Stability vs. TRF TBM formulations

There are no differences in formulations. However, the ER tablets are the manufactured from two different sites. There is no in vivo information comparing the two formulations. However, as stated previously, the Applicant utilized IVIVC method to link the two formulations.

2.5.3 What is the in vivo relationship of the pivotal clinical trial formulation, 'Updated' PR1 formulation, to the (b) (4) PR2 formulation, in terms of comparative exposure?

Tapentadol 200 mg PR1 ('updated' formulation) and PR2 (b) (4) formulations were bioequivalent.

In vitro comparison

The dissolution profile indicated that there is slight difference in release.

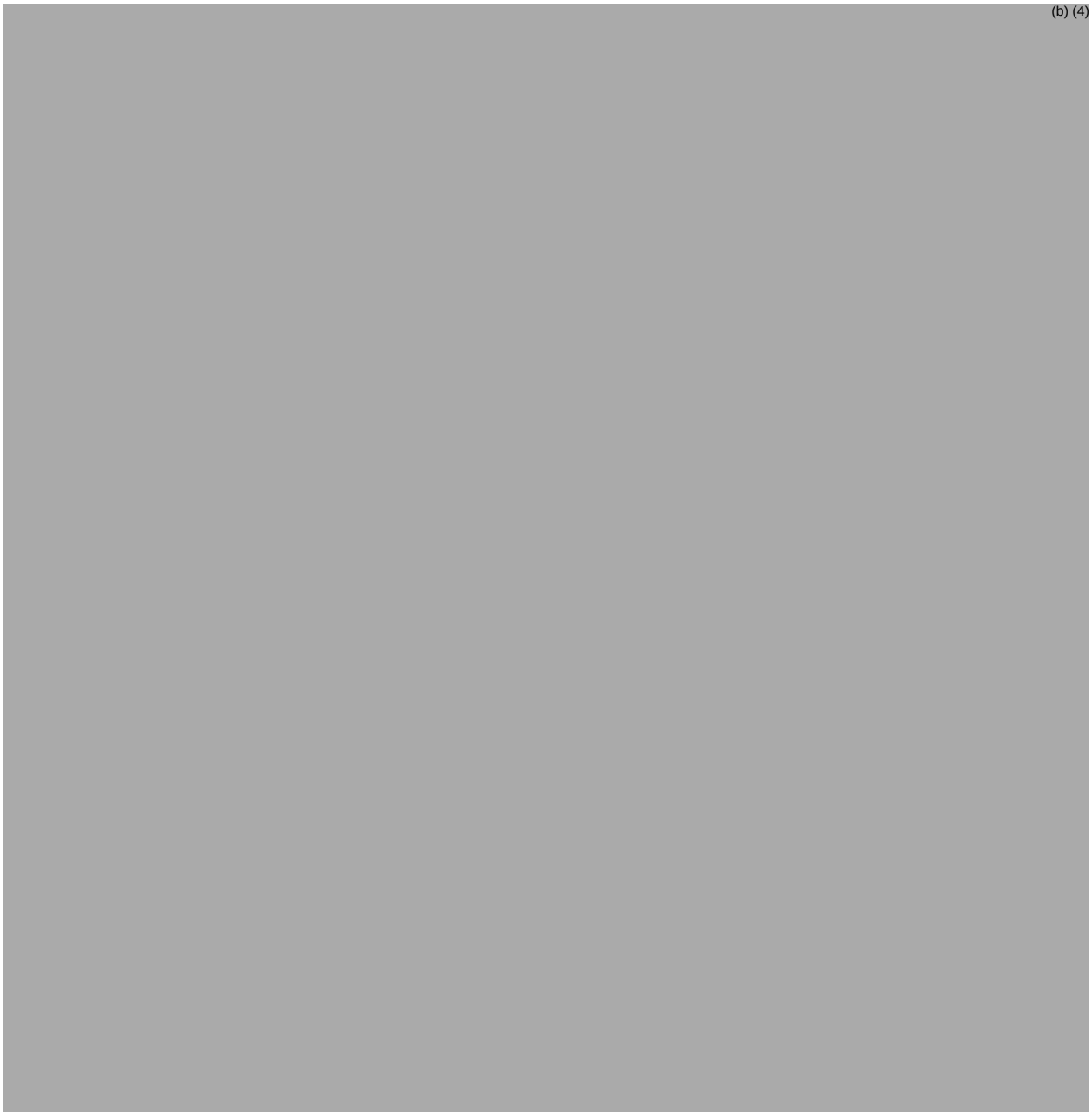
2.5.4 What is the in vivo relationship of the pivotal clinical trial formulation, PR2 'final' formulation, to the proposed to-be-marketed tamper-resistant formulation, TRF, in terms of comparative exposure?

Tapentadol 50 and 100 mg PR2 (Phase 3 formulation) and 'pilot' TRF formulations were bioequivalent in fasted state. Tapentadol 250 mg PR2 (Phase 3 formulation) and 'pilot' TRF formulations were bioequivalent in fed state. Tapentadol 50, 100, and 250 mg PR2 (Phase 3 formulation) and 'Registration' TRF formulations were bioequivalent in fasted state.

In vitro PR2 ((b) (4) Phase 3) vs. Pilot/Registration/Stability TRF formulation comparison

Examples of the dissolution profiles of 50-, 100-, and 250-mg pilot and registration stability formulations of the TRF tablets compared to the corresponding strength of PR2 that were used in the BA and BE studies are presented in below, respectively. The

Applicant stated that the dissolution between the pilot TRF and PR2 formulations, and the pilot and registration stability TRF formulations, was assessed by means of the f2 similarity test. The f2 values were greater than 50, indicating that profiles are similar between all formulations.



In vivo PR2 (b) (4) Phase 3' vs. TRF 'Pilot' formulation comparison

Study PAI-1022/HP41 was a single-center, open-label, single-dose, randomized, 2-way-crossover study to evaluate the relative bioavailability of 2 formulations of 50-mg tapentadol: TRF (TF5, pilot batch HATD46) and PR2 (Phase 3 batch HBIRB7) under fasted conditions. Healthy men (12) and women (12) received 2 doses of tapentadol and completed the study. Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol and its O-glucuronide.

The 90% CIs for the treatment ratio of tapentadol TRF and PR2 formulations for Cmax, AUClast, and AUCinf fell within the 80 to 125%. The point estimate for Cmax was 111.29% and 100% for AUClast and AUCinf. Similar results were obtained for the metabolite.

Tapentadol PK Parameters and Statistical Comparison After Single Oral Administration of Tapentadol TRF (pilot) and PR2 (Phase 3) 50-mg Tablets in the Fasted State

n=24	TRF	PR2	Geometric means		Ratio TRF/PR2, % (90% CI)
			TRF	PR2	
C_{max}, ng/mL	11.2 ± 3.12	10.8 ± 3.54	10.9	10.4	104.2 (98.16-110.7)
AUC_{last}, ng.h/mL	178 ± 51.3	182 ± 49.3	171	176	97.25 (92.22-102.6)
AUC_{inf}, ng.h/mL	183 ± 51.5 [a]	181 ± 40.2 [a]	171 [b]	179 [b]	95.51 (90.56-100.7) [b]
t_{max}, h	4.00 (2.00-12.00)	3.00 (1.00-6.03)			
$t_{1/2}$, h	5.59 ± 1.05 [a]	6.76 ± 1.87 [a]			

[a] n=23.
[b] n=22.
Data expressed as mean ± SD, except for t_{max} where median (range) are provided.

Study PAI-1023/HP36 was a single-center, open-label, single-dose, randomized, 2-way-crossover study to evaluate the relative bioavailability of 2 formulations of 100-mg tapentadol: TRF (TF4, pilot batch GLPS30) and PR2 (Phase 3 batch FHEG48) under fasted conditions. Healthy men (12) and women (12) received 2 doses of tapentadol and completed the study. Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol and its O-glucuronide.

The estimated mean Cmax, AUClast and AUCinf values were similar following dosing of the tapentadol PR2 and TRF 100-mg tablets. Estimated ratios of geometric mean Cmax, AUClast, and AUCinf for the tapentadol TRF 100-mg tablet versus the tapentadol PR2 100-mg tablet were close to 100% with the corresponding 90% CIs included within the 80 to 125% range. Similar results were obtained for the metabolite.

Tapentadol PK Parameters and Statistical Comparison After Single Oral Administration of Tapentadol TRF (pilot) and PR2 (Phase 3) 100-mg Tablets in the Fasted State (PAI-1023/HP36)

n=23	TRF	PR2	Geometric means		Ratio TRF/PR2, % (90% CI)
			TRF	PR2	
C_{max}, ng/mL	28.9 ± 8.04	29.0 ± 9.81	27.9	27.5	101.14 (93.61-109.27)
AUC_{last}, ng.h/mL	457 ± 167	444 ± 145	433	423	102.46 (97.91-107.22)
AUC_{inf}, ng.h/mL	462 ± 169	466 ± 146 [a]	438 [a]	439 [a]	99.70 (95.53-104.05) [a]
t_{max}, h	6.00 (1.50-12.00)	3.00 (1.00-6.07)			
$t_{1/2}$, h	4.9 ± 0.7	6.0 ± 1.8 [a]			

[a] n=21.
Data expressed as mean ± SD, except for t_{max} where median (range) is provided.

Study PAI-1024/HP35 was a single-center, open-label, single-dose, randomized, 2-way-crossover study to evaluate the relative bioavailability of 2 formulations of 250-mg tapentadol: TRF (TF3, pilot batch GDTC14) and PR2 (uncoated Phase 3 batch GBSP36-2) after administration of a high-fat, high-calorie breakfast. Healthy men (14) and women (18) received at least 1 dose of tapentadol and 31 subjects completed the study. Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol and its O-glucuronide.

Estimated ratios of geometric mean Cmax, AUClast, and AUCinf for the tapentadol TRF tablet versus the PR2 tablet were close to 100% and the corresponding 90% CIs were included within the commonly accepted bioequivalence range of 80.00% to 125.00%. Similar results were obtained for the metabolite.

Tapentadol PK Parameters and Statistical Comparison After Single Oral Administration of Tapentadol TRF (pilot) and PR2 (Phase 3) 250-mg Tablets in the Fed State (PAI-1024/HP35)

	TRF (n=27)	PR2 (n=27)	Geometric means (n=24)		Ratio TRF/PR2 (n=24)
			TRF	PR2	% (90% CI)
C_{max}, ng/mL	105 ± 30.8	112 ± 31.5	102	108	94.61 (85.81-104.32)
AUC_{last}, ng.h/mL	1180 ± 323	1227 ± 306	1174	1223	95.96 (90.95-101.25)
AUC_{inf}, ng.h/mL	1183 ± 323	1230 ± 306	1178	1226	96.04 (91.06-101.28)
t_{max}, h	6.00 (1.50-16.00)	6.00 (1.50-12.00)			
$t_{1/2}$, h	4.1 ± 0.5	4.3 ± 0.6			

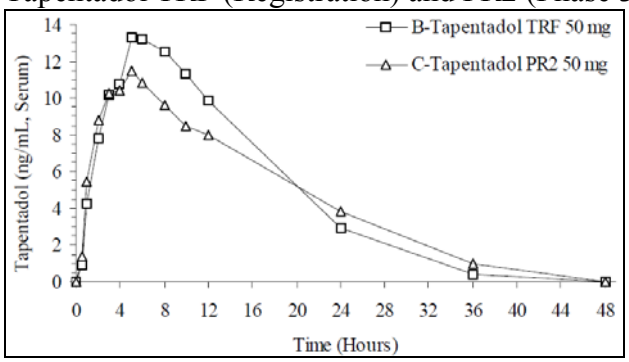
Data expressed as mean ± SD, except for t_{max} where median (range) are provided.

In vivo PR2 [redacted] (b) (4) - Phase 3' vs. TRF 'Registration' formulation comparison

Study PAI-1034/HP42 assessed the bioequivalence of the tapentadol TRF (registration batch 08G01/F029) and PR2 50-mg (Phase 3 batch PD2711) formulations in the fasted state using a single-center, open-label, single-dose, randomized, crossover study design in twenty-four healthy subjects (a CV of 20% was used, a power of 80% and a difference between formulations of 5%). Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol.

The point estimate for C_{max} was 119%. The upper boundary of the 90% CI of the treatment ratio of tapentadol TRF versus PR2 50-mg tablets for C_{max} fell marginally outside the 125% upper boundary (125.36%). The AUCs were similar between the 2 treatments; the point estimates of AUC_{last} and AUC_{inf} were close to 100% and the corresponding 90% CIs fell within the 80 to 125% range.

Mean Serum Concentration-Time Profiles of Tapentadol After Administration of Tapentadol TRF (Registration) and PR2 (Phase 3) 50-mg Tablets (PAI-1034/HP42)



Tapentadol PK Parameters and Statistical Comparison After Single Oral Administration of Tapentadol TRF (Registration) and PR2 (Phase 3) 50-mg Tablets in the Fasted State (PAI-1034/HP42)

	TRF (n=20)	PR2 (n=21)	Geometric means (n=20)		Ratio TRF/PR2 (n=20) % (90% CI)	%CV
			TRF	PR2		
C_{max}, ng/mL	14.4 ± 4.19	12.0 ± 3.26	13.8	11.6	119.36 (113.64-125.36)	8.9
AUC_{last}, g h/mL	219 ± 52.8	209 ± 49.3	213	205	103.85 (99.74-108.13)	7.1
AUC_{inf}, ng h/mL	223 ± 51.9	220 ± 47.3 [a]	220 [b]	218 [b]	101.23 (97.48-105.14) [b]	6.3
t_{max}, h	5.51 (3.00-10.01)	5.00 (2.00-8.00)				
$t_{1/2}$, h	5.4 ± 0.8	7.6 ± 2.3 [a]				

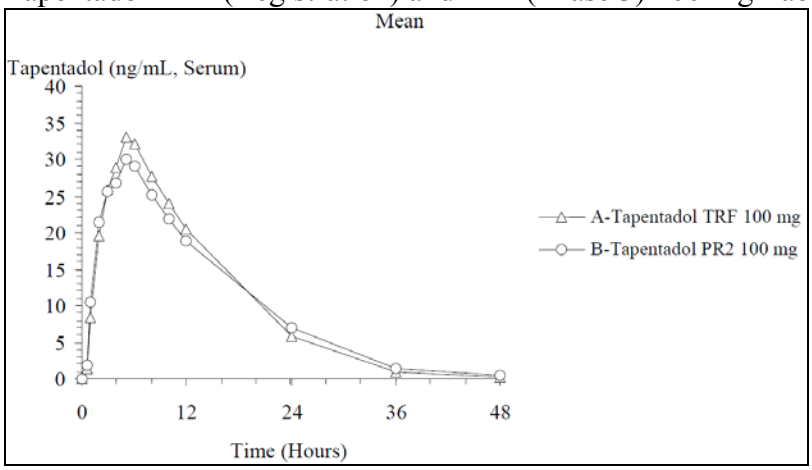
[a] n=18; [b] n=17' Data expressed as mean ± SD, except for t_{max} and t_{lag} where median (range) are provided.
%CV was derived from the MSE of the ANOVA test; %CV = % Coefficient of Variation; TRF=tamper resistant formulation; ER=tapentadol extended-release; (ER); CI: confidence interval, MSE: mean squared error

Study PAI-1046/HP61 assessed the bioequivalence of the tapentadol TRF(registration batch 08G23/F030) and PR2 100-mg (Phase 3 batch PD2977) formulations in the fasted state using a single-center, open-label, single-dose, randomized, crossover study design in healthy men (48) and women (28) (a CV of 20% was used, a power of 90% and a

difference between formulations of 13%). Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol.

The 90% CIs for the treatment ratio of tapentadol TRF and PR2 formulations for Cmax, AUClast, and AUCinf fell within the 80 to 125%. The point estimate for Cmax was 111.29% and 100% for AUClast and AUCinf.

Mean Serum Concentration-Time Profiles of Tapentadol After Administration of Tapentadol TRF (Registration) and PR2 (Phase 3) 100-mg Tablets (PAI-1046/HP61)



Tapentadol PK Parameters and Statistical Comparison After Single Oral Administration of Tapentadol TRF (Registration) and PR2 (Phase 3) 100-mg Tablets in the Fasted State (PAI-1046/HP61)

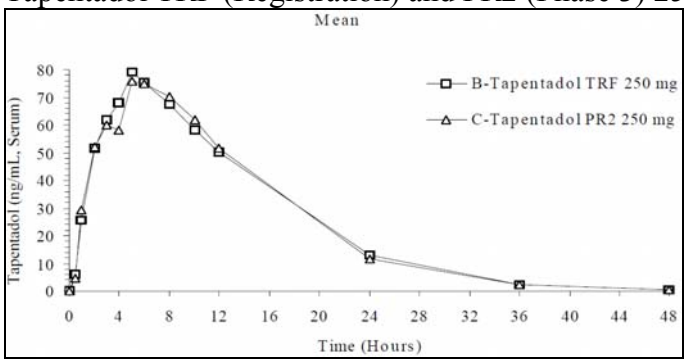
	TRF (n=74)	PR2 (n=73)	Least squares means (n=72)		Ratio TRF/PR2 (n=72) % (90% CI)	%CV
			TRF	PR2		
C_{max}, ng/mL	35.0 ± 12.5	31.5 ± 10.1	33.2	29.8	111.29 (106.87-115.89)	14.7
AUC_{last}, g.h/mL	491 ± 138	484 ± 133	477	466	102.37 (99.71-105.10)	9.5
AUC_{inf}, ng h/mL	496 ± 137	501 ± 129 [a]	497 [b]	487 [b]	102.25 (99.52-105.05) [b]	9.4
t_{max}, h	5.00 (2.98-12.00)	5.00 (1.98-12.03)				
$t_{1/2}$, h	5.4 ± 1.2	6.2 ± 1.7 [a]				

[a] n=68; [b] n=67; Data expressed as mean ± SD, except for t_{max} where median (range) are provided.
%CV=% coefficient of variation; TRF=tamper resistant formulation; ER=extended release; CI=confidence interval; MSE=mean squared error; LSM=least squares mean; N=number of subjects included in the inferential statistical analysis

Study PAI-1033/HP31 assessed the bioequivalence of the tapentadol TRF(registration batch 8G09/F033) and PR2 250-mg (Phase 3 batch PD2732) formulations in the fasted state using a single-center, open-label, single-dose, randomized, crossover study design in twenty-three healthy subjects (a CV of 20% was used, a power of 80% and a difference between formulations of 5%). Serial blood samples were collected from predose up to 48 hours postdose for the analysis of tapentadol.

The 90% CIs for the treatment ratio of TRF and PR2 formulations for C_{max}, AUC_{last}, and AUC_{inf} fell within the 80.00% to 125.00% range used for assessing bioequivalence. The point estimates for C_{max}, AUC_{last}, and AUC_{inf} were close to 100%.

Mean Serum Concentration-Time Profiles of Tapentadol After Administration of Tapentadol TRF (Registration) and PR2 (Phase 3) 250-mg Tablets (PAI-1033/HP31)



Tapentadol PK Parameters and Statistical Comparison After Single Oral Administration of Tapentadol TRF (Registration) and PR2 (Phase 3) 250-mg Tablets in the Fasted State (PAI-1033/HP31)

	TRF (n=23)	PR2 (n=23)	Least squares means (n=21)		Ratio TRF/PR2 (n=21) % (90% CI)	MSE
			TRF	PR2		
C_{max}, ng/mL	85.0 ± 35.2	86.5 ± 28.7	78.4	81.8	95.91 (87.24-105.45)	0.032
AUC_{last}, g.h/mL	1187 ± 324	1177 ± 312	1159	1159	99.98 (95.29-104.89)	0.008
AUC_{inf}, ng h/mL	1193 ± 326	1186 ± 320	1165	1166	99.89 (95.31-104.69)	0.008
t_{max}, h	5.00 (2.00-12.03)	5.00 (2.00-10.00)				
$t_{1/2}$, h	5.0 ± 1.2	5.0 ± 1.9				

Data expressed as mean ± SD, except for t_{max} where median (range) are provided.
MSE: mean squared error
LSM: least squares mean
N= subjects included in the inferential statistical analysis

2.5.5 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?

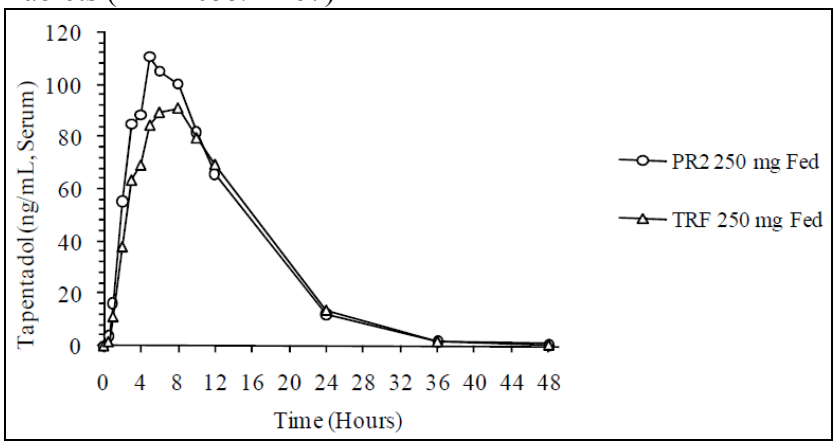
Under fed conditions, the bioavailability was similar after administration of the tapentadol TRF to-be-marketed 250-mg tablet and the tapentadol PR2 Phase 3 250-mg tablet. The bioavailability of tapentadol was similar after administration of the TRF 250-mg tablet with a high fat, high-caloric breakfast or without food. The 90% CIs for C_{max} and AUC were contained within the accepted 80 to 125% bioequivalence range for both comparisons.

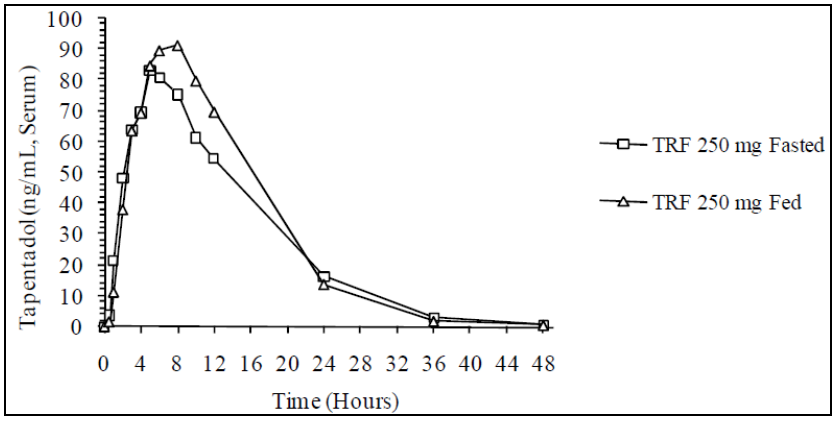
Study PAI-1055/HP67 assessed a food effect of the tapentadol TRF (to-be-marketed batch 9EG9283-X) formulation in fed (a high-fat, high-calorie breakfast) and fasted conditions using a single-center, open-label, single-dose, randomized, crossover study design in 50 healthy subjects. Serial blood samples were collected from predose up to 48

hours postdose for the analysis of tapentadol. Additionally the tapentadol PR2 formulation (PD2732) was included in the study for fed condition comparison.

The mean C_{max} following tapentadol TRF in the fed state was slightly higher than that in the fasted state and it was reached 1 hour later. Estimated ratios of geometric mean C_{max}, AUC_{last}, and AUC_{inf} for the tapentadol TRF tablet in the fed versus the fasted state were 106% for AUC and 117% for C_{max}. The corresponding 90% CIs were included within the commonly accepted bioequivalence range of 80% to 125%.

Mean Serum Concentration-Time Profiles of Tapentadol After Administration of Tapentadol TRF (To-Be-Marketed), Fed and Fasted, and PR2 (Phase 3), Fed, 250-mg Tablets (PAI-1055/HP67)





Tapentadol PK Parameters After Single Oral Administration of Tapentadol TRF (to-be-marketed) and PR2 (Phase 3) 250-mg Tablets in the Fed State; and Tapentadol TRF (to-be-marketed) 250-mg Tablets in the Fasted State (PAI-1055/HP67)

n=52	TRF fed	TRF fasted	PR2 fed
C_{max}, ng/mL	105 ± 29.5	90.2 ± 24.2	118 ± 28.4
AUC_{last}, ng h/mL	1414 ± 452	1270 ± 306[a]	1500 ± 399
AUC_{inf}, ng h/mL	1418 ± 453	1276 ± 307[a]	1504 ± 399
t_{max}, h	6.00 (2.98 – 12.00)	5.00 (2.00 – 12.00)	5.98 (2.98 – 11.98)
$t_{1/2}$, h	4.6 ± 0.6	5.1 ± 0.8[a]	4.6 ± 0.6

Statistical Comparison of Single Oral Administration of Tapentadol TRF (To-Be-Marketed) and PR2 (Phase 3) 250-mg Tablets in the Fed State; and Tapentadol TRF (To-Be-Marketed) 250-mg Tablets in the Fasted State (PAI-1055/HP67)

n=50	Least squares means		Point estimates, % (90% CI)	Point estimates, % (90% CI)
	TRF fed	TRF fasted	TRF fed / TRF fasted	TRF fed / PR2 fed
C_{max}, ng/mL	99.93	85.58	116.76 (109.91-124.04)	116.76 (109.91-124.04)
AUC_{last}, g.h/mL	1304.44	1232.77	105.81 (99.73-112.27)	105.81 (99.73-112.27)
AUC_{inf}, ng h/mL	1308.68	1238.58	105.66 (99.59-112.10)	105.66 (99.59-112.10)

2.6 Analytical Section

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

It is noted that the validated analytical methods used for ER tablets are identical to that of IR tablets as the method development initiated in 1995 with high performance liquid chromatography. As with tapentadol IR tablets, liquid chromatography coupled to tandom mass spectroscopy (LC-MS/MS) method was mainly 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 serum/plasma HPLC-fluorescence method at Grünenthal (GRT)

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 hours at room temperature 24 weeks in a freezer (-20°C and -70°C)

CV= coefficient of variation; IS= internal standard.

Validation Parameters for Serum LC-MS/MS Methods for Tapentadol and Metabolites at Grünenthal (GRT)

GRT serum LC-MS/MS methods	Tapentadol: validation original method (Mod5.3.1.4\PK564)		Tapentadol: re-validation for reduced LLOQ (Mod5.3.1.4\PK564)		Tapentadol-O-glucuronide (Mod5.3.1.4\PK659)		Tapentadol-O-sulfate (Mod5.3.1.4\PK659)	
validation period	I	II	II	II	I	II	I	II
Matrix	Serum	serum	serum	serum	serum	serum	serum	serum
sample volume	200	50	200	50	200	50	200	50
validated concentration range	0.150 to 61.7 ng/mL	0.630 to 125 ng/mL	0.150 to 125 ng/mL	0.150 to 125 ng/mL	1.90 to 750 ng/mL	2.50 to 500 ng/mL	0.630 to 251 ng/mL	2.50 to 500 ng/mL
selectivity (interference < 20% of LLOQ)	no interferences	2 of 2 sources of serum	2 of 2 sources of serum	2 of 2 sources of serum	no interferences	2 of 2 sources of serum	no interferences	2 of 2 sources of serum
intra-run accuracy (%)	n.a.	96.3 to 120.2	84.3 to 91.7	86.0 to 114.3	n.a.	91.1 to 107.4	n.a.	93.4 to 114.5
intra-run precision (%CV)	n.a.	≤ 9.62	≤ 8.48	≤ 10.3	n.a.	≤ 4.06	n.a.	≤ 11.7
intrer-run accuracy (%)	97.3 to 100.2	101.0 to 108.6	87.1	99.3	95.5 to 99.3	96.6 to 104.1	99.6 to 104.0	97.7 to 104.5
inter-run precision (%CV)	≤ 9.00	≤ 10.1	≤ 7.87	≤ 15.0	≤ 8.37	≤ 5.57	≤ 9.24	≤ 9.94
carry-over of ULOQ(in % of LLOQ)	n.a.	27.9	30.5	26.0	n.a.	31.2	n.a.	32.9
intra-run accuracy (6 x dilution) (%)	n.a.	107.6 to 109.2	n.a.	n.a.	n.a.	103.8 to 103.9	n.a.	96.2 to 96.8
intra-run precision (6 x dilution) (%)	n.a.	≤ 1.90	n.a.	n.a.	n.a.	≤ 1.85	n.a.	≤ 4.13
matrix effect (quenching in %)	n.a.	-8.72 to -5.43	n.a.	n.a.	n.a.	-5.79 to 0.27	n.a.	5.80 to 8.85
matrix effect IS (quenching in %)	n.a.	-21.7 to -20.0	n.a.	n.a.	n.a.	-3.67 to 0.40	n.a.	2.87 to 7.53
extraction recovery (%)	n.a.	73.0 to 77.0	n.a.	n.a.	n.a.	73.4 to 75.6	n.a.	85.2 to 86.1
extraction recovery IS (%)	n.a.	75.2 to 81.6	n.a.	n.a.	n.a.	78.0 to 81.5	n.a.	89.7 to 93.1
stability in matrix	3 freeze-thaw cycles 24 hours at room temperature				3 freeze-thaw cycles 24 hours at room temperature		3 freeze-thaw cycles 24 hours at room temperature	
processed sample stability	24 hours at room temperature 72 hours at 8°C				24 hours at room temperature 72 hours at 8°C		24 hours at room temperature 72 hours at 8°C	

CV= coefficient of variation; IS= internal standard; LLOQ= lower limit of quantification; ULOQ= upper limit of quantification.

Validation Parameters for Serum LC-MS/MS Methods for Tapentadol and Metabolites at (b) (4)

(b) (4) serum methods	Tapentadol: validation original method (b) (4) S_02012 [PK628] Mod5.3.1.4\PK628)	Tapentadol: re-validation after changes (b) (4) S_05083 [PK1035] Mod5.3.1.4\PK1035)	Tapentadol-O-glucuronide (b) (4) S_03053 [PK697] Mod5.3.1.4\PK697)	Tapentadol-O-sulfate (b) (4) S_03053 [PK 697] Mod5.3.1.4\PK697)
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 of 6 sources of serum		6 of 6 sources of serum	6 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 [b]	- 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 [a]		- 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]	
processed sample stability	- 24 hours at 8 ± 5°C		72 hours at 8 ± 5°C no hydrolysis to tapentadol after 192 hours at 8°C [a]	
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 [a]	

[a] from study (b) S_04004 [PK711] (Mod5.3.1.4\PK711)
CV= coefficient of variation; IS= internal standard; LLOQ= lower limit of quantification (b) (4)

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

J&JPRD serum method BA525 [PK1134] (Mod5.3.1.4\BA525)	**Tapentadol**			**Tapentadol-O-glucuronide**		
	validation original method	re-validation after method changes	2nd re-validation (amendment 1)	validation original method	re-validation after method changes:	2nd re-validation (amendment 1)
validated concentration range	0.200-200 ng/mL	0.200-200 ng/mL	0.200-200 ng/mL	10.0-10000 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	87.5-95.8	92.7-106.0	87.3-111.3	87.7-109.8
intra-run precision (%CV)	0.8-8.0	0.6-17.4	1.1-7.1	0.3-7.4	0.3-10.4	1.3-4.2
intra-run accuracy (10 x dilution) (%)	98.1			101.6		
intra-run precision (10 x dilution) (%)	4.3			2.4		
selectivity (interference < 20% of LLOQ)	5 of 6 sources of serum	6 of 6 sources of serum		6 of 6 sources of serum	6 of 6 sources of serum	
extraction recovery (%)	92.7-98.2			92.3-94.1		
extraction recovery IS (%)	95.6			90.1		
stability in serum			- 769 days in a freezer			- 769 days in a freezer
incurred sample stability (stability in study samples)			- 40 days			- 40 days
processed sample stability	- 5 days at RT - 5 days at 4°C	- 6 days at RT		- 5 days at RT - 5 days at 4°C	- 6 days at RT	
stability in methanolic stock solution	- 3 days at RT (dark and light) - 1 month in a refrigerator - 6 months in a freezer			- 3 days at RT (dark and light) - 1 month in a refrigerator - 6 months in a freezer		
incurred sample reproducibility (ISR)			- proven			- proven

CV= coefficient of variation; IS= internal standard; ISR= incurred sample reproducibility ; LLOQ= lower limit of quantification; RT= room temperature.

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

J&JPRD serum method BA1427 (Mod5.3.1.4\BA1427)	**Tapentadol**	**Tapentadol-O-glucuronide**
	validation original method	validation original method
validated concentration range	0.200-200 ng/mL	10.0-10000 ng/mL
inter-run accuracy (%)	96.8-103.9	98.1-103.4
inter-run precision (%CV)	2.4-5.6	2.7-4.2
intra-run accuracy (%)	95.5-106.6	96.2-105.2
intra-run precision (%CV)	1.0-6.4	1.1-5.4
intra-run accuracy (10 x dilution) (%)	See BA525 [a]	See BA525 [a]
intra-run precision (10 x dilution) (%)	See BA525 [a]	See BA525 [a]
selectivity (interference < 20% of LLOQ)	6 of 6 sources of serum	6 of 6 sources of serum
extraction recovery (%)	95.7-98.8	93.4-96.2
extraction recovery IS (%)	98.3	94.5
stability in serum	See BA525 [a]	See BA525 [a]
incurred sample stability (stability in study samples)	-	-
processed sample stability	96 hours at RT	90 hours at RT
stability in methanolic stock solution	See BA525 [a]	See BA525 [a]
incurred sample reproducibility (ISR)	Proven	-

[a] Mod5.3.1.4\BA525

CV= coefficient of variation; IS= internal standard; ISR= incurred sample reproducibility ; LLOQ= lower limit of quantification; RT= room temperature.

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, in RED fonts, where appropriate.

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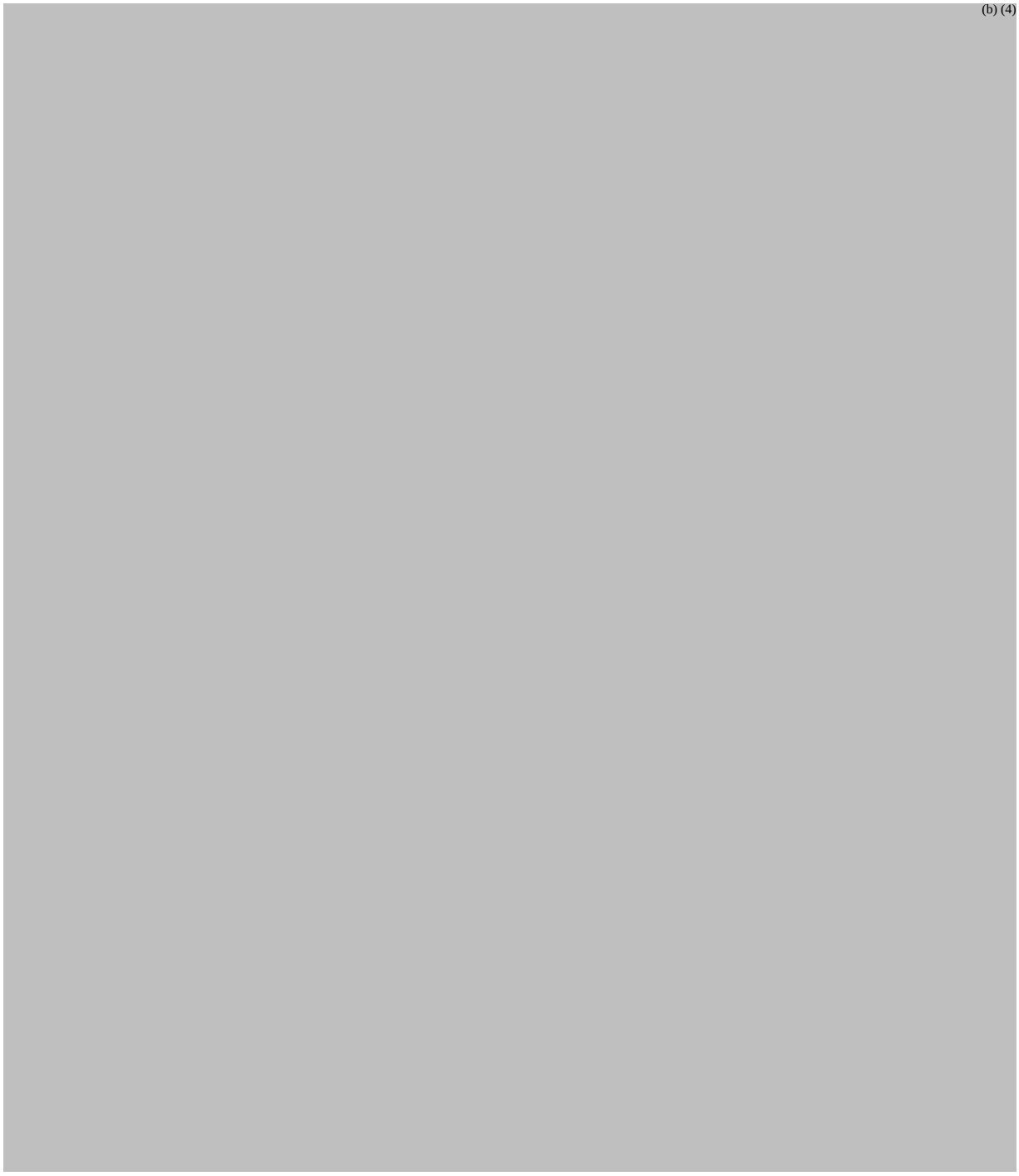
28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



4.2 Individual study review

Not Applicable.

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	200533	Brand Name		Nucynta ER
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" if included at filing	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	2	2	
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-		3	3	
single dose:	X			
multiple dose:				
Dose proportionality -		1	1	
fasting / non-fasting single dose:	X	1	1	
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -		6	6	
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 -		5	5	
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		1	1	
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?

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICALS INC	TAPENTADOL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID J LEE
08/09/2010

SURESH DODDAPANENI
08/09/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200533 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAARP		
Sponsor:	J&J Pharmaceutical and GmbH	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Nucynta™	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Tapentadol Extended Release Tablet	**Date Assigned:**	Dec 17, 2009
Indication:	Management of moderate to severe pain	**Date of Review:**	Jul 22, 2010
Formulation	Extended Release Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Nov 30, 2009	Dec 1, 2009	Dec 17, 2009	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	IVIVC models and Dissolution method and specifications		

REVIEW SUMMARY:

Nucynta (Tapentadol) IR tablet received FDA approval on November 2008 for the relief of moderate to severe acute pain in patients 18 years of age or older under NDA 22-304.

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapentadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapentadol of the TRF (tamper resistant formulation) formulation are proposed for marketing.

Initially, the sponsor proposed the use of two IVIVC models and BA studies to bridge the pilot batches (manufactured in Aachen, Germany) and the TRF registration batches (manufactured in Beerse, Belgium) to the to-be-marketed formulation (manufactured in Gurabo, Puerto Rico). However, during the review of this submission the biopharmaceutics team found the proposed IVIVC models unacceptable. The Agency's recommendations to the sponsor during a telecom dated April 21, 2010 were to reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model to (b) (4) In a submission dated June 6, 2010 the sponsor decided not to reconstruct the IVIVCs models; instead a proposal was included to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC. The sponsor proposed to submit the reports of these studies prior to the end of the 10-month review cycle in August (refer to Biopharmaceutics review dated June 14, 2010).

The dissolution method to characterize the drug release of tapentalol TRF tablets used US Pharmacopoeia (USP) Apparatus 2 (paddle) (b) (4) at 100 rpm in 900 mL of simulated intestinal fluid without enzyme, i.e., 0.05 M phosphate buffer of pH 6.8 at 37°C. This method will also be used for the to-be-marketed batches. The proposed dissolution specifications are as follows:

Strength	Acceptance criteria
50 mg	After 30 min: (b) (4) After 180 min After 360 min After 600 min
100 mg	After 30 min: After 180 min After 360 min After 600 min
150 mg	After 30 min: After 180 min After 360 min After 600 min
200 mg	After 30 min: After 180 min After 360 min After 600 min
250 mg	After 30 min: After 180 min After 360 min After 600 min

The proposed dissolution method is acceptable. However, since the proposed specifications were based on the IVIVC models, they need to be revised given that the models were found not acceptable by the Biopharmaceutics review team. The acceptance criteria recommendations will be finalized once the results of the proposed BE studies bridging the to-be marketed formulation with clinical trials and the dissolution profile comparisons data are submitted. No dose-dumping from the tapentadol TRF tablets was observed when dissolved in 40% ethanol. On the contrary, the release profiles became slower in the presence of alcohol.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed NDA 200533 (000). The proposed IVIVC models were found not acceptable. The sponsor's proposed dissolution specifications need to be revised. The following comments should be conveyed to the sponsor:

- *The proposed dissolution specifications for Tapentadol ER tables were established based on the IVIVC models which were found not acceptable by the Agency and therefore, they need to be revised. Recommendations in terms of the dissolution acceptance criteria will be finalized by the Agency upon submission and review of the following information:*
  - *Results of the proposed BE studies bridging the to-be marketed formulations with the clinical trial formulation.*
  - *Dissolution profile comparisons data.*
- *Submit the revised dissolution specifications for all the proposed strengths of Tapentadol ER Tablets.*
- *Submit dissolution profile data (raw data and mean values) from all the batches tested in the new proposed bioequivalence studies.*

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200533, TBoui, ADorantes, CBertha, DChristodoulou

Introduction

Tapentadol IR tablet formulation received FDA approval on November 2008 for the relief of moderate to severe acute pain in patients 18 years of age or older under NDA 22-304.

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapentadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapentadol of the TRF (tamper resistant formulation) formulation are proposed to be marketed.

This submission includes data from 38 completed clinical studies (28 Phase 1 studies and 10 Phase 2/3 studies), including the report for two in vitro in vivo correlation (IVIVC) models. The development of tapentadol ER tablets can be divided into several stages as follows:

- Round ER tablets used in early Phase 1 and Phase 2 studies (PR1; 21.5 to 200 mg);
- Oblong shaped ER tablets used in Phase 1 and Phase 3 studies (PR2; 50, 100, 150, 200, 250 and 300 mg of tapentadol);
- Oblong shaped (50, 100, and 150 mg of tapentadol) or oblong with a depression in the middle running lengthwise on each side (200 and 250 mg of tapentadol) ER tablets used in Phase 1 studies and proposed to be marketed (TRF).

On April 21, 2010 the Agency held a teleconference with the sponsor to discuss several deficiencies related to their proposed IVIVC models for the higher (250 mg, 200 mg and 150 mg) and lower strengths (50 mg and 100 mg) of Tapentadol ER tablets. The models were proposed to waive the requirements of in vivo BE studies needed to link a change in manufacturing site. The Agency's recommendations were to reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model (b) (4)

On June 6, 2010, the sponsor proposed to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC. The sponsor stated that the BE studies being proposed comparing 150 and 200 mg TBM TRF to Phase 3 PR2 in fasted state will complete the bridging strategy for the tapentadol TRF formulation (i.e., will complete the demonstration of the bioequivalence of the Phase 3 PR2 tablets to the commercial site TRF tablets for all strengths). The sponsor proposed to submit the reports of these studies prior to the end of the 10-month review cycle in August.

Since the composition of the 50 mg tablet is not proportionally similar to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths, the biopharmaceutics team recommended to conduct BE studies with the highest and lowest strengths instead (refer to biopharm review in DARRTS dated June 14, 2010).

Chemistry

Drug Substance Aqueous Solubility

Tapentadol HCl is freely soluble in water, 0.1N hydrochloric acid, and simulated intestinal fluid (SIF, pH 6.8) with more than 300 mg/mL at ambient temperature. Therefore, drug substance solubility is not influenced by pH values in the human physiological range. Solubility decreases significantly as the pH approaches the pKa values of 9.34 and 10.45 (Figure 1), but with more than 300 mg/mL at ambient temperature the drug substance remains soluble at pH values higher than 7.6.

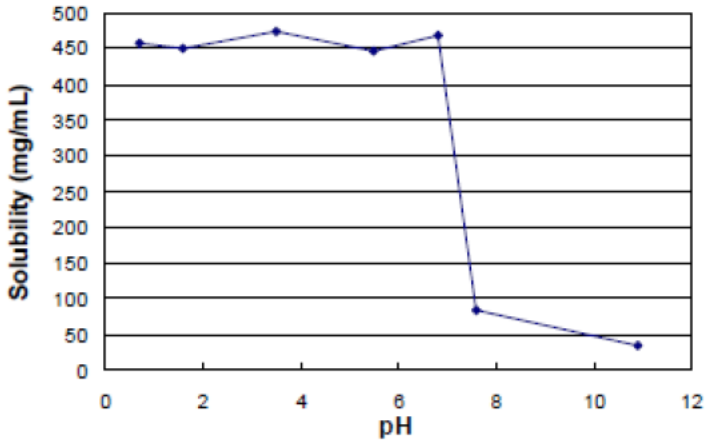


Figure 1. Solubility of Tapentadol HCl at 37 °C

Permeability

According to the sponsor, the extent of absorption in humans was determined to be ≥90%, demonstrating that tapentadol HCl is highly permeable.

Drug Product

The ER oral tablet formulation for Tapentadol in this NDA exhibits high breaking force (b) (4) These unique physical characteristics make the tablet more difficult to tamper with, thereby reducing the potential for both unintentional misuse and intentional abuse.

(b) (4)

The compositional formulas of the tapentadol ER tablets proposed for commercial manufacture are presented in Table 1 and Table 2.

Table 1. Tapentadol Extended-Release Tablets Composition - Core

Component	Quality Reference	Function	Dose Strength (Free Base of Tapentadol)									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
Tapentadol HCl (R331333)	Non-compendial	Active ingredient										(b) (4)
Polyethylene Oxide	NF	(b) (4)										
Hypromellose (b) (4)	USP											
Polyethylene Glycol (b) (4)	NF											
(b) (4)												
Vitamin E	USP											
Polyethylene Glycol (b) (4)	NF											
Total Core Tablet Weight												

Table 2. Tapentadol Extended-Release Tablets Composition - Coating

Film Coat	Quality Reference	Function	Dose Strength									
			50-mg		100-mg		150-mg		200-mg		250-mg	
			mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w	mg	% w/w
(b) (4)	Noncompendial											(b) (4)
	Noncompendial											
	Noncompendial											
	Noncompendial											
	Noncompendial											
	USP											
	Noncompendial											
	Noncompendial											
	NF											
Propylene Glycol[b]	USP											

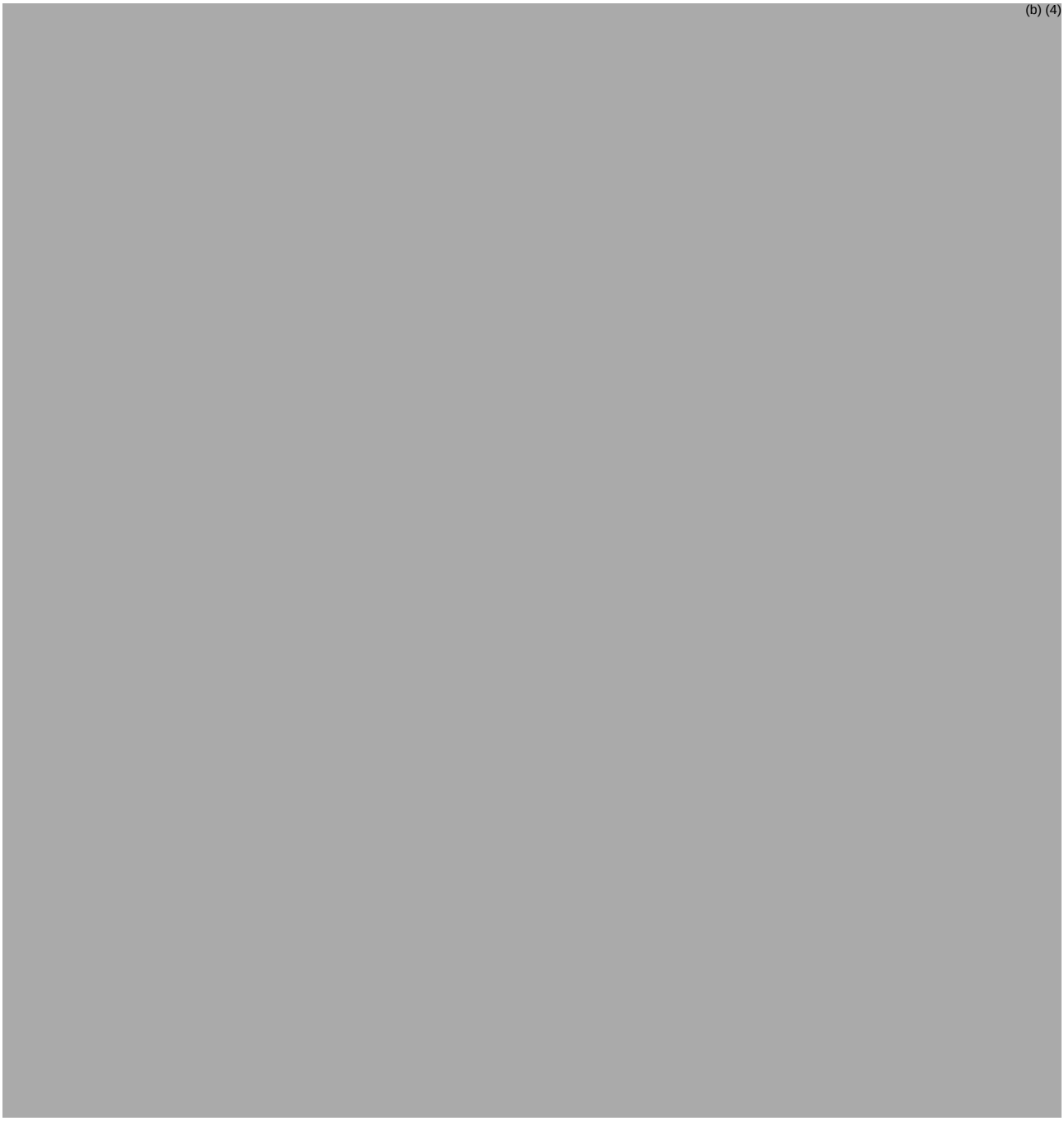
Formulation Development Summary

Phase 1 and 2 clinical studies were conducted with (b) (4) formulations of the tapentadol extended-release round tablets, designated PR1. Phase 3 clinical studies, as well as additional Phase 1 studies during that period, were conducted with the PR2 formulations. These larger oblong PR2 tablets were similar in ingredients and dissolution to the PR1 tablets. The PR2 formulations were developed to accommodate the higher doses required for Phase 3 clinical studies. The tamper-resistant formulations were subsequently developed to offer tamper-resistant properties with ER tablets are intended for commercial distribution.

(b) (4) As mentioned above, the pilot batches were manufactured by GRT in Aachen, Germany, the TRF registration batches by J&JPRD in Beerse, Belgium. The to-be-marketed formulation will be manufactured in Gurabo, Puerto Rico. The Phase 3 formulation, PR2, was bridged to the pilot, registration and to-be-marketed batches of the TRF formulation using relative bioavailability and bioequivalence studies, as well as a Level A in vitro/in vivo correlation (IVIVC).

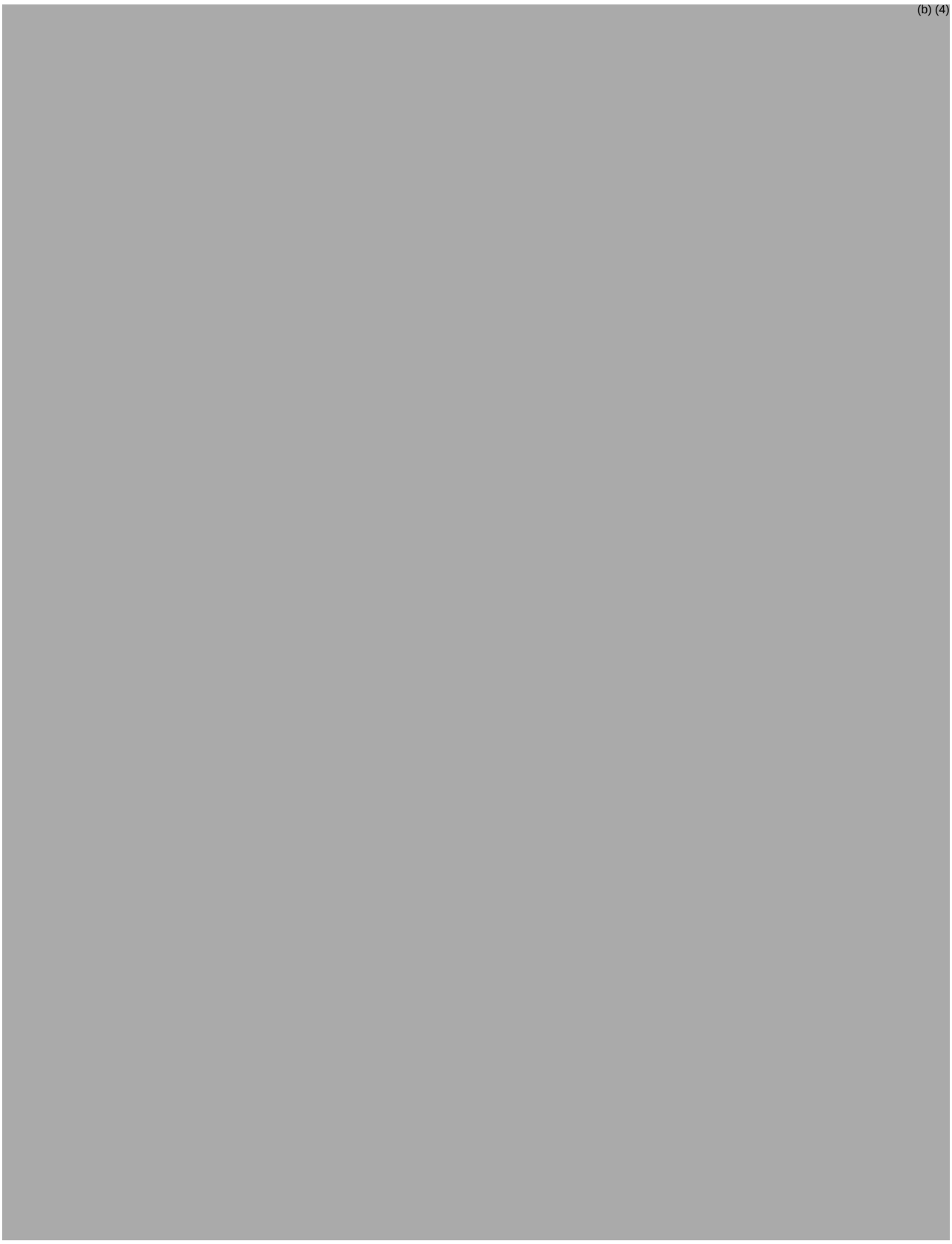
Initially, Pilot and registration batches of the TRF formulation are bridged to the to-be-marketed TRF formulation using a Level A IVIVC.

Examples of the dissolution profiles of 50-, 100-, and 250-mg pilot and registration stability formulations of the TRF tablets compared to the corresponding strength of PR2 that were used in the BA and BE studies are presented in Figure 2, Figure 3, and Figure 4, respectively. The similarity in dissolution between the pilot TRF and PR2 formulations, and the pilot and registration stability TRF formulations, was assessed by means of the f2 similarity test. The f2 values were greater than 50, indicating similar in vitro performance.



(b) (4)

The formulations for the TRF tapentadol ER tablets used in the BA clinical studies were similar to the registration stability batches used in the BE clinical trials. According to the sponsor, there were small differences in the quantitative composition of the tablet cores, which were within the normal ranges of weight variation, raw materials lot numbers and/or sources, film-coat and manufacturing conditions. (b) (4)



Dissolution Method

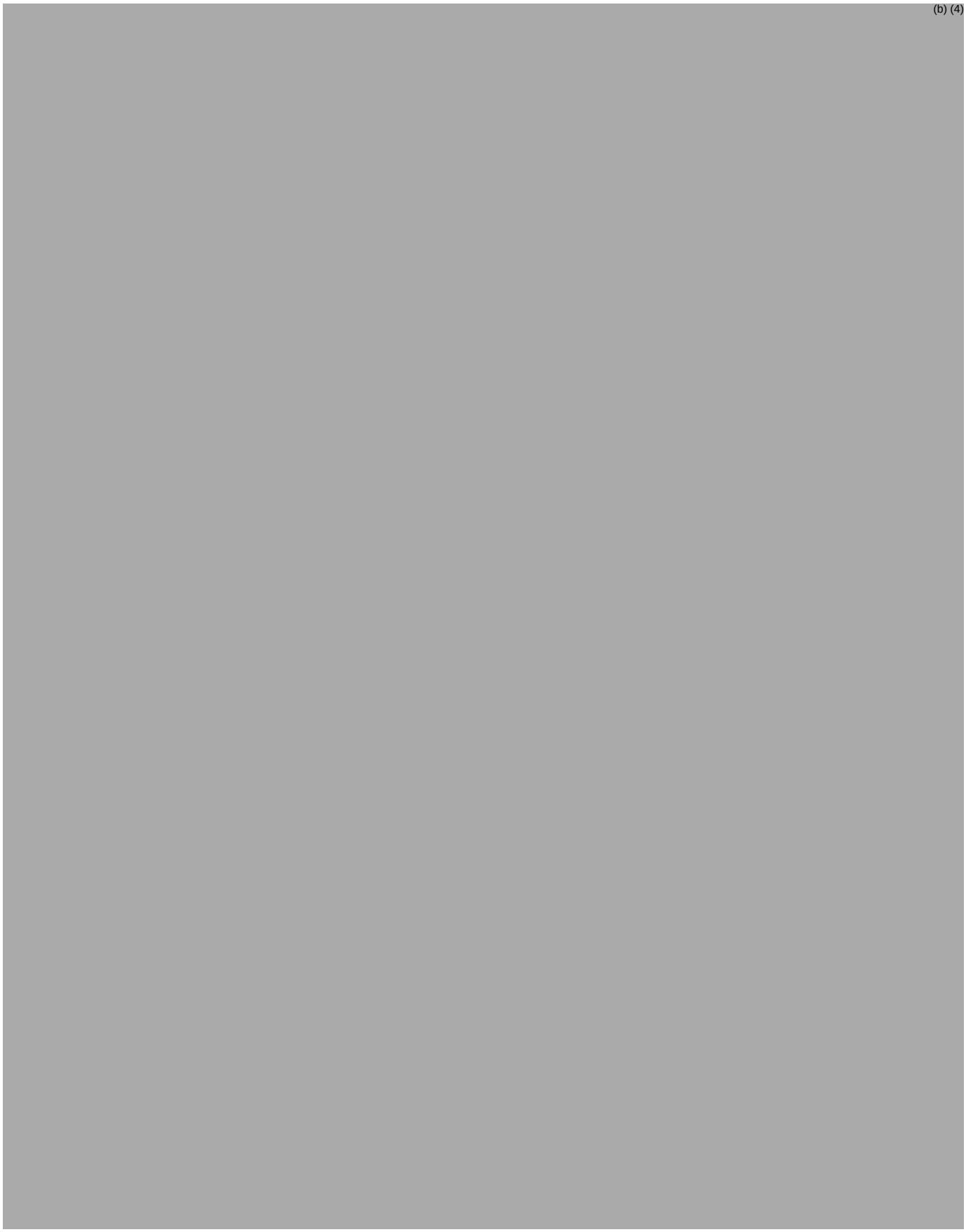
The proposed dissolution method to characterize the drug release of tapentadol TRF tablets used US Pharmacopoeia (USP) Apparatus 2 (paddles). This method will also be

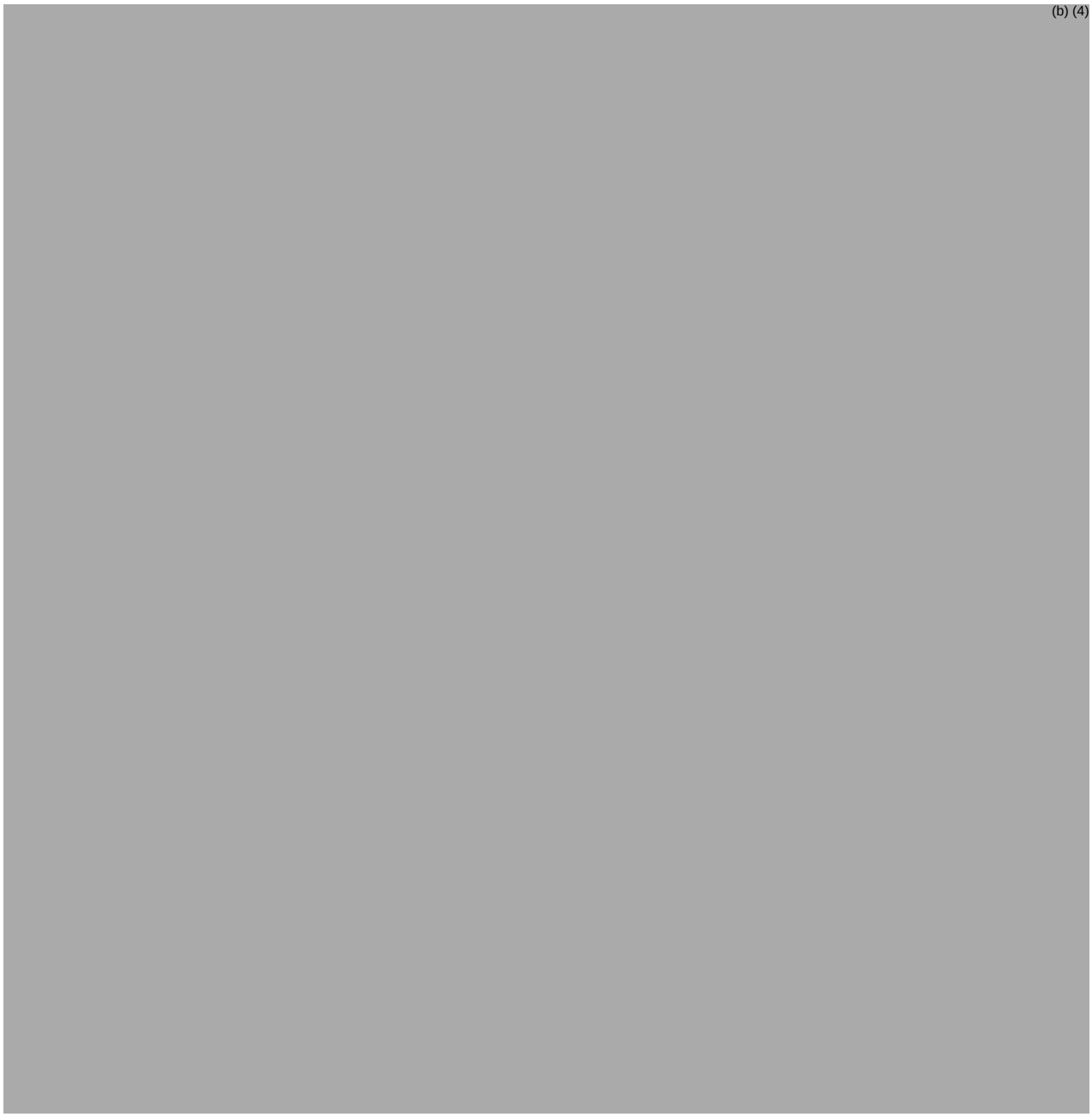
used for the to-be-marketed batches. The proposed dissolution method is summarized as follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)
Tapentadol	ER Tablet	II (paddle) (b) (4)	100	pH 6.8 phosphate Buffer, Simulated intestinal fluid (without enzyme)	900, 37 °C ± 0.5 °C

Dissolution Method Development

(b) (4)


(b) (4)



Discriminating Power of the Dissolution Method

The dissolution method was shown to be discriminating in detecting changes in the composition or manufacturing parameters of the tablets. Different tablet formulations, sizes, and shapes were evaluated and shown to impact the dissolution profile of the tapentadol ER tablets. It was shown that the dissolution method was able to discriminate among the different formulations used in the construction of the IVIVC model (Figure 11).

Dissolution Method Validation

Specificity

The specificity of the dissolution method was demonstrated by the absence of significant influence on the measurement of the API by comparing the % dissolved of a 100% reference solution and a 100% reference + 100% placebo solution measured at multiple time points (using the single wavelength correction) according to the method description. All results passed the acceptance criteria (< 2%) and therefore the method specificity was demonstrated.

Accuracy

The accuracy was assessed using 12 determinations at 4 concentration levels (5, 50, 100 and 120%). The accuracy was assessed using 3 separately prepared standard solutions with 100% placebo on each of the 4 concentration levels. Each solution was measured once. Accuracy was calculated as % recovery and the mean recovery calculated at each concentration level. All results pass the acceptance criteria and therefore the method was demonstrated to be accurate.

Precision

System repeatability was calculated as % RSD of 5 measurements of the same 100% reference solution. All results pass the acceptance criteria (<10% mean absolute difference) and therefore the method was demonstrated to be precise.

Linearity

Linearity was demonstrated using 6 determinations covering the range 5-120%, i.e. at 5, 20, 50, 80, 100 and 120%. Linearity was evaluated by visual inspection of a plot and mathematical estimates of the degree of linearity. All results pass the acceptance criteria (R>0.995) and therefore the method was demonstrated to be linear.

Robustness

The robustness of the method was tested by assessing the detection wavelength (272 ± 1 nm) for the UV part of the method. For the dissolution part of the method, the paddle rotation speed (100 ± 4 rpm) and dissolution medium temperature (37.0 ± 0.5°C) was tested with 2 worst case experiments. The robustness of the method was demonstrated by proving the validity of the method after small deliberate changes to the method parameters.

Solution Stability

The stability of the Reference Solution, Stock Solution, and the samples was determined during a period of 14 days when stored according to the storage conditions described in the method. The Sample Solutions are stable for 3 days when stored in open tubes and for 7 days when stored in closed tubes, both at ambient conditions on the laboratory table.

IVIVC Model Development

Two Level A IVIVC models with a separate set of IVIVC parameters covering high dose (150 to 250 mg) and low dose (50-100 mg) tapentadol tablet strengths were established and internally/externally validated. [redacted] (b) (4)

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICALS INC	TAPENTADOL

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/s/

SANDRA SUAREZ
07/28/2010

PATRICK J MARROUM
07/29/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200533 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAARP		
Sponsor:	J&J Pharmaceutical and GmbH	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Nycinta™	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Tapentalol Extended Release Tablet	**Date Assigned:**	May 13, 2010
Indication:	Management of moderate to severe pain	**Date of Review:**	June 14, 2010
Formulation	Extended Release Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
May 13, 2010 June 6, 2010	May 13, 2010 June 8, 2010	May 13, 2010 June 8, 2010	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	Amendment to pending application/Proposal of BE studies		

REVIEW SUMMARY:

Tapentadol IR tablet formulation received FDA approval on November 2008 for the relief of moderate to severe acute pain in patients 18 years of age or older under NDA 22-304.

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapendadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapendadol of the TRF (tamper resistant formulation) formulation are proposed for marketing.

On April 21, 2010 the Agency held a teleconference with the sponsor to discuss several deficiencies related to their proposed IVIVC models for the higher (250 mg, 200 mg and 150 mg) and lower strengths (50 mg and 100 mg) of Tapentalol ER tablets. The models were proposed to waive the requirements of in vivo BE studies needed to link a change in manufacturing site. The Agency's recommendations were to reconstruct the model using individual plasma concentration values and to eliminate a mathematical term being used in the model (b) (4)

In the present submission, the sponsor is proposing to perform additional fasted bioequivalence studies between the Phase 3 PR2 tablets and the TBM TRF tablets (manufactured in Gurabo) to support the bridging of the strengths originally proposed to be covered by the high-strength IVIVC. The sponsor states that the BE studies being proposed comparing 150 and 200 mg TBM TRF to Phase 3 PR2 in fasted state will complete the bridging strategy for the tapentadol TRF formulation (i.e., will complete the demonstration of the bioequivalence of the Phase 3 PR2 tablets to the commercial site TRF tablets for all strengths). The sponsor proposes to submit the

reports of these studies prior to the end of the 10-month review cycle in August.

Since the composition of the 50 mg tablet is not proportionally similar to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths, the sponsor is recommended to conduct BE studies with the highest and lowest strengths instead.

RECOMMENDATION:
The ONDQA/biopharmaceutics team has reviewed the amendment to pending application submitted to NDA 200533(000) on May 13, 2010. The following responses to biopharmacetics related questions should be conveyed to the sponsor:

1. Does the Agency agree that the proposed BE studies in the fasted state comparing TBM TRF of 150 and 200 mg to Phase 3 PR2 will complete the bridge for these two dosage strengths?

Biopharmaceutics Response:
No, we don't agree. The composition of the 50 mg tablet is not proportionally similar to the 100 mg strength and these two strengths are not proportionally similar to the higher strengths; therefore, we recommend that you conduct two in vivo bioequivalence studies under fasting conditions with the lowest (50 mg) and highest (250 mg) strengths instead. In addition, conduct dissolution profile comparisons with *f2* testing in the approved dissolution method for all the additional strengths not tested in *in vivo* BE studies.

2. Does the Agency agree that no further exploration of bioequivalence and food effect beyond the data obtained from the following studies is necessary for bridging between the PR2 formulation used in clinical studies and the TBM TRF?
   - PAI-1055/HP67 (Relative bioavailability of the TBM TRF and PR2 250 mg tablets, fed)
   - PAI-1034/HP42 (Bioequivalence of TRF registration and PR2 50 mg tablets, fasted)
   - PAI-1046/HP61 (Bioequivalence of TRF registration and PR2 100 mg tablets, fasted), and
   - PAI-1033/HP31 (Bioequivalence of TRF registration and PR2 250 mg tablets, fasted)

Biopharmaceutics Response:
Refer to question 1.

3. Does the Agency agree that the 2 above points enables the Sponsor to commercialize all 5 dose strengths (50, 100, 150, 200, and 250 mg) of TRF manufactured at the commercial manufacturing site in Gurabo upon approval?

To be answered by Clinical Review Team

4. Final Clinical Study Reports for the pivotal BE studies at 150 and 200 mg will be available

in August 2010. Given that submission of these reports will occur after Month 7 of the review cycle, would the Agency consider granting an extension of the PDUFA date for NDA 200533?

To be answered by OCP Review Team

5. Does the Agency agree that additional BE studies are required for 50, 100, and 250 mg and that these study reports can be submitted in a staggered fashion to the NDA during a cycle extension, if granted?

To be answered by OCP Review Team

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200533, TBoui, ADorantes, CBertha, DChristodoulou, DLee, SDoddapaneni

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	GI-1	ORTHO MCNEIL JANSSEN PHARMACEUTICALS INC	TAPENTADOL

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/s/

SANDRA SUAREZ
06/14/2010

PATRICK J MARROUM
06/14/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 200533 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DAARP		
Sponsor:	J&J Pharmaceutical and GmbH	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Nycinta™	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Tapentalol Extended Release Tablet	**Date Assigned:**	Dec 17, 2009
Indication:	Management of moderate to severe pain	**Date of Review:**	Jan 11, 2010
Formulation	Extended Release Tablet		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp Date**	**Date of informal/Formal Consult**	**PDUFA DATE**
Nov 25, 2009	Nov 26, 2009	Dec 17, 2009	Sep 24, 2010
Type of Submission:	Original NDA		
Type of Consult:	IVIVC models and Dissolution method and specifications---**FILING REVIEW**		

REVIEW SUMMARY:

Tapentadol IR tablet formulation received FDA approval on November 2008 for the relief of moderate to severe acute pain in patients 18 years of age or older under NDA 22-304.

Tapentadol, a centrally-acting analgesic compound, is being developed by the sponsor in an extended-release (ER) tablet formulation for the management of moderate to severe chronic pain in patients 18 years of age or older. The proposed therapeutic dosing regimen of tapendadol ER ranges from 100 to 250 mg twice daily. Tapentadol ER tablets of 50, 100, 150, 200 and 250 mg tapendadol of the TRF (tamper resistant formulation) formulation are proposed to be marketed.

This submission includes data from 38 completed clinical studies (28 Phase 1 studies and 10 Phase 2/3 studies), including the report for two in vitro in vivo correlation (IVIVC) models. The development of tapentadol ER tablets can be divided into several stages as follows:

- Round ER tablets used in early Phase 1 and Phase 2 studies (PR1; 21.5 to 200 mg);
- Oblong shaped ER tablets used in Phase 1 and Phase 3 studies (PR2; 50, 100, 150, 200, 250 and 300 mg of tapentadol);
- Oblong shaped (50, 100, and 150 mg of tapentadol) or oblong with a depression in the middle running lengthwise on each side* (200 and 250 mg of tapentadol) ER tablets used in Phase 1 studies and proposed to be marketed (TRF).

(b) (4)

The pilot batches were manufactured by GRT in Aachen, Germany, the TRF registration batches by J&JPRD in Beerse, Belgium. The to-be-marketed formulation will be manufactured in Gurabo, Puerto Rico. The Phase 3 formulation, PR2, was bridged to the pilot, registration and to-be-marketed batches of the TRF formulation using relative bioavailability and bioequivalence studies, as well as a Level A in vitro/in vivo

correlation (IVIVC). Pilot and registration batches of the TRF formulation are bridged to the to-be-marketed TRF formulation using a Level A IVIVC.

According to the sponsor, two Level A IVIVC with a separate set of IVIVC parameters covering high dose (150 to 250 mg) and low dose (50-100 mg) tapentadol tablet strengths were established and validated. (b) (4)

The dissolution method to characterize the drug release of tapentadol TRF tablets used US Pharmacopoeia (USP) Apparatus 2 (paddles) (b) (4) at 100 rpm in 900 mL of simulated intestinal fluid without enzyme, i.e., 0.05 M phosphate buffer of pH 6.8 at 37°C. This method will also be used for the to-be-marketed batches. The proposed dissolution specifications are as follows:

Strength	Acceptance criteria
50 mg	After 30 min: (b) (4) After 180 min After 360 min After 600 min
100 mg	After 30 min: After 180 min After 360 min After 600 min
150 mg	After 30 min: After 180 min After 360 min After 600 min
200 mg	After 30 min: After 180 min After 360 min After 600 min
300 mg	After 30 min: After 180 min After 360 min After 600 min

The biopharmaceutics review will focused on the validity of the IVIVC models, the proposed dissolution method and specifications, and the effect of alcoholic medium (40% ethanol) on the in vitro dissolution behavior of tapentalol TRF tablets.

RECOMMENDATION:

The ONDQA/biopharmaceutics team has reviewed NDA 200533(000) for filing purposes. We found this NDA filable from biopharmaceutics perspective. The sponsor has submitted a reviewable submission which also includes the data sets, control files, and output files related to the IVIVC model development and validation. There are no comments to the sponsor at this time.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: NDA 200533, TBoui, ADorantes, CBertha, DChristodoulou

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200533	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICALS INC	NUCYNTA ER Tablets (Tapentadol Hcl) 50mg, 100mg, 150mg, 200mg, 250mg

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/s/

SANDRA SUAREZ
01/12/2010

PATRICK J MARROUM
01/13/2010